Epidemiological studies among injecting drug users infected with HIV: highly active antiretroviral therapy, tuberculosis, hepatitis C, immunology
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Chapter 2

Limited effect of highly active antiretroviral therapy among HIV-positive injecting drug users on the population level

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En roken is ook niet prettig en daar ga ik het nu over hebben. Roken is verslaavend net als druks. Je kunt er aan dood gaan. O ja, bij druks ook daar kun je ook aan dood gaan.

Maisha van Asten, 2001
There is evidence that HIV-positive injecting drug users benefit less than other risk groups from highly active antiretroviral therapy that has been available since 1996. In this multicentre European study the impact of the availability of highly active antiretroviral therapy on the progression rates to AIDS and death among injecting drug users with a documented date of HIV seroconversion is studied. After highly active antiretroviral therapy became available the risk of AIDS and death for injecting drug users decreased by 28% and 36%, which is less than has been reported for other risk groups.

**METHODS**

The study population comprised 751 IDU with a known date of a seronegative and seropositive HIV test from seven cohorts in six European countries: the Valencian HIV Seroconversion Study (n=279), the Edinburgh Drug Addiction Study and the Edinburgh City Hospital Cohort Study (combined n=172), the Amsterdam Cohort Study (n=118), the Geneva HIV Cohort Study (n=65), the French SEROCO Study (n=40), the Scottish National Collaborative HIV Testing Study from Glasgow (n=52) and the Innsbruck AIDS Study (n=25). The individual cohorts started between 1982 and 1988 and the design and methodology of each cohort have been described elsewhere. Information on AIDS and cause of death was obtained from review of medical records and by matching against local and national registries. Calendar period of follow-up was evaluated as a time-dependent covariate in a Cox proportional hazards model. Three calendar periods were defined when analysing progression to AIDS: i) time before the implementation of the expanded European AIDS case definition, ii) time of the general availability of HAART and iii) time period 1997/1998. However, IDU who are eligible for HAART have a lower probability of initiating the potent drug combinations and also start HAART later following HIV infection than other risk groups. So far risk reduction estimates of AIDS and death in time of HAART specifically for IDU have not been published. Therefore, on the population level, we studied the impact of the general availability of HAART on the progression rates to AIDS and to death among IDU with documented date of HIV seroconversion.
RESULTS
Characteristics of the study population are shown in table 1. During the study period 166 persons developed AIDS and 200 persons died, of whom 88 died so prior to the development of AIDS. Since the application of the extended AIDS case definition, 101 individuals had developed AIDS, 20% as a result of one of the added diseases (17 pulmonary TB and three recurrent pneumonias). Following the change in AIDS case definition and before HAART was introduced, the risk of AIDS increased by 29% (adjusted hazard ratio 1.29 (1.00-1.77) (table 2a), 95% confidence interval (Cl): 0.88-1.90). Later on, after HAART became available, the risk of AIDS declined by 28% (adjusted HR for AIDS 0.72, 95% Cl: 0.41-1.25) (table 2a), using as reference the time period during which the new AIDS case definition was applied and before the introduction of HAART. When ignoring the impact of the 1993 AIDS definition, thus comparing only two calendar periods at risk (before and after HAART), the impact of availability of HAART is slightly less pronounced (adjusted HR 0.78 Cl: 0.45-1.34, not shown in the table). The reduction in risk of death from natural causes after HAART compared to the total period before is 36% (adjusted HR 0.64 (Cl: 0.36-1.17) (table 2b).

DISCUSSION
Until 1993 the incubation period from HIV seroconversion to AIDS in IDU was estimated to be 10.2-11.6 years. We assume the increased risk of AIDS in the 1993 to 1996 time period to be attributable to the extension of the European AIDS case definition as two of the three added diseases are mainly afflicting IDU and no changes in progression have been reported for earlier calendar periods despite earlier definition changes and the introduction of mono and bitherapy. However, when ignoring this increased risk of AIDS that is probably due to the 1993 AIDS definition, our estimated risk reduction of AIDS among IDU in the time of highly active antiretroviral therapy was altered only minimally.

Table 1 Characteristics of the study population (751 IDU seroconverters)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Median age at HIV seroconversion</td>
<td>26</td>
<td>22-30</td>
</tr>
<tr>
<td>&lt;2 years between negative and positive HIV test</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>Median seroconversion year</td>
<td>1990</td>
<td>1986-1992</td>
</tr>
<tr>
<td>Median years of follow-up</td>
<td>5.1</td>
<td>3.0-8.4</td>
</tr>
</tbody>
</table>

a: IQR: inter-quartile range

Table 2a Hazard ratios for progression from HIV seroconversion to AIDS by calendar period

<table>
<thead>
<tr>
<th>Calendar period</th>
<th>AIDS univariate</th>
<th>AIDS multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Application of 1987 AIDS definition</td>
<td>0.65 (0.45-0.93)</td>
<td>0.77 (0.52-1.14)</td>
</tr>
<tr>
<td>1993 AIDS definition until HAART (reference)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Since availability of HAART</td>
<td>0.78 (0.45-1.35)</td>
<td>0.72 (0.41-1.25)</td>
</tr>
</tbody>
</table>

a: Adjusted for age at seroconversion, gender, geographic region and setting of follow up (hospital vs. non-hospital based).

Table 2b Hazard ratios for progression from HIV seroconversion to death of natural causes by calendar period

<table>
<thead>
<tr>
<th>Calendar period</th>
<th>Death univariate</th>
<th>Death multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre HAART</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>General availability of HAART</td>
<td>0.71 (0.39-1.27)</td>
<td>0.64 (0.36-1.17)</td>
</tr>
</tbody>
</table>

a: Adjusted for age at seroconversion, gender, geographic region and setting of follow up (hospital vs. non-hospital based).
In our study, the first effect of the availability of HAART among IDU with documented HIV seroconversion is an approximate 28% decrease in risk of developing AIDS and 36% decrease in mortality. The survival benefit in our study is less than that reported in the CASCADE study in the same study period, where the overall decrease in mortality following HAART introduction was 64%, with no difference by risk group. The survival benefit in our study is also less than the 50% decrease in mortality among Italian seroconverters. The latter study does mention that the reduction was less pronounced among IDU, but not to which extent. Not only less HAART uptake, but also pre-AIDS deaths of natural causes (liver failure, bacterial infections), which are more common among IDU than other risk groups, may play a role in the limited effect of HAART on mortality. Future analyses including more follow-up time and details on individual treatment compliance will let us know whether IDU do indeed benefit less from the availability of HAART than other risk groups.

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REFERENCES


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