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Mortality in an Urban Cohort of HIV-Infected and At-Risk Drug Users in the Era of Highly Active Antiretroviral Therapy

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(See the editorial commentary by Celentano on pages 873–4)

Background. Mortality trends among drug users in the era of highly active antiretroviral therapy (HAART) remain unclear.

Methods. We examined mortality rates, causes of death, and predictors of mortality in 398 human immunodeficiency virus (HIV)–infected and 656 at-risk drug users for the period of 1996–2001. National death index reports were used to confirm deaths, and causes of death were derived from medical records. Cox proportional hazards models were used to determine factors associated with mortality.

Results. During 1996–2001, mortality rates in HIV-infected and HIV-uninfected participants were 7.3 and 1.5 deaths per 100 person-years, respectively ($P < .001$). The mean age at the time of death was 43.6 years for HIV-infected subjects and 47.7 years in HIV-uninfected subjects ($P < .001$). For 398 HIV-infected participants who were observed for 1443 person-years, death rates decreased from 11.4 to 5.4 deaths per 100 person-years over the 6-year period ($P = .04$). Among all participants, causes of death were as follows: HIV/AIDS, 27% of subjects; substance abuse, 31%; bacterial infection, 25%; other medical illness, 14%; and violence, 3%. Persons who initiated HAART at a $CD4^+$ lymphocyte count of 201–350 cells/mm^3 experienced improved survival, compared with those who initiated it at a $CD4^+$ lymphocyte count of ≤200 cells/mm^3 ($P = .01$). In a multivariate Cox model of HIV-infected subjects, factors independently associated with mortality included receipt of HAART (adjusted hazard ratio [HR_{adj}], 0.44; 95% confidence interval [CI], 0.28–0.68) and $CD4^+$ lymphocyte count of ≤200 cells/mm^3 (HR_{adj}, 4.23; 95% CI, 2.24–7.60). Use of methadone or illicit drugs did not predict mortality.

Conclusions. To further reduce mortality among drug users, interventions aimed at improving HAART use are warranted. Preventive health and timely management of treatable conditions, such as bacterial infections, also needs emphasis.

Although a rapid decrease in mortality has been observed since the introduction of HAART [1, 2], the mortality rate for HIV-infected drug users may not have decreased to the same degree as that for other individuals. Drug users not only have had suboptimal access to and utilization of HAART [3–8], but they also tend to initiate HAART at a more advanced stage of infection [9, 10]. In addition, drug use itself confers an independent risk of mortality due to overdose, hepatitis C, and bacterial infections [11, 12].

Drug users represent a large proportion of HIV-infected persons in the United States, with injection drug use implicated as an exposure risk in 33% of persons with AIDS [13]. Given that less is known about recent mortality trends in HIV-infected drug users than in other persons, we examined mortality rates, causes of death, and factors associated with mortality in the HAART era among a well-characterized cohort of opiate-dependent drug users with or at risk of acquiring HIV infection. We hypothesized that, among HIV-infected drug users, active drug use and methadone treatment significantly predict mortality, independent of HAART use and immune status.

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Table 1. Baseline demographic and clinical characteristics of subjects in a study of HIV-infected and at-risk drug users in the HAART era.

Characteristic	HIV-infected subjects (n = 398)	HIV-uninfected subjects (n = 656)	P
Male sex	237 (59.5)	375 (57.2)	.45
Race/ethnicity			
Hispanic	267 (67.1)	437 (66.6)	<.001
Black	90 (22.6)	88 (13.4)	
White	38 (9.5)	124 (18.9)	
Other	3 (0.8)	7 (1.1)	
Age in 1996, median years (range)	39 (20–58)	40 (21–69)	.47
Receipt of public assistance	356 (93.4)	471 (77.1)	<.001
Homeless during prior 6 months	22 (5.5)	55 (8.4)	.15
Incarceration during prior 6 months	57 (16.2)	83 (14.3)	.69
Any history of having smoked cigarettes	380 (95.5)	614 (93.9)	.27
Enrollment in methadone treatment program	362 (91.0)	604 (92.4)	.42
Methadone use at last visit	120 (30.9)	206 (31.8)	.76
Drug use during prior 6 months (any route)			
Any drug	185 (46.5)	307 (46.9)	.88
Crack	59 (14.8)	81 (12.4)	.26
Cocaine	64 (16.1)	126 (19.3)	.19
Heroin	129 (32.4)	213 (32.6)	.96
"Speedball"	44 (11.1)	64 (9.8)	.51
Any history of injection drug use	333 (83.7)	412 (63.0)	<.001
Injection drug use during prior 6 months	75 (18.8)	72 (11.0)	<.001
Nadir $CD4^+$ lymphocyte count, cells/mm^3			
0–50	88 (22.3)	...	
51–200	120 (30.4)	...	
201–350	85 (21.5)	...	
>350	102 (25.8)	...	
HIV RNA level at first visit, copies/mL			
<500	119 (36.3)	...	
500–10,000	108 (32.9)	...	
>10,000	101 (30.8)	...	
Any history of HAART use[a]	213 (61.2)	...	
HAART use at last visit[a]	165 (49.4)	...	

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Data were missing for public assistance (n = 62), incarceration (n = 123), enrollment in a methadone treatment program (n = 2), drug use within prior 6 months (n = 2), any history of injection drug use (n = 2), any history of having smoked cigarettes (n = 2), methadone use at last visit (n = 9), nadir $CD4^+$ lymphocyte count (n = 3), HIV RNA level at first visit (n = 70), and HAART use at last visit (n = 14).

[a] Limited to 348 people with a nadir $CD4^+$ lymphocyte count of <500 cells/mm^3.

METHODS

Study population and design. As previously described, during the period of 1985–2001, HIV-infected and at-risk drug users were recruited from methadone treatment programs in the Bronx, New York, to participate in the HIV Epidemiologic Research on Outcomes (HERO) study, a longitudinal study of HIV infection in drug users [14–16]. At semiannual visits, participants underwent standardized interviews that elicited detailed information on sociodemographic characteristics, drug use, intercurrent hospitalizations, and HAART use over the previous 6 months. HAART was defined as a regimen that contained ⩾3 antiretrovirals, including >1 nucleoside reverse-transcriptase inhibitor plus a nonnucleoside reverse-transcriptase inhibitor and/or a protease inhibitor, or abacavir [17]. At each visit, blood samples were drawn to detect serum HIV antibody (by EIA with Western blot confirmation) among participants who were not known to be HIV seropositive. Among HIV-seropositive participants, $CD4^+$ lymphocyte count and HIV viral load (beginning in 1997) were measured. All methadone treatment clients had access to on-site medical care.

Hospitalization surveillance was facilitated by the requirement that hospital staff contact methadone program staff to

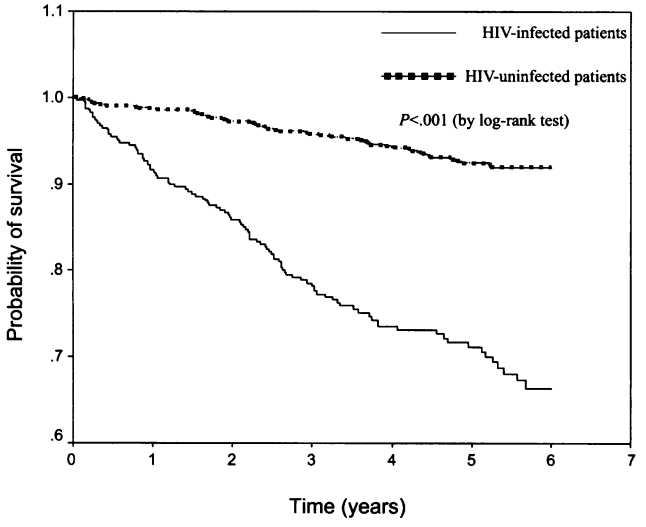

Figure 1. Kaplan-Meier survival curves comparing HIV-infected and HIV-uninfected participants in the HAART era (1996–2001).

verify methadone dosage. Hospitalization logs maintained at methadone clinics were regularly reviewed to identify hospitalizations that were not reported during interviews, and a trained medical abstractor summarized hospital records using standardized forms. All participants provided written informed consent. The study was approved by the institutional review board of Montefiore Medical Center (the Bronx, New York).

Cause of death. Participants who underwent ≥1 research visit during the period of 1 January 1996 through 31 December 2001 were included in this analysis. The first visit after 1 January 1996 was used to obtain baseline data. Death on or before 31 December 2001 was ascertained by review of hospital records, a National Death Index (NDI) search, or communication with the participant's designated contact person. NDI matches were determined on the basis of name, race, sex, date of birth, and social security number. Tracking of subjects was expedited by verification of their living status in the vital records and AIDS registries of the New York City Department of Health. Observation time was censored at date of death or 31 December 2001, whichever came first.

If a participant died in a hospital, the first author determined the cause of death by reviewing the abstracted medical record ($n = 72$). If hospital records were unavailable or the participant did not die in a hospital, the death certificate was used ($n = 76$). In the event that the above records were unavailable or inconclusive, cause of death was considered to be unknown ($n = 9$).

Cause of death was defined as the main condition that initiated the sequence of events resulting in death [18] and was classified into 1 of 5 categories: HIV/AIDS, substance abuse, bacterial infection, other medical illness, or violence. Deaths were categorized as HIV/AIDS related if review of the hospital record or death certificate demonstrated an AIDS-defining condition included in the 1993 Centers for Disease Control and Prevention AIDS case definition [19], or if review identified "HIV/AIDS" and no other comorbidity. Substance abuse–related deaths included end-stage liver disease and overdose [12, 20]. Deaths due to bacterial infection included sepsis, endocarditis, and bacterial pneumonia. Given that both HIV-infected persons and drug users are at increased risk of bacterial infection [21, 22], all bacterial infections, including recurrent bacterial pneumonia, were classified separately, so that associations between bacterial infection and HIV infection and drug use could be analyzed. Therefore, mortality secondary to bacterial infection included all deaths due to bacterial pneumonia, regardless of past history of bacterial pneumonia.

Statistical analysis. Univariate associations of factors such as drug use and cause of death with HIV serostatus were determined using χ^2 test or Fisher's exact test. Among HIV-infected participants, $CD4^+$ lymphocyte counts were compared between cause of death strata using the Mann-Whitney test or Kruskal-Wallis test. Crude mortality rates were calculated as the number of deaths divided by total person-years. Kaplan-Meier curves and log-rank tests were used to compare time to death between groups. The date of initiation of HAART was estimated to be the midpoint between the visit at which HAART was first reported and the previous visit. If HAART use was first reported at the baseline visit, the date of initiation was estimated to be 3 months prior to that visit. The $CD4^+$ lymphocyte count at the time of HAART initiation was determined on the basis of the most recent $CD4^+$ lymphocyte count, up to 9 months before the first research visit at which a participant first reported using HAART.

Cox proportional hazards models were used to examine factors associated with all-cause mortality. A separate model was performed for HIV-infected subjects. Variables examined included age, sex, race, methadone use at last visit, HIV serostatus,

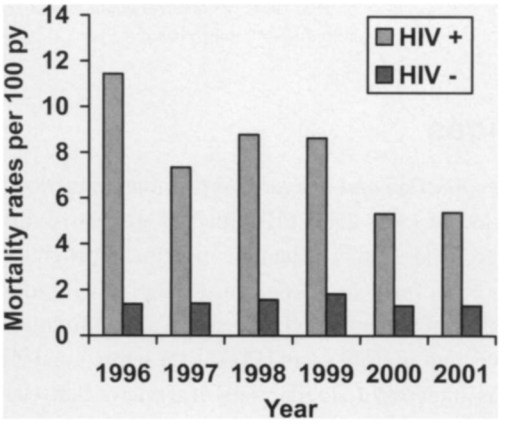

Figure 2. Mortality rates among HIV-infected (HIV+) and HIV-uninfected (HIV−) participants in the HAART era (1996–2001). py, Person-years.

Table 2. Cause-specific mortality among HIV-infected and HIV-uninfected HIV Epidemiologic Research on Outcomes (HERO) study participants (1996–2001).

Cause of death	No. (%) of subjects	
	HIV infected	HIV uninfected
All causes	104	40
AIDS		
All	39 (38)	...
HIV/AIDS not otherwise specified	18	...
AIDS-defining illness		
All	21	...
Pneumocystis jiroveci pneumonia	10	...
HIV-related wasting	3	...
Tuberculosis	3	...
Lymphoma	2	...
Histoplasmosis	1	...
Extrapulmonary cryptococcus	1	...
AIDS dementia	1	...
Substance abuse		
All	23 (22)	21 (53)
End-stage liver disease	12	15
Drug overdose	10	6
Chronic alcoholism[a]	1	0
Bacterial infection		
All	25 (24)	11 (28)
Sepsis	15	3
Bacterial pneumonia	9	6
Endocarditis	1	2
Other medical illness		
All	14 (13)	6 (15)
Non–AIDS-related malignancy	5	1
Cardiovascular disease	3	3
Pancreatitis	2	0
Hemorrhage	4	0
Renal failure	0	1
Chronic obstructive pulmonary disease	0	1
Violence	3 (3)	2 (5)

NOTE. Cause of death was determined for 104 of 106 HIV-infected participants and 40 of 47 HIV-uninfected participants.

[a] As listed on death certificate

and HAART use at last visit. Drug use (including use of heroin, cocaine, crack, or "speedballs" [i.e., an admixture of heroin and cocaine]) by any route, injection drug use, participation in a methadone treatment program, $CD4^+$ lymphocyte count, and HIV viral load were examined as time-dependent variables. In addition to variables found to be significantly associated with mortality, sex was retained in the multivariate model given that prior studies have reported sex differences in HIV/AIDS morbidity [23, 24]. Age, drug use, and methadone use were included in multivariate analyses, because these factors were considered to have clinically plausible effects on mortality. Persons who had HIV seroconversion ($n = 3$) were included starting from the date on which they tested HIV positive. Data were analyzed using SPSS software, version 10.0 (SPSS), and SAS software, version 8.1 (SAS Institute).

RESULTS

Description of the study sample. During the period of 1996–2001, a total of 1054 drug users were observed, 398 (38%) of whom were HIV infected. HIV-infected and HIV-uninfected participants were observed for a total of 1443.30 person-years and 3178.46 person-years, respectively. The median duration of follow-up for HIV-infected and HIV-uninfected participants was 3.50 and 5.45 years, respectively. Baseline participant characteristics are shown in table 1. HIV-infected participants were more likely to be black, to receive public assistance, and to report a history of injection drug use than were HIV-uninfected participants ($P < .001$). The median $CD4^+$ lymphocyte count for HIV-infected participants was 322 cells/mm^3 (interquartile range, 144–540 cells/mm^3). Among 293 HIV-infected persons with a nadir $CD4^+$ lymphocyte count of <350 cells/mm^3, 186 (63%) used HAART during the study period.

Mortality rates. During the period of 1996–2001, the mortality rates for HIV-positive and HIV-negative participants were 7.3 and 1.5 deaths per 100 person-years, respectively ($P < .001$). There was no significant difference in mortality by race or sex. Figure 1 shows Kaplan-Meier survival curves for all participants, stratified by HIV serostatus, and demonstrates increased separation over time.

For 398 HIV-infected participants who were observed for 1443.30 person-years, the death rates decreased from 11.4 deaths per 100 person-years in 1996 to 5.4 deaths per 100 person-years in 2001 ($P = .04$). Death rates remained stable during the study period (1.5 deaths per 100 person-years) for HIV-uninfected participants (figure 2). The mean age at the time of death was lower for HIV-infected participants than for HIV-uninfected participants (43.6 years vs. 47.7 years; $P < .001$). Among 106 HIV-infected persons who died, 10 (9.4%) died when they were ≤35 years of age, compared to 1 of (2.1%) 47 HIV-uninfected persons ($P = .17$).

Cause of death. Cause of death was determined for 104 (98%) of 106 HIV-infected participants and for 40 (85%) of 47 HIV-uninfected participants (table 2). Among 104 HIV-infected participants, 39 deaths (38%) were due to HIV/AIDS, 23 (22%) were due to substance abuse, 25 (24%) were due to bacterial infection, 14 (13%) were due to other medical illness, and 3 (3%) were due to violence. Among 40 HIV-uninfected participants, 21 (53%) deaths were due to substance abuse, 11 (28%) were due to bacterial infection, 6 (15%) were due to other medical illness, and 2 (5%) were due to violence.

HIV-infected participants were more likely to die of substance abuse–related reasons than were HIV-uninfected partic-

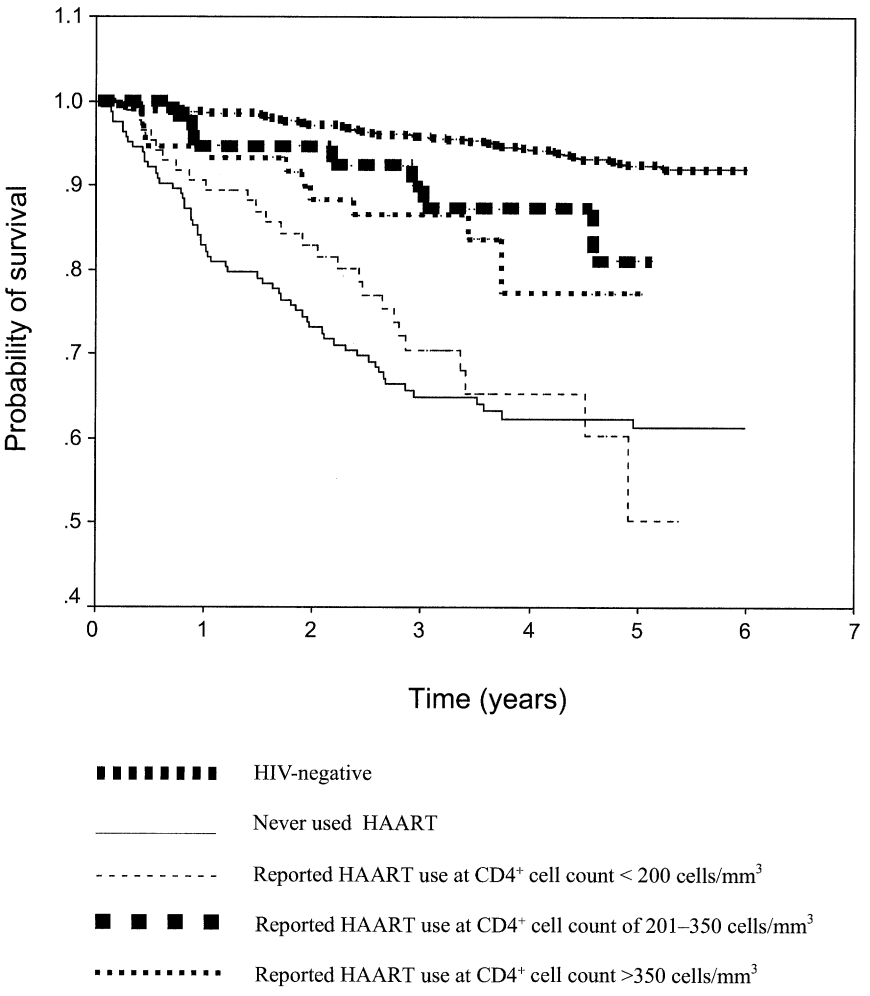

Figure 3. Kaplan-Meier survival curves, by HIV serostatus, HAART use, and $CD4^+$ lymphocyte count, at initiation of HAART. $P = .60$ for $CD4^+$ lymphocyte count of ≤200 cells/mm^3 versus no HAART; $P = .01$ for $CD4^+$ lymphocyte count of ≤200 versus 201–350 cells/mm^3; $P = .03$ for $CD4^+$ lymphocyte count of ≤200 versus >350 cells/mm^3; and $P = .49$ for $CD4^+$ lymphocyte count of 201–350 versus >350 cells/mm^3. All P values were determined with use of the log-rank test.

ipants (1.59 vs. 0.66 deaths per 100 person-years; $P = .003$). Compared with HIV-uninfected persons, HIV-infected persons had a higher rate of mortality associated with bacterial infection (1.73 vs. 0.35 deaths per 100 person-years; $P < .001$) and other medical illness (0.97 vs. 0.19 deaths per 100 person-years; $P < .001$). Mortality rates secondary to violence were not significantly different between the 2 groups (0.21 vs. 0.06 deaths per 100 person-years; $P = .17$).

$CD4^+$ lymphocyte count and HAART use. Among HIV-infected participants who died, the median nadir $CD4^+$ lymphocyte count was 98.0 cells/mm^3, compared with 210 cells/mm^3 among those who were alive by the end of 2001 ($P < .001$). The median nadir $CD4^+$ lymphocyte count for each cause-of-death category was as follows: HIV/AIDS, 36.0 cells/mm^3; substance abuse, 220.0 cells/mm^3; bacterial infection, 90.0 cells/mm^3; other medical illness, 184.0 cells/mm^3; and violence, 404.0 cells/mm^3 ($P < .001$). There was no significant association between HAART use and cause of death (data not shown).

Figure 3 shows Kaplan-Meier survival curves for HIV-uninfected persons ($n = 656$), HIV-infected persons who never received HAART ($n = 165$), and HIV-infected persons who had a $CD4^+$ lymphocyte count of ≤200 cells/mm^3 ($n = 87$), 201–350 cells/mm^3 ($n = 58$), and >350 cells/mm^3 ($n = 76$) at the time of initiation of HAART. The median nadir $CD4^+$ lymphocyte count among HIV-infected persons who never received HAART was 214 cells/mm^3. There was no significant difference in survival between HIV-infected persons who initiated HAART at a $CD4^+$ lymphocyte count of ≤200 cells/mm^3 and HIV-infected persons who never received HAART ($P = .60$). HIV-infected persons who initiated HAART at a $CD4^+$ lymphocyte count of 201–350 cells/mm^3 experienced improved survival, compared with those who initiated it at a $CD4^+$ lymphocyte

Table 3. Cox proportional hazards analysis of factors associated with mortality among 1054 participants in the HIV Epidemiologic Research on Outcomes (HERO) cohort, 1996–2001.

Variable	Univariate HR (95% CI)	Multivariate HR_{adj} (95% CI)
HIV infection	4.76 (3.37–6.72)	5.26 (3.61–7.67)
Age (per year)	1.03 (1.01–1.05)	1.03 (1.01–1.06)
Race/ethnicity		
Black	1.18 (0.67–2.07)	...
Hispanic	1.19 (0.74–1.90)	...
White	Reference	...
Female sex	0.90 (0.67–1.25)	0.97 (0.68–1.38)
Drug use by any route reported at each visit	0.87 (0.62–1.22)	0.95 (0.66–1.37)
Mean no. of monthly drug injections reported at each visit		
0	Reference	...
≤30	1.12 (0.64–1.95)	...
>30	1.06 (0.52–2.17)	...
Methadone use reported at last visit	1.00 (0.70–1.43)	1.04 (0.72–1.49)
Participation in methadone treatment program reported at each visit	1.71 (0.87–3.36)	...

NOTE. HR, hazard ratio; HR_{adj}, adjusted hazard ratio.

count of ≤200 cells/mm^3(P = .01). There was no significant survival difference between HIV-infected persons who initiated HAART at a CD4$^+$ lymphocyte count of >350 cells/mm^3 compared to those who initiated it at a CD4$^+$ lymphocyte count of 201–350 cells/mm^3 (P = .49).

Drug use. The majority of participants (745 participants [70.8%]) reported a history of ever injecting drugs; however, only 302 (28.7%) injected drugs during the follow-up period (P < .001). HIV-infected persons were more likely to use injection drugs during the follow-up period than were HIV-uninfected persons (OR, 1.28; 95% CI, 1.09–1.50).

Use of cocaine, heroin, or any illicit drug (including cocaine, heroin, crack, or "speedballs") by any route or use of injection drugs during follow-up did not significantly decrease the survival, compared no such reported behavior. There was no significant difference in the survival between participants who reported injection drug use at the last visit and those who did not.

Cox proportional hazards model. Table 3 displays hazard ratios (HRs) for all-cause death. On multivariate analysis of the entire cohort, factors independently associated with mortality included HIV serostatus (adjusted HR [HR_{adj}], 5.26; 95% CI, 3.61–7.67) and older age (HR_{adj}, 1.03 per year; 95% CI, 1.01–1.06 per year). Sex, race, methadone use at last visit, participation in a methadone treatment program, drug use by any route, and injection drug use were not significantly associated with mortality.

Table 4 shows factors associated with all-cause death in HIV-infected persons. In a multivariate Cox model, independent predictors of mortality included HAART use at last visit (HR_{adj}, 0.44; 95% CI, 0.28–0.68) and CD4$^+$ lymphocyte count of ≤200 cells/mm^3 (compared with a CD4$^+$ lymphocyte count of >500 cells/mm^3; HR_{adj}, 4.23; 95% CI, 2.24–7.60). Methadone use, participation in a methadone treatment program, drug use by any route, and injection drug use did not significantly predict mortality.

DISCUSSION

In this prospective study of HIV-infected and at-risk drug users in the inner-city, we observed a decrease in the mortality rate among HIV-infected persons (from 11.4 deaths per 100 person-years in 1996 to 5.4 per 100 person-years in 2001) coincident with increasing HAART use. Demographically and behaviorally similar uninfected drug users experienced a markedly lower mortality rate of 1.5 deaths per 100 person-years that remained stable over the 6-year follow-up. The mortality decline in our drug-using population was more modest compared to other cohorts, where HIV was largely sexually acquired [2, 25]. In fact, the mortality rates in the present study are among the highest reported among persons in developed countries with access to HAART. For example, Palella et al. noted that in the HIV Outpatient Study (HOPS), where participants were recruited from HIV care settings, mortality rates declined and then stabilized at ~2 deaths per 100 person-years by 1998 [2].

Explanations for the higher mortality rate in our cohort

Table 4. Cox proportional hazards analysis of factors associated with mortality among 398 HIV-infected persons in the HERO cohort, 1996–2001.

Variable	Univariate HR (95% CI)	Multivariate HR_{adj} (95% CI)
Age (per year)	1.01 (0.98–1.03)	1.01 (0.98–1.04)
Race/ethnicity		
Black	0.77 (0.37–1.60)	...
Hispanic	1.07 (0.57–2.02)	...
White	Reference	...
Female sex	1.07 (0.73–1.57)	1.27 (0.84–1.92)
Drug use by any route reported at each visit	0.85 (0.56–1.28)	0.86 (0.56–1.33)
Mean no. of monthly drug injections reported at each visit		
0	Reference	...
≤30	0.95 (0.49–1.83)	...
>30	0.60 (0.32–1.94)	...
Methadone use reported at last visit	1.21 (0.80–1.83)	1.27 (0.82–1.95)
Participation in methadone treatment program reported at each visit	2.01 (0.88–4.61)	...
$CD4^+$ lymphocyte count at each visit, cells/mm^3		
≥200	3.62 (2.03–6.47)	4.13 (2.24–7.60)
201–500	1.36 (0.72–2.58)	1.59 (0.83–3.04)
>500	Reference	Reference
HAART use reported at last visit	0.55 (0.36–0.83)	0.44 (0.28–0.68)
HIV RNA level (per log)[a] at each visit	1.12 (1.09–1.31)	...

NOTE. HR, hazard ratio; HR_{adj}, adjusted hazard ratio.

[a] HIV RNA level was not entered into multivariate model because data were insufficient.

include suboptimal use of HAART and competing causes of death. Only 60% of eligible persons received HAART during the study period, and as a result, excess mortality associated with HIV/AIDS was substantial. Almost 40% of deaths among HIV-infected persons were due to HIV/AIDS, compared with <30% of deaths in the HIV Outpatient Study [26]. In addition to HIV/AIDS, drug users are subject to multiple competing causes of death [20, 21, 27]. Our participants experienced substantial pre-AIDS mortality, and almost 40% of persons with HIV infection died of substance abuse–related causes, medical illness other than bacterial infection or HIV/AIDS itself, or violence.

Substance abuse accounted for >30% of deaths in the entire cohort; this is not surprising, given that drug use itself is associated with premature mortality [21]. The proportions of deaths due to bacterial infection, other medical illness, and violence were similar among HIV-infected and HIV-uninfected persons, suggesting that other factors shared by the 2 groups, such as drug use, poverty, and medical disengagement, were contributing to mortality.

Although current guidelines recommend considering HAART when the $CD4^+$ lymphocyte count is 201–350 cells/mm^3 [28], it has been reported that drug users begin HAART at a more advanced stage of HIV disease [9, 10]. In our study, HAART significantly decreased mortality, when controlling for active drug use. In addition, HIV-infected drug users who initiated HAART at a $CD4^+$ lymphocyte count of >200 cells/mm^3 experienced improved survival, compared with those who initiated it at a $CD4^+$ lymphocyte count of ≤200 cells/mm^3. Thus, drug use should not preclude timely HAART prescription; rather, substance abuse treatment and HAART should be emphasized concurrently.

Wang et al. [28] recently reported that HIV-infected drug users who initiate HAART at a $CD4^+$ lymphocyte count of >350 cells/mm^3 experienced survival similar to those of HIV-uninfected drug users. However, we did not find an incremental mortality benefit when HAART was started at a $CD4^+$ lymphocyte count of >350 cells/mm^3, compared with 201–350 cells/mm^3, nor did we find that early initiation resulted in survival similar to those for HIV-uninfected drug users. A possible explanation for our findings may be that adherence to antiretroviral therapy in our cohort was suboptimal. In a prior study that used electronic monitors to measure adherence to treatment over a 6-month period, we found that, on average, participants in the HERO study took only 53% of prescribed doses [29]. Thus, to improve survival among HIV-infected drug users, HAART should be offered earlier and in a context that fosters adherence.

Drug overdose has been reported to be the cause of 30%–50% of deaths among drug users, regardless of HIV infection status [21, 27]. However, for our entire cohort, overdose was responsible for only 15% of deaths. This may be explained by

the decrease in injection drug use during the study period, possibly reflecting increased awareness of HIV risk and higher purity of heroin [30]. Also, participants were enrolled from methadone treatment programs and, thus, represent a relatively stable group of drug users. A sample of street drug users would have likely resulted in higher rates of mortality associated with violence and overdose [31].

Drug use was not independently associated with mortality. Study participants were older than participants in other studies of drug users [20] and, thus, were at increased risk for illnesses associated with older age. Death due to end-stage liver disease secondary to hepatitis C typically occurs years after acquisition of infection from drug use. Given that drug use patterns commonly fluctuate and decline over time [32], drug use during the few years before death may not be the best measure of the effect of drug use on hepatitis C–related mortality. Other studies of HIV-infected drug users have shown only a modest or no increased risk of death with active drug use, especially when compared with other variables, such as $CD4^+$ lymphocyte count and HAART use [12, 33, 34]. Given that our study sample consisted entirely of persons with a history of drug use, we were not able to assess the effect of any history of drug use on mortality.

We did not find that participation in a methadone treatment program had a significant effect on mortality. However, the study was not powered to detect a significant effect, given that >75% of participants remained in methadone treatment throughout the study.

Of note, HIV-negative drug users experienced substantially higher mortality rates, compared with age-adjusted mortality rates in the general population in the United States (1.5 vs. 0.83 deaths per 100 person-years) [35]. Also, the mean age at the time of death for HIV-uninfected drug users was 30 years less than that of the general population (47.7 vs. 77.6 years) [35]. These findings, along with the fact that the majority of drug users died of substance abuse–related causes, bacterial infection, or cardiovascular disease, underscore the fact that regular medical care, preventive health, and substance abuse treatment need to be promoted among drug users.

A major strength of this study is the use of medical record abstraction to classify cause of death, given the inaccuracies associated with death certificate completion [36]. However, some study limitations should be noted. Our participants were recruited entirely from methadone clinics, and all were drug users. Thus, our findings may not be generalizable to other HIV exposure groups. Another limitation was that receipt of HAART was assessed by self-report and reflected "any use" in the 6 months prior to each visit, rather than duration and degree of adherence. Thus, the true benefit of sustained adherence to HAART on mortality in this cohort of drug users is likely to have been underestimated.

This study demonstrates that drug users with HIV infection and those who are at risk of acquiring HIV infection are experiencing disproportionately high mortality rates and competing causes of death, despite the availability of HAART. In addition to substantial AIDS-related mortality, 50% of deaths among HIV-infected participants were due to bacterial infection, substance abuse–related causes, or violence. In addition to placing high priority on substance abuse treatment and HAART use, interventions aimed at improving regular medical care and preventive health among drug users are warranted.

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