Highly Active Antiretroviral Therapy and Survival in HIV-Infected Injection Drug Users

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Context Highly active antiretroviral therapy (HAART) is often withheld from injection drug users (IDUs) infected with the human immunodeficiency virus (HIV) based on the belief that their unstable lifestyles may predetermine a markedly inferior outcome with HAART. However, long-term evaluations of HIV treatment outcomes among IDUs in comparison with other risk groups are not available.

Objective To compare survival rates among HIV-infected patients initiating HAART with and without a history of injection drug use.

Design, Setting, and Patients Population-based, prospective cohort study (HAART Observational Medical Evaluation and Research [HOMER]) of 3116 antiretroviral-naive HIV-infected patients in a province-wide HIV/AIDS treatment program in British Columbia, Canada. Of the 3116 patients, 915 were IDUs (29.4%), 579 were female (18.6%), and the median age was 39.4 years (interquartile range, 33.3-46.4 years). Treatment with HAART was initiated between August 1, 1996, and June 30, 2006. The median duration of follow-up was 5.3 years (interquartile range, 2.8-8.3 years) for IDUs and 4.3 years (interquartile range, 2.0-7.6 years) for non-IDUs. Patients were followed up until June 30, 2007. Data were analyzed between November 1, 2007, and May 26, 2008.

Main Outcome Measure All-cause mortality.

Results Overall, 622 individuals died (20.0%) during the study period (232 IDUs and 390 non-IDUs), for a crude mortality rate of 20.0% (95% confidence interval [CI], 18.4%-21.5%). At 84 months after the initiation of HAART, the product limit estimate of the cumulative all-cause mortality rate was similar between the 915 IDUs (26.5%; 95% CI, 23.2%-29.8%) and 2201 non-IDUs (21.6%; 95% CI, 16.9%-26.2%) (Wilcoxon $P=.47$). In multivariate time-updated Cox regression, the hazard ratio of mortality was similar between IDUs and non-IDUs (1.09; 95% CI, 0.92-1.29).

Conclusion In this study population, injection drug use was not associated with decreased survival among HIV-infected patients initiating HAART.

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SINCE THE MID-1990S, SUBSTANtial reductions in morbidity and mortality related to the human immunodeficiency virus (HIV) have been documented among HIV-infected persons receiving highly active antiretroviral therapy (HAART).[1-3] However, a large number of prior reports have demonstrated that because of issues of social instability related to illicit drug addiction,[4] HIV-infected injection drug users (IDUs) may not be deriving the full benefits of HAART.[5-8] For instance, prior studies have shown that IDUs are less likely to be prescribed HAART,[9-12] and a recent international collaboration demonstrated that a history of injection drug use was an independent predictor of worse outcome with HAART.[3] These reports may have contributed to an increasingly prevalent belief among clinicians that IDUs may be significantly less likely to benefit from antiretroviral therapy, and prior studies have shown that clinicians commonly withhold HAART from IDUs.[13-15]

Earlier reports, however, have been limited by a number of important confounders. For example, it has been acknowledged that failure to examine causes of death in this population may bias the results because IDUs are known to have a higher risk of mortality from causes unrelated to HIV (eg, illicit drug overdoses).[3,6,16] Other studies have been limited by having been conducted in the context of medical systems with significant financial barriers to HIV/AIDS care, which may disproportionately affect IDUs.[3,8,9]

This study was conducted to compare patterns of mortality between patients with and without a history of injection drug use among a cohort of antiretroviral-naive patients initiating HAART in a setting with free HIV/AIDS care.

METHODS

The HAART Observational Medical Evaluation and Research (HOMER) study is a prospective observational cohort of all antiretroviral-naive pa-

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tients aged 18 years or older initiating HAART in British Columbia, Canada, and has been described in detail elsewhere.[2,17] Briefly, all antiretroviral-naive patients initiating HAART in the province are automatically enrolled into the study. The cohort is followed up in a unique environment with a centralized free antiretroviral distribution program and a province-wide vital statistics registry. This allows for an accurate ascertainment of cause of death for all participants as well as the opportunity to study outcomes from HIV treatment in a setting in which all financial barriers to all HIV/AIDS and other medical care are eliminated.[2,17]

In the present study, analyses were restricted to antiretroviral-naive HIV-infected men and women who were first prescribed triple drug antiretroviral therapy between August 1996 and June 2006, and who were followed up to June 30, 2007. Data were analyzed between November 1, 2007, and May 26, 2008. Participants were initially prescribed HAART with regimens composed of 2 nucleoside/nucleotide reverse-transcriptase inhibitors, plus a nonnucleoside reverse-transcriptase inhibitor, or a nonboosted protease inhibitor, or a ritonavir-boosted protease inhibitor, at the discretion of the enrolling physician.

The primary end point for this analysis was time to death. Deaths that occurred during the follow-up period were ascertained on a continuous basis from physician reports and through record linkages accomplished in conjunction with the British Columbia Division of Vital Statistics. The external linkage limited losses to follow-up and enabled all patients to be followed up until death or the end of the study period even if they discontinued HAART. In the primary analysis, we evaluated all-cause mortality. Causes of death that were unlikely to be attributable to HIV infection were defined as accidental causes of death, and we conducted subanalyses in which these deaths were censored at the time of death and classified as nonevents. As previously,[2,17] accidental causes of death were defined by examining causes of death based on the *International Statistical Classification of Diseases and Related Health Problems* codes version 10.[18] We hypothesized a priori that because IDUs may be more likely to experience accidental mortality from non–HIV-related causes, such as illicit drug overdoses, mortality rates would be most similar after accidental causes were treated as nonevents.

As an initial analysis, the baseline composition of the study cohort was compared and stratified by history of injection drug use. Characteristics of the baseline study population were compared using the Pearson χ^2 test for dichotomous variables and the Wilcoxon rank-sum test for continuous variables.

For the comparison of unadjusted survival rates, Kaplan-Meier methods were used and patients were stratified based on history of injection drug use at enrollment. Cumulative mortality was compared at each 12-month interval by calculating 95% confidence intervals (CIs) using the Greenwood method.[19] Based on exploratory analyses, we found that the assumption of proportional hazards was violated, and therefore the Wilcoxon test was used to compare the Kaplan-Meier survival curves.[19-21] To visually present the product limit estimates of the cumulative mortality rate while a reasonable proportion of the cohort remained under follow-up, Kaplan-Meier curves were generated to show survival over the first 84 months, and 95% CIs were calculated around the survival probabilities at each 12-month interval (including 84 months). However, the statistical comparison of the survival curves included all follow-up data for all participants.

Time-updated Cox regression models were used to calculate adjusted hazard ratios of mortality because the differences between IDUs and non-IDUs could confound a comparison of survival patterns.[19-21] Of note, the proportional hazards assumption was not relevant to the Cox regression analysis when time-updated covariates were used in the model.[20] Potential confounders considered were defined identical to those in our prior reports[2,17] and included age, sex, a prior diagnosis of AIDS (yes vs no), protease inhibitor use in the initial regimen (yes vs no), date of therapy initiation (before or after July 1, 1997), physician experience (per 100 patients enrolled), baseline CD4 cell count ($<$50, 50-199, or $\geq$200 cells/μL), baseline HIV RNA levels ($\log_{10}$ transformed), and 95% antiretroviral adherence (yes vs no).

Adjustment for protease inhibitor use in the initial regimen was performed due to potential differences in HAART prescribing practices for IDUs vs non-IDUs, and date of therapy initiation was adjusted for because July 1, 1997, represents the date that the province's therapeutic guidelines were revised to recommend HAART (rather than dual therapy) for all patients regardless of baseline plasma HIV RNA level.[2,17] As previously described,[2] adherence was estimated based on prescription refill compliance and time-updated based on compliance during each 6-month period from the antiretroviral start date.[22]

Potential confounders were selected for inclusion in the final models using a conservative backward-selection approach that considered the magnitude of change in the coefficient of the injection drug use variable. Specifically, starting with a fixed model, which considered all available variables, potential confounders were dropped one at a time, using the relative change in the coefficient for the variable related to the injection drug use variable as a criterion, until the maximum change from the full model exceeded 5%.[23,24]

The HIV/AIDS drug treatment program and the HOMER cohort, including mandated analyses deriving from them, such as those presented herein, have been vetted and approved by the University of British Columbia Research Ethics Board at its St Paul's Hospital site. Individuals in HOMER were not required to provide written informed consent for the purposes of the analyses presented herein. These administrative analyses occur within the

Table. Baseline Characteristics of 3116 Antiretroviral-Naive Patients Initiating HAART Between August 1996 and June 2006

Characteristic	History of Injection Drug Use, No. (%)[a] Yes (n = 915)	No (n = 2201)	*P* Value[b]
Age, mean (SD), y	38.9 (8.4)	40.9 (10.3)	<.001
Female	265 (29.0)	314 (14.3)	<.001
AIDS diagnosis	125 (13.7)	342 (15.5)	.19
Protease inhibitor use	560 (61.2)	1392 (63.2)	.28
Date of therapy initiation[c]			
Prior to July 1, 1997	115 (12.6)	240 (10.9)	.18
After July 1, 1997	800 (87.4)	1961 (89.1)	
Physician experience, mean (SD)[d]	75.4 (89.8)	123.5 (131.9)	<.001
CD4 cell count, cells/μL			
≥200	137 (15.0)	374 (17.0)	.37
50-199	325 (35.5)	775 (35.2)	
<50	453 (49.5)	1052 (47.8)	
HIV RNA, mean (SD), $\log_{10}$ copies/mL	4.87 (0.64)	4.86 (0.72)	.35

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus.
[a] Unless otherwise indicated.
[b] The χ^2 and Fisher exact tests were used to compare distributions of categorical variables and the Wilcoxon rank-sum test was used for continuous variables.
[c] July 1, 1997, reflects date when local therapeutic guidelines recommended HAART for all patients.
[d] Defined as the number of patients with HIV previously enrolled by that physician at the time of enrollment.

context of a universal health care system in which individuals receive medical care, laboratory monitoring, and antiretrovirals free of charge. The ethical approval includes publication in scientific journals and presentations at scientific meetings.

The statistical analyses were conducted using SAS software version 9.1.3 (SAS Institute Inc, Cary, North Carolina). Because this was an observational study, a priori statistical power and sample size calculations were not conducted. The analyses involved 3116 individuals and 622 deaths; thus, we were confident that there was sufficient statistical power to adequately test for clinically relevant differences in mortality between patients with and without a history of injection drug use. The tests of significance were 2-sided, and a *P* value of less than .05 was used to indicate that an association was statistically significant.

RESULTS

During the study period (between August 1, 1996, and June 30, 2006), 3372 patients initiated HAART, among whom 256 individuals (7.6%) were excluded from the HOMER cohort for not having a baseline CD4 cell count and a plasma HIV RNA level available within 6 months prior to the start of antiretroviral therapy. Those excluded were more likely to be male (*P*<.001) and younger (*P*=.004), but there was no difference according to injection drug use status. These individuals were not eligible for the study and were not included in the Kaplan-Meier estimation analyses to avoid differing sample sizes between these and multivariate analyses. As noted, the group did not statistically differ by injection drug use status and such analyses would be expected to contribute little to the overall study.

Among the study sample of 3116 individuals, 915 were IDUs (29.4%), 579 were female (18.6%), and the median age was 39.4 years (interquartile range, 33.3-46.4 years). The median duration of follow-up was 5.3 years (interquartile range, 2.8-8.3 years) for IDUs and 4.3 years (interquartile range, 2.0-7.6 years) for non-IDUs. The TABLE shows the baseline characteristics of study participants stratified by history of injection drug use. In comparison with non-IDUs, patients with a history of injection drug use were more likely to have less-experienced physicians (*P*<.001), be female (*P*<.001), and be younger (*P*<.001). During the first year of follow-up, IDUs (40.7% vs 62.8%; *P*<.001) and female participants (37.8% vs 60.5%; *P*<.001) were less likely to be 95% adherent. Consistent with previous analyses,[2,22] adherent patients had improved survival (data not shown).

Overall, among the study sample of 3116 individuals, 622 individuals died (20.0%; 95% CI, 18.4%-21.5%) during the study period (232 IDUs and 390 non-IDUs). When causes of death were examined, 535 were deemed nonaccidental (86%) based on a review of the *International Statistical Classification of Diseases and Related Health Problems* codes,[18] of which 373 were deemed to be due to HIV (70.0%), 26 due to cardiovascular causes (4.2%), 21 due to liver disease (3.4%), 17 due to malignancies (2.7%), and 98 were coded as being due to various other medical causes (15.8%). Among the 87 deaths defined as accidental (14.0%), there were 62 accidental poisonings (71.2%), 16 suicides (18.4%), 6 traumas (6.9%), and 3 other causes (3.4%). As anticipated, accidental causes of death were more common among IDUs than among non-IDUs (49 [21.1%] vs 38 [9.7%], respectively; *P*=.003).

As shown in the FIGURE, through 84 months after the initiation of HAART, the product limit estimate of the cumulative all-cause mortality rate was not statistically different between the 915 IDUs (26.5%; 95% CI, 23.2%-29.8%) and 2201 non-IDUs (21.6%; 95% CI, 16.9%-26.2%) (Wilcoxon *P*=.47). In multivariate time-updated Cox regression, the hazard ratio of mortality between IDUs and non-IDUs was 1.09 (95% CI, 0.92-1.29) after adjustment for age, sex, baseline AIDS diagnosis, baseline CD4 cell count, adherence, and physician experience.

Subanalyses were conducted for the purpose of focusing on causes of death that were more likely attributable to HIV infection; the 87 accidental causes of death (14.0%) were censored as nonevents. As shown in the Figure, through

84 months after the initiation of HAART, the product limit estimate of the cumulative nonaccidental mortality rate was not statistically different between the 915 IDUs (22.4%; 95% CI, 19.2%-25.5%) and 2201 non-IDUs (19.1%; 95% CI, 17.1%-21.0%) (Wilcoxon $P = .96$). In the multivariate Cox regression, the hazard ratio of nonaccidental mortality between the IDUs and non-IDUs was 1.06 (95% CI, 0.88-1.27) after adjustment for age, sex, baseline AIDS diagnosis, baseline CD4 cell count, adherence, and physician experience.

COMMENT

The present study demonstrated mortality rates that were not significantly different between HIV-infected IDUs and non-IDUs initiating HAART in a population-based setting. Although subtle differences in survival began to emerge by 84 months, 5-year survival was virtually identical in the analysis that censored accidental causes of death (Figure). Mortality rates were not statistically different even when all-cause mortality and the entire follow-up duration were considered.

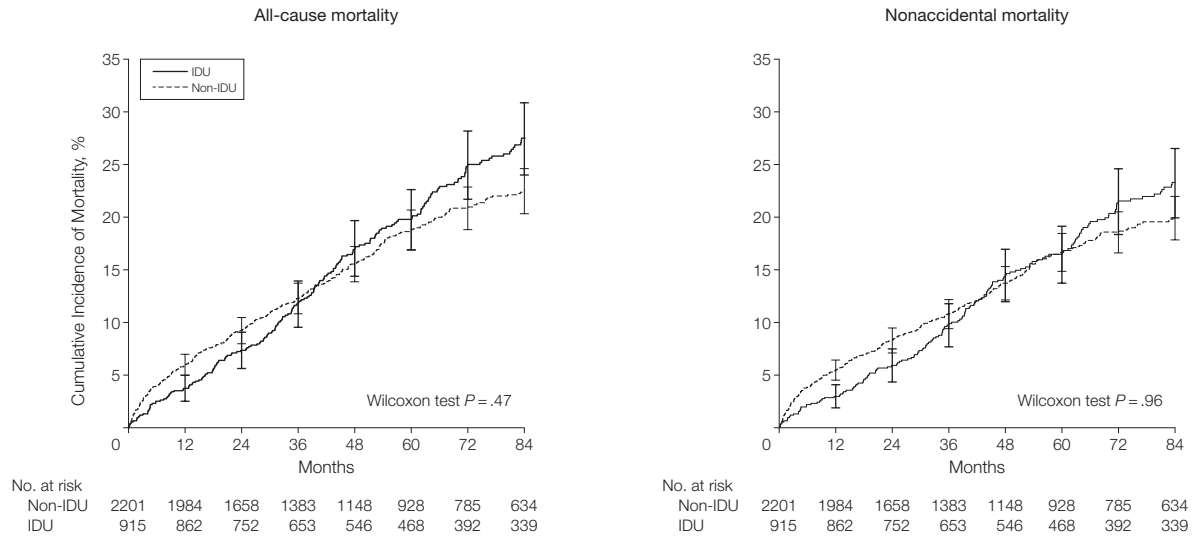
While observational studies are often considered to be limited with respect to evaluating treatment modalities, the present study is well suited for comparing real-world outcomes from HAART among IDUs and non-IDUs in a populational setting. Furthermore, the local context provides an excellent opportunity to compare survival patterns in a setting in which the potentially confounding effects of financial barriers to medical care are removed. Although it is not possible to know if the HOMER cohort is entirely representative of all HIV-infected individuals in the province, surveillance estimates indicate that similar proportions of IDUs and non-IDUs are included in the HOMER cohort.[25]

This study has several limitations. Most importantly, because this is an observational study, no conclusions about causality can be made. In addition, although our multivariate analyses adjusted for the key clinical and behavioral predictors of survival, unmeasured confounders may not have been adjusted for. For instance, although the vast majority of IDUs in the province use HAART without adherence-support programs, there are small, daily administered HAART programs accessed by some of the most unstable and mentally ill individuals.[26]

A further limitation is that we only had baseline data on injection drug use and we were not able to assess the impact of ongoing drug use. Finally, it is important to stress that we only considered patients who were prescribed HAART, and we have previously shown how IDUs are more likely to die without accessing HIV treatment.[10] Thus, if we compared survival between all HIV-infected individuals in our setting, it is likely that mortality rates would be higher among IDUs.

Although our findings cannot be generalized outside of the HOMER cohort, as efforts to improve use of HAART among IDUs expand,[27] the fact that survival patterns were not significantly different between IDUs and non-IDUs should help to challenge the increasingly prevalent belief that IDUs may be markedly less likely to benefit from HAART.[13,14] Based on these results, we conclude that HAART regimens may have effectiveness at a populational level that is not significantly different regarding the survival of individuals with and without a history of injection drug use.

Figure. Mortality Rate Among 3116 Antiretroviral-Naive Patients Initiating HAART



Overall, there were 622 deaths and the analysis of nonaccidental mortality censored 87 deaths (14.0%) as nonevents among which 62 deaths (71.2%) were accidental poisonings, 16 were suicides (18.3%), 6 were traumas (<0.1%), and 3 were classified as other (<0.1%). Survival curves were compared using the Wilcoxon test and all follow-up data for all participants. Error bars indicate 95% confidence intervals; HAART, highly active antiretroviral therapy; IDU, injection drug user.

Author Contributions: Dr Montaner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Wood, Hogg, Kerr, Montaner.
Acquisition of data: Wood, Hogg, Kerr, Yip.
Analysis and interpretation of data: Wood, Lima, Yip, Marshall.
Drafting of the manuscript: Wood.
Critical revision of the manuscript for important intellectual content: Wood, Hogg, Lima, Kerr, Yip, Marshall, Montaner.
Statistical analysis: Wood, Lima, Yip, Marshall.
Obtained funding: Wood, Hogg, Kerr.
Administrative, technical, or material support: Hogg, Lima, Kerr.
Study supervision: Wood, Montaner.

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