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Improving Survival among HIV-Infected Injection Drug Users: How Should We Define Success?

Gregory D. Kirk[1] and **David Vlahov**[1,2]

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland [2]Center For Urban Epidemiologic Studies, New York Academy of Medicine, New York, New York

More than a decade after highly active antiretroviral therapy (HAART) became available, extensive literature has documented the dramatic impact of HAART in reducing progression to AIDS and in improving survival among HIV-infected persons. However, a lingering issue regarding the effectiveness of HAART has been whether the survival benefit is fully extended to all risk groups—in particular, to injection drug users (IDUs). In this issue of *Clinical Infectious Diseases*, Muga et al. [1] provide evidence that the duration of survival among HIV-infected IDUs in Barcelona, Spain, has improved during the HAART era. In fact, among IDUs who were admitted to a drug treatment program since 1997, mortality rates for persons with and persons without HIV infection were roughly equivalent. The study reinforces the fact that HIV treatments are indeed effective among IDUs, and it highlights the discrepant results observed in comparisons of the effectiveness of HAART among IDU and non-IDU populations.

The influence of injection drug use on progressive HIV infection, developmentof AIDS, and death has been reviewed previously [2]. As early as 1987, IDUs were suggested to experience more-advanced progression to AIDS [3]. Subsequently, in longitudinal studies from the United States and Europe of persons who experienced HIV seroconversion, significant and persistent differences in the rates of declines in the $CD4^+$ cell count or in progression to AIDS were not observed [4, 5]. Since the advent of HAART, analyses of several HIV-infected cohorts have suggested that the survival benefit at a population level is more limited among IDUs than among other HIV risk groups [6–9], whereas other cohorts found no differences [5, 10–13]. In Spain, 2 multicenter studies of hospital-based HIV cohorts reported that HAART may be less effective among IDUs [14, 15]. However, comparisons of the mortality rate between IDUs and non-IDUs are fraught with limitations. Many potential confounders of HIV treatment responses, such as race, socioeconomic status, and access to medical care, differ for IDUs and other HIV risk groups. Injection drug use is a chronic medical condition with significant morbidity and mortality, and it often results from causes that are not overtly increased among other populations [16]. IDUs have higher

Reprints or correspondence: Dr. Gregory Kirk, Dept. of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe St., E-6533, Baltimore, MD 21205 (gkirk@jhsph.edu)..

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pre-AIDS rates of mortality (e.g., in association with violence, accidents,and overdose), compared with other HIV risk groups [17]. Subsequently, reductions in the all-cause mortality rate that are related to HAART among HIV-infected IDUs may be underestimated, relative to estimates for other HIV risk groups with lower baseline mortality rates.

The study by Muga et al. [1] evaluated mortality among IDUs who were admitted to a substance abuse treatment program at a single hospital in Barcelona, Spain, during the period 1987–2004. By nature of admission to a tertiary care hospital for drug treatment, the study participants represent a population of experienced injectors with severe addiction (supported by the stable >90% prevalence of hepatitis C virus infection) but who had access to hospital-based services. Throughout the period studied, persons admitted to the program and who were followed up were increasingly more experienced injectors of drugs (the median duration of injection drug use increased by ~4 years, whereas the age at the time of initiation was constant). The prevalence of HIV infection decreased from 70% to 48% from the early period (1987–1991) to the HAART period (1997–2004). During the HAART era follow-up, slightly more than one-third of HIV-infected participants were receiving antiretroviral treatment. However, most HIV-infected IDUs in the study did not have advanced immunosuppression and would not have been considered eligible for HAART. This finding of preserved immune function among HIV-infectedactive IDUs is consistent with other studies, suggesting a “healthy drug user” effect—that is, IDUs without debilitating disease related to advanced HIV infection or AIDS are often able to maintain heavy drug use (and, in this study, to require admission for drug treatment). Because HIV-infected IDUs who enrolled in the program during earlier periods were subsequentlyobserved into later periods, it would be expected that progressive decreases in the $CD4^+$ cell count would be observed. Compared with the earliest study period, the median $CD4^+$ cell count among HIV-infected IDUs who were admitted during the HAART era decreased by >150 cells to ~500 cells/μL (notably, the 25th percentile decreased by >200 cells to 265 cells/μL). Despite the progressive disease among participants, there was not an appreciable increase in the proportion of patients receiving antiretroviral treatment. From the data presented, it is unclear whether there were temporal changes in the stage of HIV infection or $CD4^+$ cell counts among new entrants into the study.

Muga et al. [1] present mortality rates for 3 distinct calendar periods: 1987–1991, 1992–1996, and 1997–2004. Mortality was determined for all IDUs admitted to the drug treatment unit with a known HIV serostatus (1181 participants, 706 of whom had HIV infection) through linkage to the Catalonian mortality registry at the end of the follow-up period. Cox regression methods performed with late entries allowed persons observed from earlier into later periods to contribute follow-up data to each. Mortality rates among HIV-infected IDUs peaked during 1992–1996 and then decreased during the HAART era (mortality rate, 5.2, 8.3, and 3.2 deaths per 100 person-years during periods 1–3, respectively). Among HIV-uninfected IDUs, the corresponding mortality rates were 2.3, 2.4, and 1.4 deaths per 100 person-years for periods 1–3, respectively. Within each period, the relative hazard for death (adjusted for age and sex) was higher among HIV-infected IDUs, but it notably decreased in the HAART era. More compelling, for persons who entered the study after HAART became

available, there was no difference in the mortality risk by HIV status (relative hazard, 0.89; 95% CI, 0.44– 1.81).

Few studies have compared survival among HIV-infected IDUs in the HAART era with an epidemiologically appropriate comparison group of HIV-uninfected IDUs [18, 19]; the present study's findings are consistent with these prior data. Kohli et al. [18] reported a 50% reduction in the mortality rate from 1996 to 2001 among a large cohort of HIV-infected and HIV-uninfected IDUs who were recruited from methadone maintenance programs in the Bronx, New York. This decrease was attributable solely to the 66% reduction in the mortality rate among HIV-infected persons who were receiving HAART. Among IDUs who were observed in the AIDS Linked to the IntraVenous Experience (ALIVE) cohort in Baltimore, Maryland, during 1997–2001, a marked survival benefit was observed among HIV-infected IDUs who were receiving HAART for all $CD4^+$ cell strata; however, the survival time for HIV-infected IDUs approximated that for HIV-uninfected IDUs only among subjects who initiated HAART at a $CD4^+$ cell count of >350 cells/μL [19].

The extent to which the results of the study by Muga et al. [1] can be generalized to other IDU populations with a different underlying risk for either AIDS-related or non–AIDS-related death is unclear. Compared with IDUs in other European countries, HIV-infected IDUs in Spain tended to initiate HAART at higher $CD4^+$ cell counts and to have a lower risk of death due to nonnatural causes (e.g., overdose, suicide, and accidents) [20]. Nonetheless, rates of HAART response and disease progression appear to be largely homogeneous among HIV-infected IDUs throughout Europe [20]. Significant barriers to accessing appropriate HIV care and to initiating HAART among eligible HIV-infected IDUs in the United States have been well documented [21]. Furthermore, access to low-threshold methadone treatment programs like those in Barcelona is more limited in the United States [22]. Despite the apparent differences in the access to care and the variation in the stage of HIV disease, the mortality rates among both HIV-infected and HIV-uninfected IDUs observed in the HAART era in the study by Muga et al. [1] were very comparable to those among IDUs in studies from urban US cities [18, 19].

The survival benefit observed by Muga et al. [1] among HIV-infected IDUs was achieved with only a 30%–40% uptake of HAART. This suggests that, in this population, which had relatively high $CD4^+$ cell counts, selection for HIV treatment was well targeted to the subset of persons at highest risk for mortality. Not surprisingly, HAART is given to the sickest persons, leaving the untreated patient group to include the relatively more healthyHIV-infected IDUs [23].

Because HAART prolongs the time to development of AIDS, the pre-AIDS mortality rate may increase, particularly among IDUs with drug-related comorbidities and a high prevalence of hepatitis C virus infection [8, 17, 24]. Interestingly, non-AIDS mortality among HIV-infected IDUs may be positively influenced by HAART use, particularly at higher $CD4^+$ cell counts [19]. Unfortunately, data on cause-specific mortality was not presented in the study by Muga et al. [1]. Assessment of the reductions in AIDS-related deaths, compared with non–AIDS-related causes of death, would be helpful for assessment of the effectiveness of HAART on both outcomes. These data would also contribute to the

ongoing discussion of when is the best time to initiate HAART. Because of the lack of significant differences in the natural history of untreated HIV infection, treatment guidelines have not differed by risk group. Despite these uniform recommendations, HAART initiation occurs at lower $CD4^+$ cell counts among IDU populations. In a recent study of patients who were observed in the Johns Hopkins HIV Clinical Cohort and who achieved prolonged viral suppression, a primary predictor of increases in the $CD4^+$ cell count was the baseline $CD4^+$ cell count at the time of HAART initiation [25]. IDUs had notably lower $CD4^+$ cell counts at baseline; however, even after adjustment for this factor, IDUs had a ~90-cell/μL lower increase in the $CD4^+$ cell count, compared with other risk groups, after 6 years of follow-up. Treatment guidelines have largely not considered variation in immunologic responses or the differing risk for non-AIDS outcomes between risk groups.

Irrespective of baseline $CD4^+$ cell count, treatment readiness, and the ability to adhere to the prescribed regimen should be a primary determinant of HAART initiation. However, clinicians do no better than chance in predicting a patient's adherence to HAART [26]. Although active injection drug use has been associated with poorer adherence to treatment and more-limited virologic responses [7], there exists a subset of occasional drug injectors who can fully adhere to treatment and who respond well to HAART. It is clear that IDUs do not constitute one homogenous risk group, and attention should be paid to the intensity of ongoing injection drug use behavior, the use of polysubstances, the social support system, attitudes toward medical care, and comorbidities when making decisions regarding HAART use. Additional research efforts should identify the determinants of provider willingness to prescribe HAART to IDUs and explore the predictors of HAART responses among the wide spectrum of IDUs. Ongoing investigations are exploring whether integrated approaches to delivering antiretroviral therapy through drug treatment programs may improve access, adherence, and responses to HAART for IDUs [27]. Future epidemiologic and clinical studies should move beyond a simple categorization of IDU as a “risk group” and instead provide more-refined evaluations of injection and noninjection drug use.

Muga et al. [1] have documented improved survival for HIV-infected IDUs during the HAART era, with mortality rates approaching those for HIV-uninfected IDUs among persons newly admitted to a drug treatment program during this period. In combination with other studies, the conclusion is that HAART can be very effective among IDUs. Debates on whether IDUs benefit equally from HAART divert attention from other important research questions and from daunting programmatic issues. Our goals now should be to more fully define and ensure optimal HIV care for IDUs. This will include ensuring appropriate access and continuity of HIV care, minimizing the delay of HAART initiation, maximizing adherence to treatment, and managing comorbidities among IDUs. Furthermore, the discrepancies in background mortality between IDUs and other risk groups reinforce the need to improve life expectancy among all IDUs, irrespective of whether they have HIV infection. Both injection drug use and HIV infection are chronic medical conditions that necessitate long-term treatment strategies that are best provided as a partnership betweenpatient and providers. Success in management of both conditions will be achieved when the differences in the mortality rates between risk groups are not so clearly evident.

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