

I N F E C T I O U S D I S E A S E S

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

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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.

Keywords: Europe, highly active antiretroviral therapy, HIV disease progression, IV drug users, survival analysis

It is not yet clear whether HIV-positive injecting drug users (IDU) benefit as much as other risk groups from the general availability since 1996 of HAART (highly active antiretroviral therapy). Studies on the population level that include, among others, the IDU risk group, do show a reduced risk of AIDS and death in 1997 and 1998^{1–4} and these improvements have been shown to be associated with therapy usage.⁵ However, most of these studies concern seroprevalent cohorts in which adjusting fully for duration of HIV infection is not possible, which leads to survival estimates in the HAART era that are too optimistic.⁶ Only two studies of seroconverters (thus with known duration of infection) have been published so far, showing a decreased risk of death of 50% (Italy) and 64% (Europe) for several risk groups combined in the

1997/1998 time period.^{5,7} 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.^{8–11} 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.

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.¹² 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 implementation of the

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expanded definition but before general availability of HAART and iii) time since general availability of HAART. The reason for distinguishing between time before and after the 1993 extended AIDS case definition is that this revision has been shown to increase the number of AIDS cases especially in IDU^{13,14} because in Europe cervix carcinoma, recurrent pneumonia and pulmonary tuberculosis were added,¹⁵ of which the latter two are common among IDU.^{16–18} Hence, disregarding the increase in AIDS hazard in the second period which may be due to the change in AIDS case definition might underestimate the effect of HAART on progression to AIDS in IDU. For progression to death from natural causes (thus excluding death from suicide, overdose and unintentional injuries) the first two calendar periods were combined, as a change in AIDS definition would not affect survival. In contrast to other studies, and to avoid misclassification, country-specific cut-off dates were used for each time period: the 1993 AIDS case definition was introduced between 1–1–1993 or 1–1–1994 in the different countries and starting dates for general availability of HAART varied between March 1996 and September 1996. Follow-up was calculated from the estimated time of seroconversion through the endpoint (AIDS or natural death), lost to follow up or censor date (maximally 1–1–1998). For AIDS analyses persons who died pre-AIDS were censored at death and for survival analyses persons who died of a non-natural cause were censored at death. In multivariate analyses the effect of calendar period was also corrected for a combination variable of geographic region and setting of follow up, as a clinical setting has been shown to be associated with faster progression¹⁹ and the cohort in Southern Europe was younger, thus in an earlier stage of disease progression in each calendar period.

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 did 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 pneumonia). Following the change in AIDS case definition and before HAART was introduced, the risk of AIDS increased by 29% (adjusted hazard ratio 1.29 (1/0.77) (*table 2a*), 95% confidence interval (CI): 0.88–1.90). Later on, after HAART became available, the risk of

AIDS declined by 28% (adjusted HR for AIDS 0.72, 95% CI: 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 CI: 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 (CI: 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.^{19–21} 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 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.²² 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)

Female	33%	
Median age at HIV seroconversion	26	IQR ^a 22–30
<2 years between negative and positive HIV test	70%	
Median seroconversion year	1990	IQR 1986–1992
Median years of follow-up	5.1	IQR 3.0–8.4

a: IQR: inter-quartile range

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

Calendar period	AIDS univariate	AIDS multivariate ^a
Application of 1987 AIDS definition	0.65 (0.45–0.93)	0.77 (0.52–1.14)
1993 AIDS definition until HAART (reference)	1	1
Since availability of HAART	0.78 (0.45–1.35)	0.72 (0.41–1.25)

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

Calendar period	Death univariate	Death multivariate ^a
Pre HAART	1	1
General availability of HAART	0.71 (0.39–1.27)	0.64 (0.36–1.17)

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.⁷ 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.⁵ 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.¹² 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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