Survival of HIV-Infected Injection Drug Users (IDUs) in the Highly Active Antiretroviral Therapy Era, Relative to Sex- and Age-Specific Survival of HIV-Uninfected IDUs

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(See the editorial commentary by Kirk and Vlahov on pages 377–80)

Background. In the era of highly active antiretroviral therapy (HAART), it remains unclear whether human immunodeficiency virus (HIV)–infected injection drug users (IDUs) have durations of survival similar to those for comparable HIV-uninfected IDUs. The goal of this study was to compare survival durations of HIV-infected and HIV-uninfected IDUs for the period 1987–2004.

Methods. Demographic data, drug use characteristics, and biological markers were obtained at the time of admission to a substance abuse treatment program. The outcome of interest was the duration of survival after admission, and the primary exposure was HIV infection. Vital status was ascertained by means of the mortality register by the end of 2004. Three calendar periods, which were defined on the basis of use of specific therapies, were considered: 1987–1991 (the antiretroviral monotherapy era), 1992–1996 (the dual combination therapy era and the era when methadone was introduced in Spain), and 1997–2004 (the era of HAART and of established methadone programs). We used Cox regression methods allowing for late entries to handle the contribution of persons who survived a given period and entered the following period with nonzero time. We compared HIV-uninfected and HIV-infected IDUs with adjustments for age, sex, and duration of follow-up after admission.

Results. A total of 1209 IDUs were admitted to the hospital during the period from January 1987 through December 2004, and 1181 were eligible for the study. The majority (81.3%) of patients were men. The mean age ($\pm$ standard deviation) at admission was 27.8 $\pm$ 5.6 years, and the mean duration of injection drug use ($\pm$ standard deviation) was 7.6 $\pm$ 5.0 years. The prevalences of HIV and hepatitis C virus infections were 59.0% and 92.3%, respectively, and the total duration of follow-up was 10.116 person-years. Although survival duration for HIV-uninfected IDUs in 1997–2004 was similar to the duration in earlier periods, the duration for HIV-infected IDUs improved significantly since 1997 ($P < .01$). Furthermore, among patients admitted in the last period, the survival durations for HIV-uninfected and HIV-infected IDUs was virtually the same (relative hazard, 0.89; 95% confidence interval, 0.44–1.81).

Conclusions. The duration of survival of HIV-infected IDUs has improved substantially since 1997, reaching rates similar to the rates for HIV-seronegative IDUs who accessed the health care system in the era of HAART.

Mortality rates among injection drug users (IDUs) have been historically high and are still significantly higher than the rates for the general population. Frequent causes of death among IDUs include bacterial infection, overdose, accidents, and AIDS [1–4]. Nonetheless, cohort studies from Western Europe and the United States have revealed decreased mortality rates among HIV-infected individuals (including IDUs) in the past decade that have resulted from the introduction of HAART and the intensification of clinical care [5–8]. Even though HIV-infected IDUs are less likely to start taking HAART, their response to therapy (in terms of survival)

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is similar to that for other exposure groups, as long as adherence to treatment is satisfactory [9, 10]. In Spain, overdose is the primary cause of death among HIV-uninfected substance abusers [11], and AIDS still accounts for an important number of deaths. In addition, Spain has experienced one of the largest HIV epidemics in Europe, primarily in association with injection drug use [12].

In parallel to reductions in HIV/AIDS-related mortality, other studies have focused on the impact of harm reduction interventions and substitution treatment with methadone on mortality rates, which have also decreased with regard to overdose-related deaths [13, 14]. However, few studies have compared the mortality rate among HIV-infected persons with that among HIV-uninfected subjects who belong to the same risk category [15, 16].

The first goal of the present study was to explore the change over time in survival for IDUs once they are admitted to a substance abuse treatment program. In particular, our aim was to characterize how survival at the population level was changed in the era of HAART, the era of improved prophylaxis, and the era of harm reduction interventions. The second objective focused on determining whether, in the HAART era, survival rates among HIV-infected IDUs were comparable to those among HIV-uninfected patients.

Here, we report the mortality rates for 18 years of observation for a cohort of IDUs who were admitted to a substance abuse treatment program in a tertiary hospital. On the basis of the years of introduction of methadone maintenance treatment programs and HAART in Spain, the follow-up period was divided into the following intervals: 1987–1991 (the antiretroviral monotherapy era), 1992–1996 (the dual-combination treatment era and when methadone treatment was introduced), and 1997–2004 (the era of HAART and of established methadone programs).

PATIENTS AND METHODS

The study population comprised IDUs who were admitted to a substance abuse treatment program at the University Hospital Germans Trias i Pujol in Badalona (Spain) during the period of January 1987 through December 2004. The majority of patients were injection heroin users and were referred from municipal outpatient clinics located in Badalona and Santa Coloma, the 2 cities contiguous to the hospital. The criteria for referral generally depended on the severity of addiction but not on the person's HIV serostatus. At admission to the substance abuse treatment program, wide-raging information on sociodemographic characteristics, drug use, and clinical variables was recorded. In addition, patients underwent a comprehensive medical examination and routine laboratory testing for biological markers, including a history of infectious diseases (e.g., hepatitis B), determination of immune parameters, and standard biochemistry tests (e.g., hemoglobin assessment). During the period 1987–1991, treatment of substance abuse mainly consisted of detoxification from heroin, followed by treatment with opiate antagonists. Patients who reported abuse of additional drugs (i.e., cocaine, alcohol, and/or benzodiazepines) were treated accordingly to avoid withdrawal. Starting in 1992, methadone was the most widely used treatment, either as a detoxification agent or as substitution therapy for long-term heroin abusers.

In addition to surveillance through regular medical care, follow-up information was obtained through regular linkage with other databases, as described elsewhere [15]. Final vital status was ascertained by a complete linkage of the whole study cohort with the Catalonian mortality register by 31 December 2004.

The outcome of interest was the elapsed survival time from the first admission to either death or 31 December 2004, the end of the follow-up period, and the study considered mortality due to all causes. The primary exposure was HIV infection. Survival curves for HIV-uninfected and HIV-infected IDUs were estimated using the Kaplan-Meier method and were compared using the log rank test. For multivariate analysis, which was adjusted for age and sex, comparisons were performed with a proportional hazard regression model.

All analyses treated the 3 calendar periods as an external time dependent covariate (i.e., period analyses) [17–19]. As mentioned above, the calendar periods considered were 1987–1991 (period 1), 1992–1996 (period 2), and 1997–2004 (period 3). Using the period analysis approach, individuals contributed as many records to the analyses as periods in which they were observed at risk. Thus, a survival time is treated as left-truncated (late entry) if admission to a substance abuse treatment program occurred in a previous period, and it was right-censored if the individual was alive at the end of the period. An important advantage of period analysis over traditional cohort analysis is that it furnishes up-to-date estimates of long-term survival rates [5, 20, 21].

During follow-up, several IDUs who were HIV uninfected at admission acquired HIV infection. The time of HIV infection was defined by the midpoint of the interval from the last seronegative test result to the first seropositive test result. These persons who experienced seroconversion contributed survival times to both groups of HIV infection: as seronegative subjects, the (right-censored) survival time lasted from admission until HIV infection; as seropositive subjects, the survival time lasted from the duration after admission to HIV infection, until either death or the end of follow-up.

To check the proportional hazards assumption of the models applied, we performed tests that are based on the Schoenfeld residuals of the Cox regression model. If proportionality

holds, these residuals are distributed randomly along the survival time [22].

Statistical analyses were performed using the statistical software R (in particular, the Event History Analysis package, which accomplishes survival analysis in the framework of period analysis [23]). Test results were considered to be statistically significant if the resulting P value was $<.05$.

RESULTS

From January 1987 through December 2004, a total of 1209 IDUs were admitted for the first time to a substance abuse treatment program. Twenty-eight (2.3%) of these subjects were excluded from the study cohort because their HIV serostatus was unknown; these were mainly individuals who left the detoxification unit the day after admission. Admission numbers, according to the calendar periods, for the remaining 1181 subjects included in the study were as follows: 490 subjects (41.5%) for 1987–1991 (period 1), 393 subjects (33.3%) for 1992–1996 (period 2), and 298 subjects (25.2%) for 1997–2004 (period 3).

The baseline characteristics of the 1181 IDUs are presented in table 1. According to calendar period, the median age (25, 27, and 31 years for periods 1–3, respectively) and median duration of injection drug use (6, 7, and 10 years for periods 1–3, respectively) increased over time, whereas the median age at which drugs were first injected remained constant (19 years for all periods). The proportions of male IDUs and of subjects with past history of imprisonment were lowest in period 2 (78.9% and 34.8%, respectively) and highest in period 3 (85.9% and 48.8%, respectively). With respect to biological markers, a constant prevalence of hepatitis C virus (HCV) infection (>90%) and a decreasing prevalence of HIV infection (from 70.0% to 48.3%) were observed. Among the IDUs who were HIV uninfected at the time of admission, 48 (10.1%) became infected with HIV during the follow-up period.

Table 2 shows the baseline characteristics of individuals seen at different periods, as stratified by calendar period and HIV status. Approximately one-third of HIV-infected IDUs were receiving antiretroviral treatment at the time of admission; these rates were consonant, with moderately high $CD4^+$ cell counts noted at admission among HIV-infected subjects. Specifically, 75% of these patients had a baseline $CD4^+$ cell count greater than 480, 310, and 265 cells/μL in periods 1–3, respectively. The term "admissions in period" refers to IDUs who were admitted to a substance abuse treatment program during the period. Thus, the differences between these numbers and the total number of IDUs seen during a period involve subjects who had started undergoing treatment in a previous period and who survived until the beginning of the present period. Mortality rates were highest during the second period and lowest during the third period, and HIV-infected individuals had higher mortality rates than did HIV-uninfected individuals.

Mortality rates for the 3 periods are depicted in figure 1 by means of the extended Kaplan-Meier estimates of the survival curves (i.e., the estimates that incorporated late entries). Maximum durations of follow-up were 5 years (1987–1991), 10

Table 1. Baseline characteristics of 1181 injection drug users at the time of admission to a substance abuse treatment program.

Characteristic	Calendar period		
	1987–1991 (n = 490)	1992–1996 (n = 393)	1997–2004 (n = 298)
Sociodemographic and drug use variables			
Male sex	80.4	78.9	85.9
Age, years	25 (23–28)	27 (24–31)	31 (27–35)
History of imprisonment	42.4	34.8	48.8
Alcohol consumption⩾ 40 g/day	…[a]	42.4	31.7
Duration of injection drug use, years	6 (4–8)	7 (3–11)	10 (5–15)
Age at first use of injection drugs, years	19 (17–22)	19 (17–23)	19 (17–23)
Biological marker			
Hemoglobin concentration of <13.5 g/L for men or 11.5 g/L for women	19.2	26.1	31.5
$CD4^+$ cell count, cells/μL	749 (526–1052)	840 (390–1333)	768 (416–1234)
$CD8^+$ cell count, cells/μL	796 (591–1078)	1016 (774–1386)	881 (691–1146)
HIV infection	70.0	53.4	48.3
HCV infection	91.0	94.1	92.1
HBsAg positive	10.1	5.9	6.9

NOTE. Data are median value (interquartile range) for continuous variables and relative frequency (among nonmissing observations) for categorical variables. HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

[a] Not recorded before 1992.

Table 2. Baseline characteristics of injection drug users, according to HIV infection status and calendar period.

Characteristic	Calendar period					
	1987–1991		1992–1996		1997–2004	
	HIV-uninfected patients	HIV-infected patients	HIV-uninfected patients	HIV-infected patients	HIV-uninfected patients	HIV-infected patients
No. of subjects seen	147	363[a]	303	548[a]	415	544[a]
Admissions during period, % of patients	100	100	60.4	41.8	37.1	28.1
Male sex, % of patients	83.0	79.1	83.8	78.1	84.6	78.1
Date of admission	1989.7	1989.6	1992.9	1991.4	1995.3	1993.7
Age, years	25 (22–29)	25 (23–28)	26 (23–29)	26 (23–30)	27 (24–31)	28 (24–32)
Age at first use of injection drugs, years	20 (17–23)	18 (16–21)	20 (18–24)	18 (16–21)	20 (18–24)	18 (16–21)
$CD4^+$ cell count, cells/μL	930 (692–1302)	660 (480–971)	1235 (900–1548)	540 (310–821)	1215 (904–1475)	507 (265–732)
$CD8^+$ cell count, cells/μL	841 (608–1030)	784 (590–1100)	960 (750–1189)	900 (640–1263)	903 (704–1159)	942 (690–1297)
Antiretroviral treatment, % of patients	NA	…[b]	NA	32.6	NA	37.4
Total time at risk, no. of person-years	301.5	850.0	958.8	1886.2	2672.3	3446.6
No. of deaths	7	44	23	157	38	110
Mortality rate, no. of deaths per 100 person-years	2.32	5.18	2.40	8.32	1.42	3.20

NOTE. Data are median value (interquartile range) for continuous variables and relative frequency (among nonmissing observations) for categorical variables, unless otherwise indicated. NA, not available.

[a] Includes 20 patients (1987–1991), 19 patients (1992–1997), and 9 patients (1997–2004) who experienced seroconversion.

[b] Not recorded before 1992.

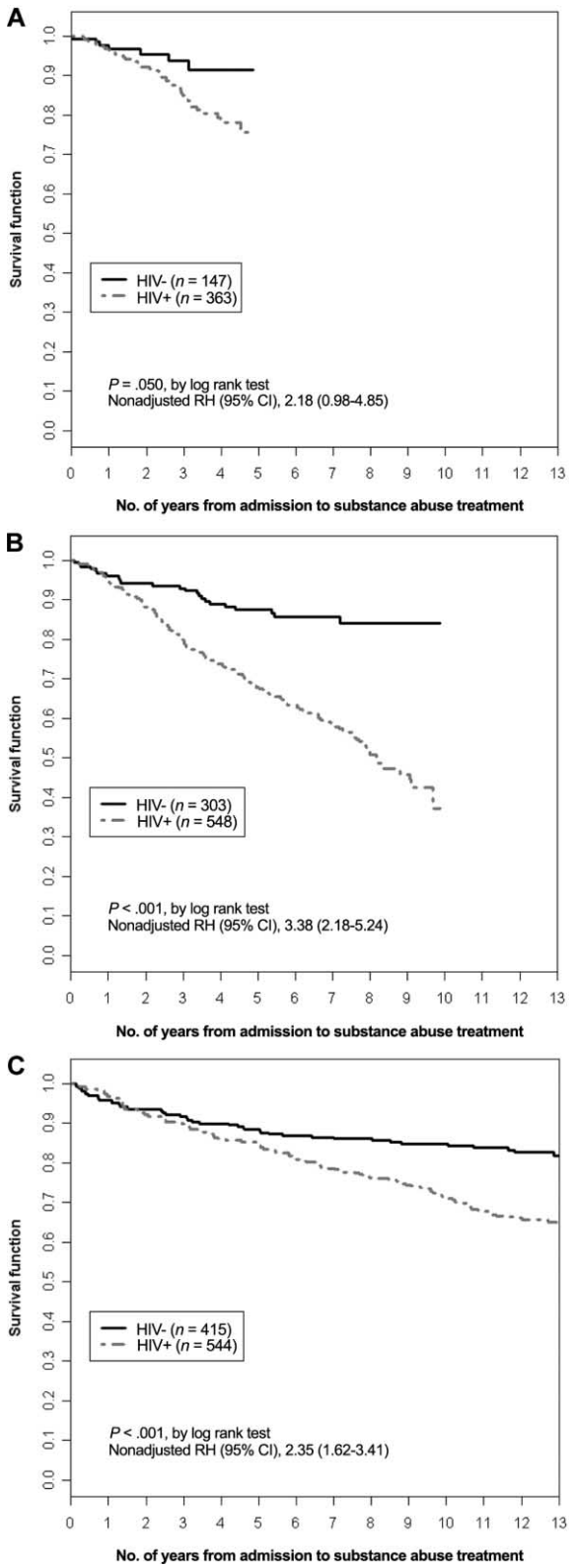

Figure 1. Kaplan-Meier estimates of survival during 1987–1991 *(A)*, 1992–1996 *(B)*, and 1997–2004 *(C)*. RH, relative hazard; +, positive; −, negative.

years (1992–1996), and 18 years (1997–2004). Although, during each of the 3 periods, the durations of survival for HIV-infected IDUs were worse than those for HIV-uninfected patients ($P = .047$, $P < .001$, and $P < .001$ for periods 1–3, respectively, by log rank test), the survival durations for HIV-infected IDUs have improved significantly since 1997 ($P < .01$). By contrast, the duration of survival for HIV-uninfected IDUs in 1997–2004 was similar to that in earlier periods. This is reflected by a lower (unadjusted) relative hazard for period 3 (2.34; 95% CI, 1.62–3.39), compared with period 2 (3.39, 95% CI, 2.18–5.25). Figures 1*B* and 1*C* illustrate the observed diminished differences between both groups.

To further characterize survival in the era of HAART (1997–2004), we stratified the group according to whether patients were admitted to the substance abuse treatment program during that period. Figure 2 demonstrates that the survival durations for HIV-uninfected and HIV-infected IDUs who were admitted after the introduction of HAART in 1997 were very similar ($P = .75$) during the available maximum follow-up time of 8 years; it also shows that the only patient group with poor survival was that of HIV-infected patients who were admitted to the detoxification program during periods preceding 1997. Figure 2 clearly shows that differences in survival for HIV-infected individuals who were admitted to the program during the pre-HAART era were nullified by those for patients who were admitted during the HAART era.

To assess the statistical significance of the differences between HIV-uninfected and HIV-infected individuals over calendar periods, table 3 shows the results of proportional hazards models that adjusted for age and sex. There were no significant dif-

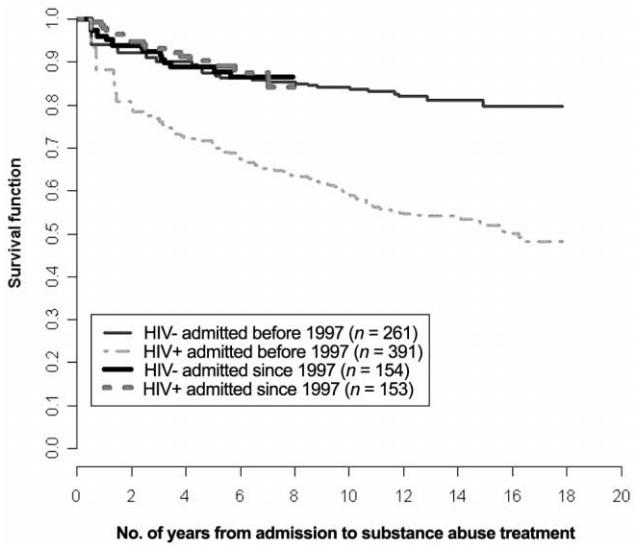

Figure 2. Kaplan-Meier estimates of survival during 1997–2004, according to the year of admission to a substance abuse treatment program. +, Positive; −, negative.

Table 3. Cox regression models including HIV serostatus, sex, and age in injection drug users who were admitted to a substance abuse treatment program during 1987–2004.

Period, variable	Coefficient	Relative hazard (95% CI)	*P*
1987–1991 (n = 510)			
HIV infection	0.799	2.224 (0.999–4.952)	.05
Male sex	−0.147	0.864 (0.447–1.667)	.662
Age	0.040	1.041 (0.975–1.111)	.225
1992–1996 (n = 851)			
HIV infection	1.217	3.379 (2.178–5.243)	<.001
Male sex	0.337	1.401 (0.931–2.108)	.106
Age	0.069	1.071 (1.040–1.103)	<.001
1997–2004 (n = 959)			
HIV infection	0.844	2.326 (1.603–3.373)	<.001
Male sex	0.379	1.462 (0.927–2.305)	.103
Age	0.036	1.037 (1.005–1.070)	.022
1997–2004 (n = 307)[a]			
HIV infection	−0.114	0.892 (0.441–1.807)	.752
Male sex	0.356	1.427 (0.434–4.696)	.559
Age	0.023	1.024 (0.962–1.089)	.457

[a] Restricted to patients admitted to a substance abuse treatment program during the period.

ferences between male and female IDUs, and the risk of dying increased with increasing age in periods 2 ($P < .001$) and 3 ($P = .022$). More importantly, at the bottom of table 3, we show that there were no significant differences between HIV-uninfected and HIV-infected IDUs during the HAART era, when we restricted attention to persons who were admitted to the program during that era. Testing for proportional hazards showed that assumptions hold reasonably well ($P > .05$ for all models).

DISCUSSION

This study of patients at risk of AIDS and of drug-related complications found that survival durations for HIV-infected IDUs have improved substantially since 1997, reaching rates similar to those for HIV-seronegative persons who accessed the health care system in the era of HAART and substance abuse treatment (figure 2). Comparable findings were described by Wang et al. [16], who reported similar survival durations for HIV-uninfected IDUs and HIV-infected IDUs with $CD4^+$ cell counts of >350 cells/μL.

Because only one-third of the HIV-infected IDUs in our study received HAART, other factors are likely to have contributed to the improved survival among contemporary HIV-infected heroin users—namely, access to substitution therapy with methadone, prophylaxis for opportunistic infections, harm reduction interventions, and regular clinical care, as shown by previous studies [24].

The differences in survival duration between HIV-uninfected and HIV-infected IDUs also held when we adjusted the proportional hazards regression models for additional covariates, such as a history of imprisonment, duration of injecting drug use, hemoglobin concentration, and HCV infection. Anderson et al. [25] stated that HCV-HIV coinfection increased the risk of death among HIV-infected individuals. The present study could not confirm this finding in our cohort of IDUs, because nearly 95% of all HIV-infected IDUs were also infected with HCV.

A recent study by Lucas et al. [26] focused on the association between patterns of drug use (i.e., nonuse, intermittent use, and persistent use) and HIV-1 disease progression. The authors reported a better duration of survival among intermittent drug users than among persistent drug users. Although, in our study, all patients were persistent drug users before admission, the pattern of use during and after drug abuse treatment was subject to high variability; this may have contributed to the improved survival shown here. One of the strengths of the present study is the time axis for our analysis (i.e., the number of years since the admission to a substance abuse treatment program), because this analysis defines a well-known starting point available for all study participants that is independent of the HIV serostatus of the patients. Another strong point is the completeness of follow-up. Specifically, we performed an exhaustive linkage of the complete database of 1181 patients with the Catalonian mortality register.

HAART has been proven to be an extremely effective therapy for HIV-infected individuals. We have shown that HIV-infected IDUs who received health care during the period 3 exhibited mortality rates comparable to those for IDUs who were not infected with HIV. In contrast, HIV-infected IDUs who were admitted to the health care system before 1997 did experience higher mortality rates. This may be explained in part by suboptimal treatment strategies before the HAART era, with subsequent treatment failure and pharmacological resistance once the individuals reached the period in which HAART became available.

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