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The relationship between non-injection drug use behaviors on progression to AIDS and death in a cohort of HIV seropositive women in the era of highly active antiretroviral therapy use

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Abstract

Aims—To evaluate the effects of longitudinal patterns and types of non-injection drug use (NIDU) on HIV progression in the highly active antiretroviral therapy (HAART) era.

Design—Women's Interagency HIV Study (WIHS), a prospective cohort study conducted at six US sites.

Methods—Data were collected semi-annually from 1994 to 2002 on 1046 HIV^+ women. Multivariate Cox proportional hazards modeling was used to estimate relative hazards for developing AIDS and for death by pattern and type of NIDU.

Findings—During follow-up, 285 AIDS events and 287 deaths, of which 177 were AIDS-related, were reported. At baseline, consistent and former NIDU was associated with $CD4^+$ counts of < 200 cells/μl (43% and 46%, respectively) and viral load > 40 000 copies/ml (53% and 55%, respectively). Consistent NIDU reported less HAART use (53%) compared with other NIDU patterns. Stimulant use was associated with $CD4^+$ cell counts of < 200 cells/μl (53%) and lower HAART initiation (63%) compared with other NIDU types. In multivariate analyses, progression to AIDS was significantly higher among consistent (RH = 2.52), inconsistent (RH = 1.63) and former (RH = 1.56) users compared with never users; and for stimulant (RH = 2.04) and polydrug (RH = 1.65) users compared with non-users. Progression to all-cause death was higher only among former users (RH = 1.48) compared with never users in multivariate analysis. NIDU behaviors were not associated with progression to AIDS-related death.

Conclusions—In this study, pattern and type of NIDU were associated with HIV progression to AIDS and all-cause mortality. These differences were associated with lower HAART utilization among consistent NIDU and use of stimulants, and poor baseline immunological and virological status among former users.

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Keywords

Acquired immunodeficiency syndrome; highly active anti-retroviral therapy; human immunodeficiency virus; mortality; non-injection drug use

INTRODUCTION

Evidence from early, pre-highly active antiretroviral therapy (HAART) era epidemiological studies of human immunodeficiency virus (HIV) progression in homosexual men and injection drug users suggested that drug use may be a potential co-factor in immunological, virological and clinical progression of HIV infection [1–4]. These findings were consistent with reports from *in vitro* [5–9] and animal studies [10–12] which showed that opiates and cocaine, when administered individually, were associated with altered immune function and HIV replication. Most notably, results from animal models of Simian immunodeficiency virus (SIV) and other retroviruses similar to HIV suggested that distinct patterns of drug use, such as intermittent administration and structured withdrawal from heroin and opiates, may induce immunological changes associated with worse AIDS-related outcomes compared to chronic exposure to heroin and opiates or in controls not exposed to drugs [10,11].

Subsequent reports from recent, large-scale epidemiological cohort studies of HIV-infected individuals indicated only modest differences in immunological, virological or clinical progression of HIV by use of drugs [13–15]. A potential explanation for the discrepancy in findings between laboratory and observational cohort studies may be due to the way in which drug use itself was previously examined. Most epidemiological studies examined the influence of drug use on HIV disease progression by focusing on chronic drug users, considering only injection drug use, and not examining the impact of drug use by type or class of drug being used (i.e. stimulants versus depressants). Although a study by Lyles and colleagues [16] found no effect by frequency of drug use, binge use, episodes of withdrawal or overdose on $CD4^+$ cell decline between consecutive visits, this study was restricted to injection drug users and was not able to examine the effects of longitudinal, transient patterns of drug use on course of HIV infection. Analyses of drug use on HIV progression based on data from cohort studies must include more specific measures of drug use that consider not only other routes of administration (e.g. non-parenteral) but also examine differences by long-term patterns of drug use. These refinements are necessary because effects of tolerance to long-term drug use [17,18], competing causes of morbidity and mortality among injection drug users [19], injection drug use behaviors (i.e. syringe sharing) [20] and polydrug use [21] may minimize or offset the physiological impact of drug use itself on immunological activity and clinical disease progression, as seen in observational studies.

In addition, most epidemiological studies of HIV progression were conducted prior to the introduction of HAART; thus there is limited information describing the impact of drug use on the benefits of potent antiretroviral regimens. As some pharmacokinetic studies suggest that there may be unique toxicities resulting from the concomitant use of drugs and antiretroviral medications [22,23], the effects of drug use on HIV progression in the HAART era warrants continued consideration. Finally, epidemiological studies that have examined the effect of drug use on HIV progression have compared injection drug users with other risk groups (i.e. men who have sex with men) or studied predominantly male cohorts. Because information on this issue in women is sparse, we examined whether progression to AIDS and death differed by longitudinal patterns and type of non-injection drug use (NIDU), in a cohort of HIV seropositive women. In particular, we were interested

in examining the relationship between NIDU and HIV disease progression to an AIDS defining event or death in the era of widespread HAART utilization.

METHODS

Study design

The Women's Interagency HIV Study (WIHS) is a multi-site longitudinal cohort study of HIV infection among women in the United States. Recruitment into the WIHS occurred between 1994 and 1995 at six US sites: Bronx/Manhattan, NY; Brooklyn, NY; Chicago, IL; Los Angeles/Southern California/Hawaii; San Francisco/Bay Area, CA; and Washington, DC. Details of study objectives, design and methodology have been published previously [24]. Briefly, the original study objectives were to investigate clinical and behavioral factors associated with disease progression and effects of treatment on the clinical course of HIV disease.

Participants were screened and enrolled into the study if they met the following eligibility criteria: were at least 13 years or older; agreed to be tested for HIV; could complete assessments in either English or Spanish; and were able to travel to and from the study site. The baseline visit consisted of interviewer-administered, structured assessments concerning socio-demographic characteristics, mental and physical health history, alcohol, drugs and sex behaviors, medication and health-care utilization; physical examination; and phlebotomy. WIHS participants returned for follow-up visits semi-annually to complete similar assessments, physical examinations and specimen collection. Follow-up data for these analyses come from visits up to March 2002, allowing for up to 8 years of follow-up per participant. All participants were offered remuneration for baseline and follow-up interviews consistent with local Institutional Review Board and community advisory board guidelines. Written informed consent to participate in study activities was obtained from all women enrolled into the WIHS.

Sample

Between October 1994 and November 1995, 2059 HIV seropositive women were enrolled into the WIHS. Because this analysis focused on the impact of longitudinal patterns and type of non-injection drug use on HIV progression, the overall sample was restricted to 1046 HIV seropositive women who completed at least 1 year of follow-up (two visits) after the baseline visit, did not have a gap of ≥ 2 years (four visits) during subsequent follow-up visits and did not report injection drug use. A total of 216 participants (10%) had less than 1 year of follow-up, 100 participants (5%) had a period of missing follow-up ≥ 2 years and 275 (13%) reported engaging in injection drug use at some point during the course of follow-up visits. An additional seven participants were excluded from these analyses due to lack of baseline data on drug use behaviors. Finally, in order to include women for whom treatment with HAART would be recommended, all participants included here had a $CD4^+$ cell count ≤ 500/μl at baseline, thus excluding 415 individuals with $CD4^+$ cell counts > 500/μl.

Study outcomes

The primary outcomes of interest for this analysis were: (1) time to a clinical AIDS-defining event and (2) time to all-cause and AIDS-related deaths over the follow-up period. Events were classified as AIDS-defining based on the 1993 Centers for Disease Control and Prevention (CDC) class C definition of AIDS [25] and do not include the immunological criteria of $CD4^+$ cell count < 200/μl. Ascertainment of data on cause and date of death was conducted via active and passive surveillance throughout the duration of the study using the following sources: death certificates, National Death Index, local death or AIDS registries,

local physician or hospital records and reports from family members or friends. Deaths were classified, similar to prior WIHS publications [26], as AIDS-related if the stated cause of death was an AIDS-defining illness or malignancy or if the $CD4^+$ cell count at the visit preceding death notification was less than 200 cells/μl. Non-AIDS deaths included cases where the cause of death was a known non-AIDS associated condition (drug overdose, homicide/suicide/accident, liver failure, non-AIDS-related malignancy, kidney failure, cardiovascular, gastrointestinal or central nervous system diseases where the $CD4^+$ cell count at last study visit was ≥ 200 cells/μl). Causes of death were considered unknown if adequate information could not be ascertained or indeterminate if the cause of death was non-specific.

Independent variables

The primary exposures of interest in this analysis were pattern and type of NIDU. Definitions of NIDU behaviors were based on self-reported, non-parenteral use of heroin, cocaine, crack, alcohol or marijuana during the 6 months preceding each study visit. Alcohol use was classified as moderate to heavy consumption of alcohol based on NIAAA guidelines [27]. Mutually exclusive NIDU patterns were defined as follows: ‘never use’ included participants reporting no drug use prior to baseline and during follow-up visits; ‘former use’ included those who reported NIDU prior to study enrollment but not during follow-up and ‘active use’ included participants who reported NIDU during the course of follow-up visits. Active use was further distinguished as ‘inconsistent use’ and ‘consistent use’. Consistent use included participants who reported NIDU at every follow-up visits whereas inconsistent use included individuals whose NIDU behavior fluctuated between periods of use and non-use during follow-up visits. Average frequencies of marijuana, alcohol, heroin, cocaine and crack use were also examined to understand the extent of drug use in this sample. Specifically, average drug use for individuals classified as consistent and inconsistent users, at the baseline visit and across all follow-up visits where an individual reported using a given drug, was examined to determine whether any differences existed between these two groups of active NIDU. At baseline, inconsistent and consistent NIDU reported using drugs at least on a weekly basis (and up to more than daily) with use of marijuana, heroin and cocaine reported to be at least once per week; use of crack was somewhat higher at two to three times per week. Alcohol use at baseline involved, on average, consumption of five drinks (range: three to 13 drinks) per week. At follow-up, average use of these drugs for both inconsistent and consistent NIDU was similar to that reported at baseline. Consequently, we found no statistically significant differences in average use of the specific drugs examined here when comparing inconsistent and consistent NIDU at baseline and at follow-up.

Type of non-injection drug use was categorized based on the physiological actions of individual drugs. Individuals reporting the exclusive use of alcohol, marijuana or heroin at baseline and during follow-up visits were identified as ‘depressant only users’, whereas those reporting the exclusive use of cocaine or crack were considered ‘stimulant only users’. Individuals reporting the use of drug combinations that included both stimulants and depressants were defined as ‘polydrug users’. Participants who did not report the use of any type of non-injection drug during follow-up visits were considered ‘non-users’.

Covariates

Covariates of interest included baseline $CD4^+$ cell counts, HIV viral load levels and use of HAART after 1 April 1996, as previous studies by the WIHS investigators have identified these factors as salient prognostic indicators of HIV disease progression [28]. Socio-demographics, health-care access, health-care utilization and drug treatment were also examined given their documented association with both drug use behaviors and HIV

progression [29,30]. Socio-demographic characteristics of interest included baseline measures of age, race/ethnicity, educational achievement, yearly income below poverty level (≤ $12 000), employment status and receiving public assistance. Health-care access and utilization were assessed by self-reported public or private forms of health insurance coverage, having a health-care provider and use of emergency rooms for medical care. Use of drug treatment services included self-reported use of in-patient and out-patient drug treatment services as well methadone maintenance programs. Based on Department of Health and Human Services/Kaiser guidelines, women reporting use of one of the following antiretroviral combinations since their last study visit were considered to be on HAART: (1) two or more nucleoside reverse transcriptase inhibitors (NRTIs) with at least one protease inhibitor (PI) or one non-nucleoside reverse transcriptase inhibitor (NNRTI); (2) one NRTI with at least one PI and at least one NNRTI; (3) a combination of ritonavir and saquinavir with one NRTI; or (4) an abacavir-containing regimen of three or more NRTIs with no PIs or NNRTIs [31]. Combinations of zidovudine and stavudine with either a PI or an NNRTI are not recommended as HAART regimens because this combination is considered antagonistic.

Laboratory methods

As described previously [24], enumeration of T cell subsets was performed by flow cytometry using whole blood methods and plasma HIV viral load was quantified using nucleic acid sequence based amplification (NASBA) commercial assays (Organon Teknika, Durham, NC, USA). Due to the availability of increasingly sensitive HIV viral load assays during later stages of follow-up, the lower limit of detection decreased from an initial level of 4000 copies/ml to 400 copies/ml in October 1997 to 80 copies/ml by January 1999.

Statistical analysis

Survival time estimates for AIDS and death were measured in number of years from the baseline visit date to the midpoint between the last study visit date at which an individual reported being AIDS-free or alive and the first visit date at which an AIDS-defining event was reported or an individual was known to have died. Participants who remained AIDS-free or alive were right censored at the date of their last follow-up visit. We calculated Kaplan–Meier probabilities of developing AIDS and of death, stratified by NIDU pattern and by type of NIDU separately for HAART users and non-users, and compared survival distributions using log-rank tests. Cox proportional hazards models were employed to test formally for significant differences in progression to AIDS and death by pattern and type of NIDU [32]. Separate univariate Cox proportional hazards models were fitted to estimate hazard ratios and 95% confidence intervals (CI) by NIDU pattern and type of NIDU on the probability of progressing to AIDS and death. Multivariate models were fitted to examine the impact of NIDU behaviors on probability of developing AIDS and survival after adjusting for baseline $CD4^+$ cell count, HIV viral load, use of HAART and other covariates found to be significant in univariate models. Statistical and graphical approaches were used to test the proportional hazards assumption [33]. All analyses were conducted using SAS (version 8.0, Cary, NC, USA).

Sample characteristics

Table 1 presents baseline socio-demographic characteristics of women in this sample overall, by NIDU pattern and by type of NIDU. Among these 1046 participants, the average age was 36 years with most women self-identifying as either African American (55%) or Hispanic/Latino (25%). While 34% of women had less than a high school education, 76% reported being currently unemployed and 58% reported an annual income of less than $12 000.

Health-care access and utilization were widespread, as 85% reported having either public or private forms of health insurance coverage, 86% reported a doctors' or clinic visit in the 2 months preceding baseline, whereas 18% reported an emergency room visit for medical attention during the same time period.

By drug use pattern, consistent and former users were, on average, older (mean age = 37.9 years for both) than inconsistent and never users (mean age = 35.4 and 35.5 years, respectively, *P*-value < 0.001). Active NIDU, both consistent and inconsistent use, was associated with self-identifying as African American, having an annual income < $12 000, receiving public assistance and being unemployed. While there were no differences in proportions by health-care utilization, former users were more likely to report health insurance coverage (93%) compared with active NIDU and never users. Additionally, a smaller proportion of consistent users reported use of drug treatment programs (19%) compared with inconsistent (28%) and former (30%) users (*P*-value < 0.001).

By type of NIDU, women reporting the use of stimulants were younger (mean age = 34 years) than polydrug, depressant and non-users. Stimulant-only users and polydrug users were more likely to be African American (*P*-value < 0.001), have less than a high school education (*P*-value = 0.047), to be unemployed (*P*-value < 0.001), report receiving public assistance (*P*-value < 0.001) and attending drug treatment programs (*P*-value < 0.001). However, depressant-only users were more likely to report an annual income below poverty level compared with other NIDU types (*P*-value = 0.001). Although the proportion of women reporting health insurance or doctor's visit did not differ by type of NIDU, stimulant users were more likely to report emergency room visits (*P*-value = 0.001).

RESULTS

Summary of HIV-related health status and NIDU behaviors

As shown in Table 2, a total of 287 deaths were reported during follow-up, of which 177 were AIDS-related. Among the 701 individuals AIDS-free at baseline, 285 new AIDS cases were reported during follow-up visits. Former and active (inconsistent and consistent) users were more likely to report AIDS-defining events compared with never users (*P*-value = 0.023). Reports of death, from all causes (41%, *P*-value < 0.001) and AIDS-related conditions (27%, *P*-value < 0.001) were significantly higher among consistent NIDU compared with other NIDU patterns. It is important to note that HAART utilization was reported by a smaller proportion of consistent users (53%, *P*-value < 0.001) compared with former or never users, despite similarities in baseline immunological and virological indicators between consistent, former and never users. In contrast, inconsistent drug users were more likely than consistent, former and never users to have $CD4^+$ cell counts ≥ 200 cells/μl (*P*-value = 0.003) and viral loads < 40 000 copies/ml (*P*-value = 0.002) at baseline and to report HAART utilization (81%, *P*-value < 0.001) during follow-up.

By type of NIDU, AIDS (63%, *P*-value = 0.013), all-cause mortality (43%, *P*-value < 0.001) and AIDS-related deaths (33%, *P*-value < 0.001) were more common among stimulant users compared with depressant, polydrug and non-users. Baseline $CD4^+$ cell counts < 200 cells/μl were more frequent among stimulant users (43%, *P*-value < 0.001), while viral load levels > 40 000 copies/ml were more frequent among non-users (56%, *P* = 0.002). Despite lower baseline $CD4^+$ levels, HAART use was reported by a smaller proportion of stimulant users (63%) compared with-non-users, depressant and polydrug users (69%, 79% and 73%, respectively; *P*-value = 0.007).

Analysis of progression to AIDS and death

Figure 1 shows Kaplan–Meier curves for AIDS and all-cause death among women reporting the use of HAART. Time to AIDS differed significantly by both pattern and type of NIDU with consistent users and stimulant-only users showing greater likelihood of progressing to AIDS (LRT, *P*-values = 0.001 and 0.007, Fig. 1a,b, respectively) compared with other categories in their respective groups. Survival probability for all-cause death among individuals who reported initiating HAART was significantly different by pattern of NIDU (Fig. 1c, LRT, *P*-value = 0.04) indicating a greater likelihood of death among former users compared to other patterns of NIDU. Time to all-cause death did not differ significantly by type of NIDU (Fig. 1d, LRT, *P*-value = 0.11). Additionally, survival probabilities did not differ significantly for AIDS-related deaths by either pattern (LRT, *P*-value = 0.60) or type (LRT, *P*-value = 0.43) of NIDU among those not reporting HAART initiation during follow-up (figures not shown).

Table 3 shows univariate and multivariate proportional hazards models for time to AIDS by pattern and type of NIDU as well as baseline $CD4^+$ cell count, HIV viral load, emergency care and use of HAART as these covariates were found significant in univariate analyses. In multivariate analysis, hazard ratios for progression to AIDS were significantly higher for consistent (RH = 2.52; 95% CI = 1.60–3.96), inconsistent (RH = 1.63, 95% CI = 1.15–2.30) and former use (RH = 1.56, 95% CI = 1.05–2.32) compared with the referent group of never use (RH = 1.00). By type of NIDU, progression to AIDS was significantly higher in both stimulant (RH = 2.04, 95% CI = 1.06–3.94) and polydrug users (RH = 1.65, 95% CI = 1.21–2.24) compared with the referent group of non-users (RH = 1.00).

Table 4 shows analyses of all-cause and AIDS-related mortality end-points. By NIDU pattern, all-cause mortality was significantly higher in former users (RH = 1.48, 95% CI = 1.05–2.09) and, although not statistically significant, in consistent users (RH = 1.43, 95% CI = 0.95–2.15) than in never users (referent group, RH = 1.00) after adjustment for baseline $CD4^+$ cell count, viral load, age and emergency room visits. With respect to type of NIDU, use of depressants was associated with a lower hazard for death (RH = 0.71, 95% CI = 0.53–0.95) compared with non-use (referent group, RH = 1.00). In multivariate models examining AIDS-related deaths, neither pattern nor type of NIDU was associated significantly with increased mortality from AIDS-associated illnesses. Formal tests of interaction between HAART use and pattern and then type of NIDU were performed for both outcomes: AIDS and death (all-cause and AIDS-related). Our results indicated no statistically significant interaction in multivariate models, suggesting that NIDU behaviors did not impact the benefit of HAART on AIDS- or mortality-related outcomes (data not shown).

DISCUSSION

In this cohort of HIV seropositive women, increased progression to AIDS and all-cause death was observed for distinct patterns and types of drugs used by non-parenteral routes of administration compared to those not reporting NIDU behaviors. By NIDU patterns, progression to AIDS was faster for both active (consistent and inconsistent) and former NIDU than never users, while all-cause mortality was significantly higher for former users and less so for consistent users than non-users. By type of NIDU, progression to AIDS was faster among stimulant and polydrug users than other groups, and all-cause mortality risks were lowest among depressant users. Progression to AIDS-related death did not differ by distinct patterns or types of NIDU behaviors.

Earlier laboratory studies of infection and immunity led to the hypothesis that worse clinical outcomes would be expected for inconsistent as opposed to consistent, former or non-use patterns of drug administration [11,34,35]. While findings from the present study do not

conform strictly to this hypothesis, other factors may have contributed to the observed results, namely, baseline immunological and virological status of participants and use of potent antiretroviral therapies. First, it appears that consistent users were less likely to report HAART utilization during the course of follow-up, despite similar baseline immunological and virological indicators between consistent, former and non-users. Similar findings of lower HAART initiation and utilization among women actively using drugs were noted in earlier reports [36,37], and are in line with DHHS guidelines on initiation of antiretroviral therapies among active drug users when there are concerns of lower adherence to complex treatment regimens that may lead to greater resistance to these medications [31]. Nonetheless, physicians should actively encourage HIV-positive women who report drug use to seek drug treatment and support services in order to address these potential barriers to medication uptake and adherence. Secondly, these results are plausible when noting that NIDU characterized by inconsistent pattern of use and exclusive use of depressants were more likely than the other categories of drug pattern or type to have both higher $CD4^+$ levels and lower HIV viral loads at baseline as well as more widespread use of HAART throughout follow-up. While inconsistent use and use of depressants is still a concern, it appears that this group was considered by clinicians to be appropriate candidates for HAART. A potential explanation for the higher use of HAART among inconsistent users may be that clinicians will prescribe HAART to individuals who present as non-users during clinic visits, but who will report drug use at study interviews. Finally, we might have expected clinical progression in former users to be equivalent to non-users, but given that former users had lower $CD4^+$ cell counts and higher HIV viral load levels at baseline, they can be characterized as sicker at baseline and more likely to experience a negative outcome during follow-up.

Upon closer inspection of AIDS-defining events reported during follow-up, almost 50% were characterized as pulmonary conditions, including *Pneumocystis carinii* pneumonia (16%), candidias (15%), bacterial pneumonia (12%) and tuberculosis (6%). It must be noted that individuals reporting former and active NIDU (51%) were significantly more likely to report a pulmonary AIDS-defining illness compared with those who never engaged in NIDU (35%, *P*-value = 0.034). The increased susceptibility to pulmonary illness among those who used drugs via non-parenteral modes of administration is attributed to the harmful effects caused by inhalation of smoke on proper respiratory functioning among HIV-positive individuals [38]. The use of crack or cocaine has also been shown in previous studies to be associated with respiratory AIDS infections [39,40] and may also explain the increased progression to AIDS among stimulant users observed here.

Previous studies have suggested that faster HIV progression in some groups may be related to unequal access to health care or utilization of health-care services, especially among individuals who use drugs [41]. Specifically, injection drug use is associated with poorer utilization of out-patient medical services [42]. It is unlikely that limited access or use of health-care services would account for our findings, as the majority of this sample was recruited from clinical settings across the United States; there was widespread reporting of health insurance coverage (either pubic or private) and overall health-care utilization, irrespective of NIDU pattern or type of NIDU. As recent reports have indicated differences in HAART initiation, especially if clinicians are concerned with adherence to complex therapeutic regimens and development of resistance due to non-compliance [37]; these differences may have played a role in the findings observed here, given the lower proportion of active drug users reporting HAART compared with non-users.

Among individuals reporting HAART utilization, drug use has been cited as a major predictor of inadequate adherence to HAART [43,44]. Howard and colleagues [44] found that while a history of injection drug use was not associated with reduced adherence, active

drug use predictive of lower adherence to antiretroviral medications. A recent cross-sectional analysis of factors associated with adherence to antiretroviral regimens in a subsample of the WIHS cohort showed that active use of cocaine, crack or heroin, irrespective of route of administration, was associated with lower adherence to HAART (OR = 2.27, 95% CI, 1.32–3.91) [45]. Based on these previous findings, we examined whether adherence to HAART was associated with pattern or type of NIDU in the present report. However, a subsample analysis did not indicate significant differences in self-reported adherence to HAART by pattern or type of NIDU (data not shown). This suggests that the findings of increased risk for progression to AIDS and death by pattern and type of NIDU observed here were not related to differential treatment adherence by NIDU behaviors.

Several study limitations should be considered before conclusions are drawn. First, this study sample reflects recruitment of volunteers from HIV clinics, thus the extent to which these results are generalizable to other HIV infected women is difficult to determine. Secondly, although AIDS events were based on self-report, efforts were made to verify AIDS diagnoses via medical record abstraction and registry check. The results of these efforts suggest a high degree of accuracy of self-reported AIDS conditions compared to those reported to registries [46]. Thirdly, ascertainment of cause of death from death certificates is a concern. Despite active and passive surveillance procedures, missing death reports may artificially lower mortality estimates, which can be a problem if this occurred differentially between groups. However, as many of these participants were recruited from clinical care settings, this concern is reduced. Fourthly, data on HAART utilization is also based on participant self-reports and may be subject to over-reporting. Finally, the validity and accuracy of self-reported drug use behaviors are often cause for concern as drug users may under-report drug use due to socially desirable responding [47]. Results from toxicology analysis for cocaine and opiates on a subset of WIHS participants (n = 168) suggest a high degree of validity in self-reported drug use behaviors [48].

In conclusion, these findings suggest that distinct patterns and types of NIDU were associated with occurrence of AIDS and all-cause mortality but not AIDS-related death, as reported in this cohort of HIV seropositive women. While initiation of HAART was lower among active NIDU, these findings do not indicate reductions in the overall benefit of HAART among those women who did report the use of HAART, irrespective of drug use status. Although our findings on AIDS-related mortality are consistent with prior studies, differences in progression to AIDS events suggest that these results may have significant implications for future epidemiological research into drug use as a co-factor in HIV progression. The complex nature of and factors influencing drug use necessitates careful ascertainment of drug use behaviors and more precise examination in future analyses. Greater collaboration between researchers conducting laboratory and animal model trials and those conducting observational studies are also called for in order to understand better the dynamic interplay between long-term use of licit and illicit drugs and drugs of treatment, in particular HAART. In the meantime, health-care practitioners and public health educators need to develop appropriate interventions to address non-injection drug use among HIV seropositive individuals.

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References

1. Des Jarlais DC, Friedman SR, Marmor M, Cohen H, Mildvan D, Yancovitz S, Mathur U, el Sadr W, Spira TJ, Garber J. Development of AIDS, HIV seroconversion, and potential co-factors for T4 cell loss in a cohort of intravenous drug users. AIDS. 1987; 1:105–111. [PubMed: 2896511]
2. Munoz A, Carey V, Saah AJ, Phair JP, Kingsley LA, Fahey JL, Ginzburg HM, Polk BF. Predictors of decline in CD4 lymphocytes in a cohort of homosexual men infected with human immunodeficiency virus. Journal of Acquired Immune Deficiency Syndromes. 1988; 1:396–404. [PubMed: 2905743]
3. Weber R, Ledergerber B, Opravil M, Siegenthaler W, Luthy R. Progression of HIV infection in misusers of injected drugs who stop injecting or follow a programme of maintenance treatment with methadone. BMJ. 1990; 301:1362–1365. [PubMed: 1980219]
4. Chaisson RE, Keruly JC, Moore RD. Race, sex, drug use, and progression of human immunodeficiency virus disease. New England Journal of Medicine. 1995; 333:751–756. [PubMed: 7643881]
5. Peterson PK, Gekker G, Chao CC, Schut R, Molitor TW, Balfour HH Jr. Cocaine potentiates HIV-1 replication in human peripheral blood mononuclear cell coculture: Involvement of transforming growth factor-beta. Journal of Immunology. 1991; 146:81–84.
6. Peterson PK, Sharp BM, Gekker G, Portoghese PS, Sannerud K, Balfour HH Jr. Morphine promotes the growth of HIV-1 in human peripheral blood mononuclear cell cocultures. AIDS. 1990; 4:869–873. [PubMed: 2174676]
7. Donahoe RM, Vlahov D. Opiates as potential cofactors in progression of HIV-1 infections to AIDS. Journal of Neuroimmunology. 1998; 83:77–87. [PubMed: 9610676]
8. Klein TW, Friedman H, Specter S. Marijuana, immunity and infection. Journal of Neuroimmunology. 1998; 83:102–115. [PubMed: 9610678]
9. Cabral GA, Dove Pettit DA. Drugs and immunity: cannabinoids and their role in decreased resistance to infectious disease. Journal of Neuroimmunology. 1998; 83:116–123. [PubMed: 9610679]
10. Donahoe RM, Byrd LD, McClure HM, Fultz P, Brantley M, Marsteller F, Ansari AA, Wenzel D, Aceto M. Consequences of opiate-dependency in a monkey model of AIDS [Review]. Advances in Experimental Medicine and Biology. 1993; 335:21–28. [PubMed: 8237597]
11. Veyries ML, Sinet M, Desforges B, Rouveix B. Effects of morphine on the pathogenesis of murine Friend retrovirus infection. Journal of Pharmacology and Experimental Therapy. 1995; 272:498–504.
12. Weber RJ, Gomez-Flores R, Smith JE, Martin TJ. Immune, neuroendocrine, and somatic alterations in animal models of human heroin abuse. Journal of Neuroimmunology. 2004; 147:134–137. [PubMed: 14741445]
13. Pezzotti P, Galai N, Vlahov D, Rezza G, Lyles CM, Astemborski J. Direct comparison of time to AIDS and infectious disease death between HIV seroconverter injection drug users in Italy and the United States: results from the ALIVE and ISS studies. AIDS link to intravenous experiences. Italian Seroconversion Study. Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology. 1999; 20:275–282.
14. The Italian Seroconversion Study. Disease progression and early predictors of AIDS in HIV seroconverted injecting drug users. AIDS. 1992; 6:421–426. [PubMed: 1616637]
15. Prins M, Veugelers PJ. Comparison of progression and non-progression in injecting drug users and homosexual men with documented dates of HIV-1 seroconversion. European Seroconverter Study and the Tricontinental Seroconverter Study. AIDS. 1997; 11:621–631. [PubMed: 9108944]
16. Lyles CM, Margolick JB, Astemborski J, Graham NM, Anthony JC, Hoover DR, Vlahov D. The influence of drug use patterns on the rate of $CD4^+$ lymphocyte decline among HIV-1-infected injecting drug users. AIDS. 1997; 11:1255–1262. [PubMed: 9256944]
17. West JP, Lysle DT, Dykstra LA. Tolerance development to morphine-induced alterations of immune status. Drug and Alcohol Dependence. 1997; 46:147–157. [PubMed: 9250473]

18. Rahim RT, Adler MW, Meissler JJ Jr, Cowan A, Rogers TJ, Geller EB, Eisenstein TK. Abrupt or precipitated withdrawal from morphine induces immunosuppression. Journal of Neuroimmunology. 2002; 127:88–95. [PubMed: 12044979]
19. Wilson LE, Thomas DL, Astemborski J, Freedman TL, Vlahov D. Prospective study of infective endocarditis among injection drug users. Journal of Infectious Diseases. 2002; 185:1761–1766. [PubMed: 12085322]
20. Mientjes GH, van Ameijden EJ, van den Hoek AJ, Goudsmit J, Miedema F, Coutinho RA. Progression of HIV infection among injecting drug users: indications for a lower rate of progression among those who have frequently borrowed injecting equipment. AIDS. 1993; 7:1363–1370. [PubMed: 8267910]
21. Donahoe RM, Nicholson JK, Madden JJ, Donahoe F, Shafer DA, Gordon D, Bokos P, Falek A. Coordinate and independent effects of heroin, cocaine, and alcohol abuse on T-cell E-rosette formation and antigenic marker expression. Clinical Immunology and Immunopathology. 1986; 41:254–264. [PubMed: 3095006]
22. McCance-Katz EF, Rainey PM, Jatlow P, Friedland G. Methadone effects on zidovudine disposition. AIDS Clinical Trials Group 262. Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology. 1998; 18:435–443.
23. Rainey PM, Friedland G, McCance-Katz EF, Andrews L, Mitchell SM, Charles C, Jatlow P. Interaction of methadone with didanosine and stavudine. Journal of Acquired Immune Deficiency Syndromes. 2000; 24:241–248. [PubMed: 10969348]
24. Barkan SE, Melnick SL, Preston-Martin S, Weber K, Kalish LA, Miotti P, Young M, Greenblatt R, Sacks H, Feldman J. The Women's Interagency HIV Study: WIHS Collaborative Study Group. Epidemiology. 1998; 9:117–125. [PubMed: 9504278]
25. Centers for Disease Control and Prevention. Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. Morbidity and Mortality Weekly Report. 1993; 41:1–19.
26. Cohen MH, French AL, Benning L, Kovacs A, Anastos K, Young M, Minkoff H, Hessol NA. Causes of death among women with human immunodeficiency virus infection in the era of combination antiretroviral therapy. American Journal of Medicine. 2002; 113:91–98. [PubMed: 12133746]
27. National Institutes of Alcohol Abuse and Alcoholism. National Longitudinal Alcohol Epidemiologic Survey. 2002. Available at: http://www.niaaa.nih.gov
28. Anastos K, Barron Y, Miotti P, Weiser B, Young M, Hessol N, Greenblatt RM, Cohen M, Augenbraun M, Levine A, Munoz A. Risk of progression to AIDS and death in women infected with HIV-1 initiating highly active antiretroviral treatment at different stages of disease. Archives of International Medicine. 2002; 162:1973–1980.
29. McFarland W, Chen S, Hsu L, Schwarcz S, Katz M. Low socioeconomic status is associated with a higher rate of death in the era of highly active antiretroviral therapy, San Francisco. Journal of Acquired Immune Deficiency Syndromes. 2003; 33:96–103. [PubMed: 12792361]
30. Celentano DD, Galai N, Sethi AK, Shah NG, Strathdee SA, Vlahov D, Gallant JE. Time to initiating highly active antiretroviral therapy among HIV-infected injection drug users. AIDS. 2001; 15:1707–1715. [PubMed: 11546947]
31. DHHS & Henry J. Kaiser Family Foundation. Panel on Clinical Practices for the Treatment of HIV Infection. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents, February 2002 Revision. 2002. Available at: http://AIDSinfo.nih.gov
32. Cox, DR.; Oakes, D. Analysis of Survival Data. London: Chapman & Hall; 1984.
33. Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. Statistics in Medicine. 1995; 14:1707–1723. [PubMed: 7481205]
34. Donahoe RM. Multiple ways that drug abuse might influence AIDS progression: clues from a monkey model. Journal of Neuroimmunology. 2004; 147:28–32. [PubMed: 14741423]
35. Tashkin DP. Evidence implicating cocaine as a possible risk factor for HIV infection. Journal of Neuroimmunology. 2004; 147:26–27. [PubMed: 14741422]

36. Cook JA, Cohen MH, Grey D, Kirstein L, Burke J, Anastos K, Palacio H, Richardson J, Wilson TE, Young M. Use of highly active antiretroviral therapy in a cohort of HIV-seropositive women. American Journal of Public Health. 2002; 92:82–87. [PubMed: 11772767]
37. Cohen MH, Cook JH, Grey D, Young M, Hanau LH, Tien P, et al. Medically eligible women who do not use HAART: the importance of abuse, drug use and race. American Journal of Public Health. 2004; 94:1147–1151. [PubMed: 15226135]
38. Caiaffa WT, Vlahov D, Graham NMH, Astemborski J. Drug smoking, *Pneumocystis carinii* pneumonia, and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus-seropositive injection drug users. American Journal of Respiratory and Critical Care Medicine. 1994; 150:1493–1498. [PubMed: 7952605]
39. Webber MP, Schoenbaum EE, Gourevitch MN, Buono D, Klein RS. A prospective study of HIV disease progression in female and male drug users. AIDS. 1999; 13:257–262. [PubMed: 10202832]
40. Hirschtick RE, Glassroth J, Jordan MC. Bacterial pneumonia in persons infected with the human immunodeficiency. New England Journal of Medicine. 1995; 333:845–851. [PubMed: 7651475]
41. Gardner LI, Holmberg SD, Moore J, Arnsten JH, Mayer KH, Rompalo A, Schuman P, Smith DK. Use of highly active antiretroviral therapy in HIV-infected women: impact of HIV specialist care. Journal of Acquired Immune Deficiency Syndromes. 2002; 29:69–75. [PubMed: 11782593]
42. O'Connor PG, Selwyn PA, Schottenfeld RS. Medical care for injection-drug users with human immunodeficiency virus infection. New England Journal of Medicine. 1994; 331:450–459. [PubMed: 8035842]
43. Arnsten JH, Demas PA, Grant RW, Gourevitch MN, Farzadegan H, Howard AA, Schoenbaum EE. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. Journal of General International Medicine. 2002; 17:377–381.
44. Howard AA, Arnsten JH, Lo Y, Vlahov D, Rich JD, Schuman P, Stone VE, Smith DK, Schoenbaum EE. A prospective study of adherence and viral load in a large multicenter cohort of HIV-infected women. AIDS. 2002; 16:2175–2182. [PubMed: 12409739]
45. Wilson TE, Barron Y, Cohen M, Richardson J, Greenblatt R, Sacks HS, Young M. Adherence to antiretroviral therapy and its association with sexual behavior in a national sample of women with human immunodeficiency virus. Clinical Infectious Diseases. 2002; 34:529–534. [PubMed: 11797182]
46. Hessol NA, Schwarcz S, Ameli N, Oliver G, Greenblatt RM. Accuracy of self-reports of acquired immunodeficiency syndrome and acquired immunodeficiency syndrome-related conditions in women. American Journal of Epidemiology. 2001; 153:1128–1133. [PubMed: 11390333]
47. Latkin CA, Vlahov D, Anthony JC. Socially desirable responding and self-reported HIV infection risk behaviors among intravenous drug users. Addiction. 1993; 88:517–526. [PubMed: 8485429]
48. Landay A, Benning L, Bremer J, Weiser B, Burger H, Nowicki M, Kovacs A. Correlates of immune activation marker changes in human immunodeficiency virus (HIV)-seropositive and high-risk HIV-seronegative women who use illicit drugs. Journal of Infectious Diseases. 2003; 188:209–218. [PubMed: 12854075]

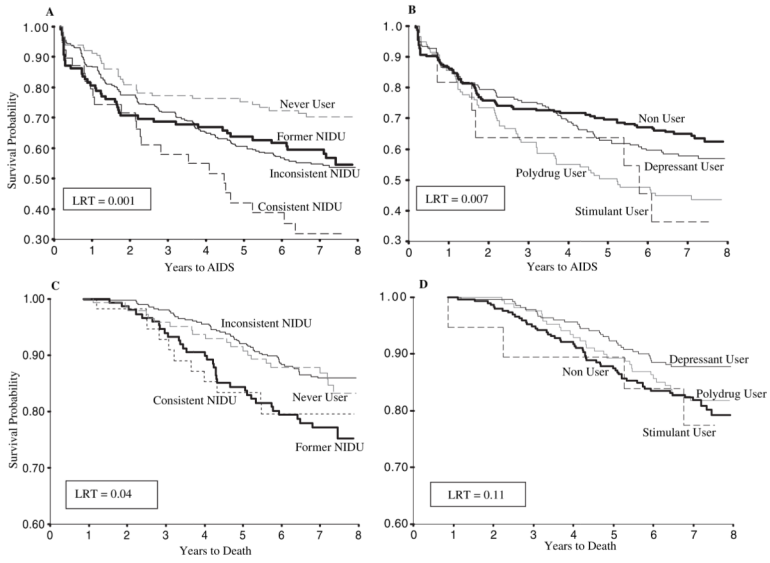

Figure 1.

Kaplan–Meier curves of cumulative probabilities of survival for AIDS (n = 701) and death (n = 1046) by pattern and type of NIDU among HAART users, WIHS. LRT: log-rank test

Table 1

Baseline socio-demographic and health-care utilization characteristics of WIHS participants by pattern and type of non-injection drug use (n = 1046).

	Drug use pattern						Drug use type				
Characteristic	**Total sample**	**Never use**	**Former use**	**Inconsistent use**	**Consistent use**	**Signif.**	**Non-use**	**Depressant use**	**Stimulant use**	**Polydrug use**	**Signif.**
Total *n*	1046	202	231	505	108		433	348	30	235	
Demographics											
Mean age, years (SD)	36.3 (7.9)	35.5 (9.7)	37.9 (6.9)	35.4 (7.4)	37.9 (8.1)	< 0.001	36.8 (8.4)	35.2 (8.2)	34.3 (4.3)	37.1 (6.8)	0.005
Race/ethnicity											
African American	55	38	58	59	59	< 0.001	49	47	83	74	< 0.001
Hispanic	25	48	20	16	27		33	25	13	14	
White	17	11	20	22	11		16	24	3	10	
Other	3	3	2	3	3		2	4	–	1	
Education (< HS)	34	40	25	37	33	0.005	32	32	43	41	0.047
Yearly income (= $12 000)	58	55	51	63	60	0.028	47	46	28	27	< 0.001
Currently employed (no)	76	70	74	79	79	0.063	72	71	83	90	< 0.001
Receiving public assistance	58	48	58	62	65	0.007	53	57	60	70	< 0.001
Health care											
Health insurance coverage	85	74	93	85	85	< 0.001	84	86	70	86	0.127
Doctors' visit (last 2 months)	86	84	87	86	85	0.768	86	88	83	84	0.448
ER visit (last 2 months)	18	13	16	19	24	0.102	15	16	37	24	0.001
Drug treatment (last 6 months)	22	NA	30	28	19	< 0.001	16	19	33	37	< 0.001

Results are shown as percentage of total unless otherwise stated. NA = not applicable.

Table 2

Baseline immunological and virological status, antiretroviral utilization and clinical characteristics by non-injection drug use pattern and by type of drug used (n = 1046).

	Drug use pattern					Drug use type				
Characteristic	**Never use**	**Former use**	**Inconsistent use**	**Consistent use**	**Signif.**	**Non-use**	**Depressant use**	**Stimulant use**	**Polydrug use**	**Signif.**
Total *n*	202	231	505	108		433	348	30	235	
AIDS cases*	31	40	43	50	0.023	35	40	63	49	0.013
All-cause deaths	27	38	20	41	< 0.001	33	19	43	27	< 0.001
AIDS-related deaths	19	20	12	27	< 0.001	20	14	33	15	< 0.001
Baseline $CD4^+$ cell count/μl										
< 200	46	46	33	43	0.003	46	38	53	27	< 0.001
200–350	30	29	35	27		29	33	20	35	
> 350	24	25	31	33		25	29	27	38	
Baseline HIV RNA (copies/ml)										
< 4000	17	21	25	18	0.002	19	25	27	23	0.002
4000–40 000	26	24	33	29		25	30	27	36	
> 40 000	57	55	42	53		56	45	46	41	
HAART use (yes)	74	65	81	53	< 0.001	69	79	63	73	0.007

Results are shown as percentage of total. *Based on n = 701 participants not reporting a clinically defined AIDS condition at baseline.

Table 3

Factors affecting the probability of progression to AIDS by drug patterns and type among NIDU with $CD4^+$ < = 500 (*n* = 701).

Predictor variable	Crude HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)
Drug pattern			
Never user	1.00		1.00
Former user	1.55 (1.05–2.30)		1.56 (1.05–2.32)
Inconsistent user	1.41 (1.00–1.98)		1.63 (1.15–2.30)
Consistent user	2.37 (1.52–3.70)		2.52 (1.60–3.96)
Drug type			
Non-use	1.00	1.00	
Depressant-only use	1.07 (0.81–1.41)	1.19 (0.90–1.58)	
Stimulant-only use	1.88 (0.98–3.59)	2.04 (1.06–3.94)	
Polydrug use	1.39 (1.04–1.87)	1.65 (1.21–2.25)	
HAART use (yes)	0.81 (0.60–1.09)	0.79 (0.58–1.07)	0.82 (0.60–1.12)
$CD4^+$ cell count/μl at baseline			
< 100	1.00	1.00	1.00
101–200	0.55 (0.39–0.78)	0.61 (0.43–0.87)	0.61 (0.43–0.87)
201–350	0.32 (0.23–0.44)	0.36 (0.26–0.51)	0.38 (0.27–0.53)
351–500	0.20 (0.14–0.29)	0.24 (0.17–0.35)	0.25 (0.17–0.36)
HIV-1 RNA at baseline			
≤ 4000	1.00	1.00	1.00
4001–40 000	2.11 (1.45–3.06)	1.81 (1.23–2.64)	1.81 (1.24–2.65)
> 40 000	3.29 (2.32–4.66)	2.38 (1.65–3.44)	2.41 (1.68–3.48)
ER visit in last 2 months	1.44 (1.06–1.96)	1.39 (1.01–1.91)	1.38 (1.00–1.90)

*Adjusted model includes all covariates listed in table.

Table 4

Factors affecting the probability of progression to all-cause and AIDS related deaths by drug patterns and type among NIDU, $CD4^+ <= 500$ (n = 1046).

	All cause mortality			Aids-related mortality		
Predictor variable	**Crude HR (95% CI)**	**Adjusted* HR (95% CI)**	**Adjusted* HR (95% CI)**	**Crude HR (95% CI)**	**Adjusted* HR (95% CI)**	**Adjusted* HR (95% CI)**
Drug pattern						
Never user	1.00	–	1.00	1.00	1.00	–
Former user	1.49 (1.06–2.08)	–	1.48 (1.05–2.09)	1.12 (0.74–1.72)	1.27 (0.82–1.96)	–
Inconsistent user	0.63 (0.45–0.88)	–	0.91 (0.65–1.27)	0.56 (0.38–0.84)	0.99 (0.66–1.50)	–
Consistent user	1.85 (1.24–2.75)	–	1.43 (0.95–2.15)	1.66 (1.02–2.68)	1.42 (0.87–2.33)	–
Drug type						
Non-use	1.00	1.00	–	1.00	–	1.00
Depressant only use	0.51 (0.39–0.69)	0.71 (0.53–0.95)	–	0.60(0.42–0.86)	–	0.95 (0.66–1.37)
Stimulant only use	1.42 (0.80–2.51)	1.45 (0.82–2.58)	–	1.81 (0.94–3.48)	–	1.65 (0.85–3.20)
Polydrug use	0.72 (0.54–0.97)	0.88 (0.65–1.19)	–	0.64 (0.43–0.96)	–	0.89 (0.59–1.31)
Age (continuous)	1.03 (1.02–1.05)	1.03 (1.02–1.05)	1.03 (1.01–1.05)	1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.01 (0.99–1.03)
$CD4^+$ count/μl (baseline)						
< 100	1.00	1.00	1.00	1.00	1.00	1.00
101–200	0.39 (0.28–0.52)	0.57 (0.42–0.79)	0.55 (0.40–0.75)	0.25 (0.17–0.37)	0.42 (0.28–0.63)	0.42 (0.28–0.64)
201–350	0.18 (0.13–0.25)	0.23 (0.16–0.31)	0.22 (0.15–0.31)	0.09 (0.05–0.14)	0.12 (0.07–0.21)	0.13 (0.08–0.21)
> 350	0.13 (0.09–0.19)	0.16 (0.11–0.24)	0.16 (0.11–0.24)	0.05 (0.03–0.09)	0.07 (0.04–0.14)	0.07 (0.04–0.14)
HIV-1 RNA copies/ml (baseline)						
≤ 4000	1.00	1.00	1.00	1.00	1.00	1.00
4001–40 000	1.22 (0.79–1.88)	1.32 (0.85–2.06)	1.33 (0.85–2.07)	2.38 (1.12–5.04)	2.27 (1.06–4.88)	2.32 (1.08–4.97)
> 40 000	3.42 (2.37–4.94)	2.35 (1.56–3.53)	2.34 (1.56–3.51)	8.33 (4.25–16.35)	3.81 (1.85–7.83)	3.86 (1.89–7.93)
HAART use (yes)	0.12 (0.09–0.15)	0.09 (0.07–0.12)	0.09 (0.07–0.12)	0.09 (0.06–0.12)	0.07 (0.05–0.10)	0.07 (0.05–0.09)
ER visit in last 2 months	1.49 (1.17–1.97)	1.17 (0.88–1.57)	1.19 (0.89–1.59)	1.56 (1.10–2.21)	1.15 (0.80–1.65)	1.11 (0.77–1.59)

*Adjusted models includes all covariates listed in table.