Epidemiological studies among injecting drug users infected with HIV: highly active antiretroviral therapy, tuberculosis, hepatitis C, immunology
van Asten, L.C.H.I.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 3

Do HIV disease progression and HAART response vary among injecting drug users in Europe?

Accepted by European Journal of Epidemiology
Dus nooit doen.
Want je hept kans op dood gaan.

Maisha van Asten, 2001
Do HIV disease progression and HAART response vary among injecting drug users in Europe?

Liselotte van Asten¹, Robert Zangerle², Ildefonso Hernández Aguado³, Faroudy Boufassa⁴, Barbara Broers⁵, Raymond P. Brettle⁶, J. Roy Robertson⁷, Jim McMenamin⁸, Roel A. Coutinho⁹, Maria Prins¹

¹Municipal Health Service, Cluster Infectious Diseases, Amsterdam, The Netherlands. ²AIDS Unit, University of Innsbruck, Innsbruck, Austria. ³On behalf of the Valencian HIV Seroconversion Study, Department of Public Health, Miguel Hernandez University, Alicante, Spain. ⁴SEROCO study group, Inserm U 292, Hôpital de Bicêtre, Le Kremlin Bicêtre, France. ⁵Division of Infectious Diseases, Geneva University Hospital, Geneva, Switzerland. ⁶Infectious Diseases Unit, Western General Hospital, Edinburgh, UK. ⁷Edinburgh Drug Addiction Study, Muirhouse Medical Group, Edinburgh, UK. ⁸Scottish Center for Infection and Environmental Health, Glasgow, Scotland. ⁹Academic Medical Centre, University of Amsterdam, Department of Human Retrovirology, Amsterdam, The Netherlands.

Prior to HAART availability, there was no evidence of a geographical variation in HIV disease progression among injecting drug users (IDU) from different European regions. Nowadays, factors of importance regarding HIV disease progression in the face of HAART availability, such as HAART access, adherence, and the organisation of care for IDU may differ across Europe. Therefore we studied HIV disease progression in a European study of IDU with known dates of HIV-seroconversion. Results show that with ongoing HAART availability, the risk of HIV disease progression has continued to decrease. When accounting for pre-AIDS death (in AIDS analyses) and non-natural deaths (suicide, overdose, accidents and homicide, in analyses of death) which are common among IDU, the risk of AIDS and death has decreased by as much as 65% and 75%, respectively, in 2000/2001. Results show little geographic variation in progression to AIDS. All-cause mortality was higher in IDU from Glasgow than elsewhere, while in the Valencian region (Spain) IDU were at a significantly lower risk of non-natural deaths. The timing of HAART initiation by treatment-naive IDU likewise differed across Europe: IDU in Amsterdam, Innsbruck, and Edinburgh started at significantly lower CD4 counts than IDU in Paris, Geneva, Glasgow, and the Valencian region, but the subsequent short-term immune response was similar. In conclusion, the risk in progression to AIDS or natural death is similar across western Europe although IDU across Europe differ in other factors, such as the risk of non-natural death and the timing of HAART initiation.

Introduction

Since highly active antiretroviral therapy (HAART) became generally available, the risk of HIV disease progression has greatly decreased among injecting drug users (IDU), although not as much as in other HIV-infected groups [1-7]. In general, IDU are less likely to be on HAART [8,9], and are less compliant than other HIV-infected individuals [10]; in those taking HAART [11-14], the immunological and virological responses are less pronounced in the short term [15-17] and in the long term [18]. The rate of coinfections is high among IDU and hepatitis C virus (HCV) infection has also been suggested to play a role in the decreased effect of HAART seen in this group [1]. All these factors may differ from country to country, as also the specific antiretroviral drug combinations prescribed and the general approach to patient management and the organisation of care for HIV-infected drug users.

Prior to HAART availability, there seemed to be no geographical variation in HIV disease progression among IDU from different European regions [19]. When HAART first became generally available (mid 1996-1997), the probability for IDU to initiate HAART likewise seemed not to vary across Europe [8]. However, data on regional differences thereafter are lacking. Therefore we studied whether the rates of HIV disease progression and response to HAART vary among European IDU in different countries since HAART became widespread, using data from a collaborative study of IDU cohorts from 7 different cities or regions in Europe.
Methods

Study population

The study population comprised 790 IDU with a known date of a seronegative and seropositive HIV test. They were followed in 8 cohorts (as described elsewhere [20]) in 6 European countries: Spain (Valencian region = 280), Scotland, UK (Edinburgh, 2 cohorts n= 185, and Glasgow, n= 70), the Netherlands (Amsterdam, n= 123), Switzerland (Geneva, n= 61), France (mostly Paris, n= 41), Austria (Innsbruck n= 30). In these cohorts, started between 1982 and 1988; participants visit every 4-6 months for interviews, medical examination (including medication registration) and the sampling of blood for laboratory testing and storage. Information on AIDS and cause of death are obtained from review of medical records and by matching against local and national registries. For each individual, the date of HIV-seroconversion was calculated conditional upon the last negative HIV test and the first positive HIV test, using a cohort-specific estimate of the cumulative HIV seroincidence over calendar time [21].

Survival analysis

Cox proportional hazards analyses were used to estimate the effect of study site and calendar period on progression to AIDS and death, with adjustment for age and gender. For death, analyses were conducted for three different endpoints: 1) all-cause mortality, 2) death due non-natural causes such as accidents, suicide, overdose and homicide, and 3) death due to natural causes. Non-natural causes were analysed as a separate endpoint because they are common in IDU but not clearly related to HIV disease progression [20,22]. Progression to AIDS was studied for two endpoints: 1) AIDS, and 2) AIDS combined with pre-AIDS death from natural causes. The second endpoint was included because, among IDU, death from natural causes commonly occurs without the individual having experienced an AIDS defining event and is in part the result of HIV disease progression [20,23] but prevents an individual from reaching an AIDS endpoint (it is possibly a competing risk).

Duration of follow-up was calculated from the estimated time of seroconversion through each endpoint of interest, or to the date of loss to follow-up or the censor date (maximally 1-1-2002). IDU entered the analyses at their estimated date of HIV seroconversion or, at the date of their 1st study visit if HIV-positive at study entry (left truncation). For the progression to AIDS, persons who died without having experienced an AIDS-defining event were censored at death. For progression to natural death analysis, those who died a non-natural death were censored at the date of that death and for progression to non-natural death analysis those who died a natural death were censored at that date. For both endpoints, IDU with an unknown cause of death were censored at death (n= 11, 4%, Glasgow excluded). The calendar period of follow-up was evaluated as a time-dependent covariate in a Cox proportional hazards model. Four calendar periods were defined: 1) time before the general availability of HAART: < mid-1996, 2) the first years of HAART availability: mid 1996-1997, 3) 1998-1999 and 4) 2000-2001. All analyses were adjusted for age (continuous) and gender, and pairs of variables were checked for interactions.

Modeling the mean CD4+ T cell trajectory

For all IDU who initiated HAART and for whom CD4+ T cell measurements were available (n= 224) the mean CD4+ T cell trajectory after HAART initiation was assessed with regression analysis for repeated measurements using the mixed procedure statement (PROC MIXED) in SAS [24,25]. To correct for the dependence between consecutive CD4+ T cell measurements within each individual, we used a random effects model with random intercept and random slopes. To satisfy the normality and homoscedasticity assumption, CD4+ T cell numbers were modelled on a square-root scale [26]. The CD4+ T cell trajectory was modelled from 3 years prior to HAART initiation until 2 years after HAART initiation (2683 CD4+ T cell measurements) in a piece-wise manner, allowing for 3 different slopes: 1) the 3 years prior to HAART initiation, 2) the first 6 months after HAART initiation and, 3) the period between 6 months and 2 years after HAART initiation. Three slopes were used because the strong increase in CD4+ T cell numbers in the first few months of HAART is generally followed by a slower response thereafter. Data were analysed based on intention to continue treatment, ignoring treatment interruptions or discontinuation. Analyses were adjusted for non-naïve initiation of HAART. HAART was defined as any regimen including a protease inhibitor or a non-nucleoside reverse transcription inhibitor or at least 3 nucleoside reverse transcription inhibitors.
Results

The study population of 790 IDU with a documented date of HIV seroconversion was followed for a total of 5317 person years (characteristics shown in table 1). Of this group, 209 IDU developed AIDS. In total 276 IDU died: 197 from natural causes, 54 from non-natural causes, and 25 - mostly from Glasgow (14) - from unknown causes. Of those IDU who died, almost 50% died without an AIDS diagnosis (n=132): 60 due to a natural cause, 52 due to non-natural cause (31 overdose, 11 suicide, 7 accident, and 3 homicide) and 20 IDU due to unknown cause. The contribution made by liver-related deaths (indicated as HCV, cirrhosis, or liver failure) has increased from 4% in the pre-HAART era to 14% of all deaths in the 2000/2001 period (table 2). Comparing the proportion in 2000/2001 with the proportion of liver-related deaths in the previous time periods combined the increase was marginally significant (p=0.06, Fisher’s exact test). Deaths from Glasgow were excluded in the calculation of the percentages because of the high numbers of unknown causes of death (14/31, 45%). Of the 530 IDU in follow-up in the HAART era, 227 IDU received HAART. Of 216 IDU the observed CD4+ T cell count at or up to maximally one year prior to HAART initiation was known with a median of 242 cells/microliter (inter quartile range(IQR): 107-401) and varied largely by site (149 Edinburgh, 192 Innsbruck, 220 Amsterdam, 308 Geneva, 326 Paris, 330 Valencian region, and 421 cells/microliter in Glasgow).

Table 1. Characteristics of injecting drug users (HIV seroconverters) by study site

<table>
<thead>
<tr>
<th>Seroconverters</th>
<th>Valencian region</th>
<th>Edinburgh</th>
<th>Amsterdam</th>
<th>Glasgow</th>
<th>Geneva</th>
<th>Paris</th>
<th>Innsbruck</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, # (%)</td>
<td>280</td>
<td>185</td>
<td>123</td>
<td>70</td>
<td>61</td>
<td>41</td>
<td>30</td>
</tr>
<tr>
<td>Male, # (%)</td>
<td>203 (73%)</td>
<td>124 (67%)</td>
<td>73 (59%)</td>
<td>52 (74%)</td>
<td>42 (69%)</td>
<td>27 (66%)</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Age at seroconversion, years (IQR)</td>
<td>25</td>
<td>24</td>
<td>30</td>
<td>27</td>
<td>26</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Seroconversion interval, years (IQR)</td>
<td>1.1</td>
<td>1.3</td>
<td>0.4</td>
<td>1.7</td>
<td>1.4</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>AIDS cases</td>
<td>57</td>
<td>69</td>
<td>33</td>
<td>11</td>
<td>16</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Deaths</td>
<td>46</td>
<td>98</td>
<td>62</td>
<td>31</td>
<td>22</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>With AIDS</td>
<td>30</td>
<td>59</td>
<td>26</td>
<td>8</td>
<td>13</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Pre AIDS</td>
<td>16</td>
<td>39</td>
<td>35</td>
<td>23</td>
<td>9</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

1 IQR: interquartile range
2 time between the last negative HIV test and first positive HIV test.

Table 2. Causes of death among HIV-positive injecting drug users in 4 calendar periods, Glasgow excluded*.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV/cirrhosis/liver failure</td>
<td>6 (4%)</td>
<td>0 (0%)</td>
<td>2 (5%)</td>
<td>3 (14%)</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>Other natural cause</td>
<td>116 (74%)</td>
<td>21 (75%)</td>
<td>26 (67%)</td>
<td>13 (62%)</td>
<td>176 (72%)</td>
</tr>
<tr>
<td>Non-natural death1</td>
<td>32 (20%)</td>
<td>6 (21%)</td>
<td>9 (23%)</td>
<td>1 (5%)</td>
<td>48 (20%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (2%)</td>
<td>1 (4%)</td>
<td>2 (5%)</td>
<td>4 (19%)</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>Total deaths</td>
<td>157 (100%)</td>
<td>28 (100%)</td>
<td>39 (100%)</td>
<td>21 (100%)</td>
<td>245 (100%)</td>
</tr>
</tbody>
</table>

* Glasgow excluded due to many deaths without a documented cause (14/31, 45%).
1 Death due to overdose, homicide, suicide, and accidents.
2 Pre-HAART era: time period prior to the general availability of highly active antiretroviral therapy for HIV. HAART became available between March 1996 and September 1996 depending on the study site.
3 HAART became available in 1996, starting between March and September depending on the study site.
Survival analysis

From widespread HAART availability until 2001, the risk of progression to AIDS and progression to all-cause death has continued to decrease among IDU (table 3). For AIDS the initial decrease in the early years of HAART (mid 1996-1997) was not very pronounced and not significant whereas for death the rate of decrease was greatest in this initial HAART period. When pre-AIDS death from natural causes (which is associated with HIV disease progression in IDU [20]) is also included as an AIDS endpoint, the initial decrease in the risk of progression to AIDS in the 1996-1997 calendar period is amplified (changing from a 29% reduction to a 41% reduction in risk) and becomes significant. Although the initial risk reduction was already more pronounced for death than for AIDS, an even greater risk reduction for death in the initial years of HAART is seen when analyses are restricted to natural causes of death only (changing from a 38% reduction to a 53% reduction); the risk reductions in the later time periods likewise became more pronounced. In contrast to natural death, progression to non-natural death showed no clear trend in time. Changing the reference category and thus comparing the later time periods to the early HAART period the further improvements in 2000/2001 for progression to AIDS, death, and death due to natural causes were marginally significant (p-values between 0.06 and 0.10).

Sites did not differ greatly in their risk of progression to AIDS and the combined endpoint of AIDS and pre-AIDS death, except that IDU in Innsbruck showed a more than two-fold greater risk than the reference category. The risk for all-cause mortality was highest in Glasgow (and statistically significant) and lowest in Paris and the Valencian region (but not significant at either site). Separating all-cause death into natural and non-natural causes of death yielded no apparent difference among sites in the risk of death due to natural causes. IDU in the Valencian region appeared to be at a decreased risk for non-natural death but not for death due to natural causes. For Glasgow, these separate analyses could not be performed due to the large numbers of death with unknown cause. Changing the reference category for the study site did not reveal any other significant differences in the risk of death among regions. For AIDS, the risk appeared significantly lower in Geneva when compared to Valencia. No significant interactions between variables were observed.

CD4+ T cell response

Of 227 IDU known to have initiated HAART, 90 were naïve for any prior antiretroviral treatment. Of these 90, measurements of CD4+ T cell numbers between 3 years prior to and 2 years after HAART initiation were available for 88 IDU (98%, 905 CD4+ T cell measurements), for whom the mean CD4+ T cell trajectory is shown in figure 1. The values of the intercepts and slopes of the CD4+ T cell trajectory, stratified by site, are shown in table 4. Treatment-naïve IDU from Edinburgh, Amsterdam and Innsbruck initiated HAART at lower CD4+ T cell numbers than did IDU from the other sites (fig.1). Defining Valencia as the reference category this was significant (p<0.05) with estimated average CD4+ T cell counts at HAART initiation of 206, 221, 240 respectively compared to 353 cells/microliter in the Valencian region. The subsequent rate of increase in CD4+ T cell numbers in the first 6 months after HAART initiation was significant but did not differ significantly across sites. After the initial response, the increase leveled off or changed to a slight decrease for all sites except Glasgow, where an increase in CD4+ T cells seemed sustained for the total period after naïve initiation of HAART (24 months). However, this increase in comparison with the other sites did not reach statistical significance.
### Table 3a. Adjusted Hazard ratios for progression to AIDS among injecting drug users in Europe\(^1\).

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Year</td>
<td>AIDS p-value</td>
<td>AIDS and pre-AIDS death p-value</td>
<td></td>
<td></td>
<td>Site p-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Haart</td>
<td>&lt;0.001</td>
<td>1 (ref)</td>
<td>0.71 (0.46-1.11)</td>
<td>0.44 (0.27-0.73) *</td>
<td>0.35 (0.16-0.79) *</td>
<td>0.59 (0.39-0.90) *</td>
<td>0.45 (0.29-0.71) *</td>
<td></td>
<td></td>
<td>2.61 (1.30-5.23) *</td>
<td>1.02 (0.51-2.05)</td>
<td>1.86 (1.15-3.01) *</td>
<td></td>
</tr>
<tr>
<td>1996-1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998-1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000-2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 3b. Adjusted Hazard ratios for progression death among injecting drug users in Europe\(^1\).

<table>
<thead>
<tr>
<th>Year</th>
<th>All cause death p-value</th>
<th>Death due to natural causes p-value</th>
<th>Death due to non-natural causes p-value</th>
<th>Site p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Haart</td>
<td>&lt;0.001</td>
<td>1 (ref)</td>
<td>1.38 (0.56-3.44)</td>
<td>0.28</td>
</tr>
<tr>
<td>1996-1997(^4)</td>
<td>0.62 (0.41-0.93) *</td>
<td>0.48 (0.29-0.81) *</td>
<td>2.07 (0.91-4.72)</td>
<td></td>
</tr>
<tr>
<td>1998-1999</td>
<td>0.51 (0.34-0.77) *</td>
<td>0.35 (0.21-0.60) *</td>
<td>0.52 (0.07-4.04)</td>
<td></td>
</tr>
<tr>
<td>2000-2001</td>
<td>0.35 (0.20-0.60) *</td>
<td>0.25 (0.13-0.51) *</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Notes:

1. Adjusted for age and gender.
2. Excluding non-natural pre-AIDS deaths (suicide, accidents, overdose, and homicide).
3. Suicide, accidents, overdose, and homicide.
4. HAART became available in 1996, starting between March and September depending on the study site.
5. Glasgow excluded because of the high numbers (14/31, 45%) of unknown causes of death.

\(^*\) p<0.05
Figure 1. Mean CD4+ T cell numbers before and after HAART initiation of treatment-naive injecting drug users. The lines are created using coefficients obtained from a piece-wise repeated measurements model. ** IDU in Amsterdam, Edinburgh, and Innsbruck initiate HAART at significantly lower CD4 numbers than do IDU in Valencia (defined as reference), p<0.05.

Table 4. Estimates of the mean CD4+ T cell trajectory in treatment-naive injecting drug users before and after HAART initiation, by study site.

<table>
<thead>
<tr>
<th>Parameters of the mean √CD4+ T cell trajectory</th>
<th>Estimate of the mean absolute CD4+ T cell number at 3 specific time points (cells per μl blood)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam: 21 (250)</td>
<td>14.87 (ref)</td>
</tr>
<tr>
<td>Edinburgh: 13 (182)</td>
<td>14.35</td>
</tr>
<tr>
<td>Geneva: 5 (25)</td>
<td>20.74 *</td>
</tr>
<tr>
<td>Glasgow: 12 (124)</td>
<td>19.33 *</td>
</tr>
<tr>
<td>Innsbruck: 8 (80)</td>
<td>15.50</td>
</tr>
<tr>
<td>Paris: 3 (33)</td>
<td>17.66</td>
</tr>
<tr>
<td>Valencian region: 26 (211)</td>
<td>18.79 *</td>
</tr>
</tbody>
</table>

1 parameters obtained from a piece-wise mixed linear regression model.
2 to satisfy the normality and homoskedasticity assumption, CD4+ T cell numbers were modelled on a square-root scale [47,48].
3 √CD4/month
4 (intercept) ²
5 ((intercept + 6 × slope in the first 6 months)) ²
6 ((intercept + 6 × slope in the first 6 months) + (18 × slope in month 6 to 24)) ²
* Significantly (p<0.05) higher than Amsterdam (defined as reference).
Discussion

This study shows that in the HAART era there is no clear variation among HIV-infected IDU from different European cities in the trends of progression to AIDS and natural death; however, there is some geographical variation in the risk of all-cause death and the risk of death due to non-natural causes. The timing at which HAART is initiated also differs across Europe, with IDU in several countries starting HAART at significantly lower CD4+ T cell counts than in other countries, but the response seems comparable in terms of increase in CD4 cell counts. Since the introduction of HAART in 1996, the risk of HIV disease progression to both AIDS and death has continued to decrease in IDU in Europe but these reductions are underestimated when deaths due to non-natural causes (for progression to death) are included and, to a lesser extent when pre-AIDS mortality due to natural causes (for progression to AIDS) are not considered. However, even when accounting for these specific types of death categories which are common among IDU, the risk reductions remain of a lesser magnitude than the reductions reported for European homosexual men and heterosexual individuals with estimated dates of seroconversion [1,3,27] but they are not less than has been reported for hemophiliac patients [1].

In the present study, the risk of death among IDU differed when analysing 3 different definitions of death. All cause mortality may not be the ideal disease endpoint to study for HIV-infected IDU, especially when comparisons are made across risk-groups [30]. Among IDU, non-natural causes of death such as suicide, overdose, accidents, and homicide are unrelated to progressing HIV disease [22] and occur more frequently than among other risk groups [22,29,30]. When censoring these causes of deaths, thus limiting analyses to deaths due to natural causes, the risk reductions remain of a lesser magnitude than the reductions reported for European homosexual men and heterosexual individuals with estimated dates of seroconversion [1,3,27] but they are not less than has been reported for hemophiliac patients [1].

In the pre-HAART era, increasing age was the only predictor of faster HIV disease progression for all HIV risk groups [38]. Interestingly, as we did not find a significant interaction between calendar time and age, the post-HAART effect of age was not diminished in our subjects, whilst in mixed risk-groups the importance of age decreased enormously [1]. Our finding does not reflect a lack of power to detect an interaction, because even when the pre- and post-HAART era were analysed separately, the effect of age remained the same (RR of AIDS per 10 year increase in age: 1.05 for both time periods). In general, treatment compliance improves with patient age [39] and this might contribute to the reported decreased importance of age on progression. However in the current study, older age was still associated with accelerated progression but it is not known whether older IDU displayed better adherence. However, in studies on CD4 response, older age has been shown to be associated with a poorer CD4 response [39,40] which might result in a higher rate of clinical disease progression [41]. Whether older IDU are less responsive to HAART than younger IDU is not clear.

Our study sites showed a few significant differences in progression rates to AIDS and death. One site, Innsbruck, showed an increased risk of progression to AIDS, probably because its cohort was the only one in which no IDU were
‘lost to follow-up’ allowing all diagnoses of AIDS to be known. The increased risk of AIDS thus may be attributable to a completeness of information as linkage with AIDS registrations was not possible at all sites. This is particularly supported by the fact that the risk of death was not elevated in Innsbruck because contrary to AIDS, the endpoint of death is easier to trace through linkage with death registries for any IDU who was lost to follow up in the other cohorts. Like others, we found the risk of death to be significantly increased among IDU from Glasgow compared to other cities [42]. Whether this was attributable to natural or non-natural causes was not known. The risk of all-cause death was lowest in IDU from Paris and the Valencian region and appeared to be mainly attributable to a decreased risk of non-natural death, which was statistically significant for the Valencian region only. It has been hypothesized that non-natural deaths due to suicide, overdose and accidents are low in Spain due to a better supportive social network [20]. However, it should be noted that the power to look at progression to non-natural death, either temporally or according to region, was limited (54 of the 790 IDU had died of a non-natural death during the study period) and this is reflected in the relatively wide confidence intervals.

For those IDU who receive HAART, the timing at which HAART is initiated clearly differs across Europe. IDU in Amsterdam, Edinburgh and Innsbruck started HAART at significantly lower CD4+ T cell counts than IDU in Paris, Geneva, Glasgow and the Valencian region. However such variation did not lead to variation in the subsequent increase in the CD4 T-cell numbers: neither in the first 6 months after HAART initiation nor in the longer-term response. This finding is in accordance with data from a larger cohort of seroconverters (all risk-groups combined) showing no benefit in terms of short-term immune response from initiating HAART at CD4+ T cell counts above 350 cells/ul compared to 200-350 cells/ul [15] although the CD4+ T cell numbers reached at 2 years after HAART initiation were higher in IDU who initiated HAART at higher CD4+ T cells. In the present study CD4+ T cell counts did not seem to continue to increase after 6 months after HAART initiation and even displayed a slight decrease at most sites. Several studies have already shown suboptimal; immunological response to HAART in IDU [43,13], even after a good initial response [18]. However even in a non-IDU population with controlled viraemia a considerable proportion may experience a decrease in CD4+ T cell counts instead of an increase (35% of treatment naïve individuals over a 3 year period on HAART) [44]. Factors that have been associated with an impaired CD4 cell recovery and virologic failure in IDU are continued drug use, treatment breaks and low adherence [43,45,13]. Glasgow and Geneva were the only sites without decreasing CD4+ T cell numbers (but with a zero or positive slope) after the first 6 months of HAART. These were also the only sites where no IDU used saquinavir as part of the initial regime. Saquinavir was used by 10-33% of IDU at the other sites and perhaps the inferior immunological and virological responses associated with early saquinavir hard gel might also have played a role in the decrease of CD4+ T cells observed at these sites after 6 months of HAART [13,46].

In conclusion, trends in progression to either AIDS or death due to natural causes in IDU are similar across western Europe. There also were no variations in the short-term immune response to HAART therapy, although sites clearly differed in the timing of HAART initiation. An increase in CD4+ T cells from 6 months after HAART onwards was absent in treatment naïve IDU at all sites, except possibly among IDU in Glasgow. Risk of death due non-natural causes, an endpoint which is not associated with HIV disease progression, was significantly lower in the Valencian region of Spain.

Acknowledgements
We thank Ronald Geskus for critical reading of the manuscript and Lucy Phillips for editorial review. We also thank the clinicians and health workers who contributed by collecting data, the laboratories collaborating with the original studies for determining lymphocyte subsets, and the participants for their ongoing participation.
References


