Non-injection Drug Use and HIV Disease Progression in the Era of Combination Antiretroviral Therapy

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Abstract

Little is known about the effects of non-injection drug use (NIDU) on HIV antiretroviral treatment outcomes. We conducted a systematic literature search and identified 9 publications from prospective cohort studies investigating the relationship between NIDU and clinical HIV disease progression. Hazard ratios from studies estimating the effect of drug use on time to AIDS-related mortality ranged from 0.89 to 3.61 and only two of these were statistically significant. Hazard ratios from studies assessing time to an AIDS-defining event ranged from 1.19 to 2.51, with 8 of the 14 estimates falling between 1.55 to 1.65 regardless of drug use definition and measurement of use or frequency. It is suggested that NIDU may have a moderate effect of increasing the risk of progression to AIDS, but its impact on AIDS-related mortality is uncertain. NIDU may affect HIV antiretroviral treatment outcomes primarily through interaction with antiretroviral therapy and, to a lesser extent, through immune-modulation and deterioration of general health. The limitations about published studies are discussed and future perspectives on research on this topic are provided.

Keywords

Non-injection drug use; HIV; antiretroviral therapy; disease progression

1. Introduction

Illicit drug use is an important factor in the HIV/AIDS pandemic. The annual prevalence of illicit drug use is 4.8% worldwide, representing 208 million people between 15–64 years of age who have used an illicit drug at least once in the past 12 months (United Nations Office of Drugs and Crime, 2008); only 5–10% of those drug users are injecting drugs (Mathers, et al., 2008). Injection drug use (IDU), particularly sharing of contaminated injection tools, is an efficient means of HIV transmission, and an estimated 3 million (range 1–7 million) injectors may be living with HIV. Non-injection drug use (NIDU), defined as the non-

medical, self-administration of any psychoactive substance by any route other than intravenous (e.g. via intranasal, inhalation, or ingestion), is also an important risk factors indirectly associated with HIV infection by various mechanisms: (1) the effects of drug use adversely affect judgment and decision-making, resulting in high-risk sexual behavior; (2) trading sex or participating in risky sexual practices in exchange for drugs; and (3) the immune-modulating effects of drugs have been shown to increase HIV viral load, decrease host defense to viral exposure, up-regulate HIV-specific cellular receptors, and increase the presence of lesions due to other bacterial or viral infections (Astemborski, Vlahov, Warren, Solomon, & Nelson, 1994; Brewer, Zhao, Metsch, Coltes, & Zenilman, 2007; Cabral, 2006; de Souza, Diaz, Sutmoller, & Bastos, 2002; Edlin, et al., 1994; Ramirez-Valles, Garcia, Campbell, Diaz, & Heckathorn, 2008).

Illicit drug use, and NIDU in particular, are common among HIV-infected individuals. A nationally representative probability sample in the United States of persons receiving HIV care found that 40% reported using an illicit drug other than marijuana during the preceding 12 months (Bing, et al., 2001). Another study found that 28% of HIV-infected men who have sex with men (MSM) reported illicit drug use in the past 30 days (Cofrancesco, et al., 2008). The Women's Interagency HIV Study (WIHS) specifically evaluated the prevalence of NIDU among a prospective cohort in 6 U.S. sites and found 59% of HIV-positive women were actively using non-injection drugs (Kapadia, et al., 2005). Many other studies of HIV-infected individuals have found the prevalence of recent marijuana use to range from 10% to 63% and recent cocaine use to range from 4% to 47% (Cofrancesco, et al., 2008; Hessol, et al., 2007; Prestage, et al., 2007; Purcell, Moss, Remien, Woods, & Parsons, 2005; Sohler, et al., 2007; Tucker, Burnam, Sherbourne, Kung, & Gifford, 2003).

Since highly active combination antiretroviral therapy (cART) became available in the mid-1990s, the effect of illicit drug use on cART treatment outcomes has become a medical and public health concern and has been widely studied, primarily among IDUs. The Antiretroviral Therapy Cohort Collaboration (ART-CC) (Antiretroviral Therapy Cohort Collaboration, 2007; Egger, et al., 2002; May, et al., 2007) and others (Nicastri, et al., 2005; Perez-Hoyos, et al., 2006) have reported a positive relationship between IDU and more rapid disease progression. Some smaller studies, however, have reported no association (Eskild, et al., 1997; Pehrson, Lindback, Lidman, Gaines, & Giesecke, 1997; Wood, et al., 2008). Numerous methodological issues arise from these studies. First, the measure of IDU is often based on reported HIV transmission category. This measure likely represents a history of drug use rather than active drug use and, therefore, misclassification may occur. Furthermore, it does not distinguish duration and/or frequency of drug injection. Second, the IDUs are often compared to MSM, which necessarily restricts the results to men, discarding all information on IDUs who are women. Few studies have assessed the effect of active IDU, duration, or frequency with disease progression and they have reported inconsistent findings (Greub, et al., 2000; Pezzotti, et al., 1999).

Non-injection drug use likely plays an important role in HIV disease progression because it shares similar biologic, social, and behavioral consequences as IDU. Nevertheless, its role in HIV disease progression is an understudied medical and public health concern given that the majority of illicit drug users consume drugs via non-injection. The purpose of this review is to systematically report on studies of NIDU and its effect on HIV disease progression in the cART era.

2. Methods

2.1. Definition of exposure and outcome variables

For the purposes of this review, the exposure of interest is NIDU. Studies were considered to have measured NIDU if the study definition of drug use included at least one reference to a non-injection drug (such as marijuana), crack (a form of inhalational cocaine), or use of an illicit drug via non-injection routes. As such, some studies have a general definition of drug use that combines both injection and non-injection use. Alcohol abuse is often considered NIDU, but will not be considered here because a separate review by Azar et al. will be published soon (Azar, Springer, Meyer, & Altice, 2010).

The outcome of interest in this review is clinical HIV disease progression identified as an AIDS-defining illness or AIDS-related death. Studies that focused only on surrogate measures of disease progression, such as CD4 cell count decline or an increase in HIV viral load, were not considered. While these are precursors to AIDS, they may vary over time and are reversible with effective treatment. A clinical diagnosis of AIDS is not a reversible event (Centers for Disease Control and Prevention, 1992).

2.2. Search strategy

We searched the PubMed database to identify peer-reviewed studies of NIDU and HIV disease progression published between January 1996 and December 2009. We used four categories of terms for literature search: study type, drug use, HIV/AIDS, and HIV disease progression. Specifically, the following combination of terms was used: (prospective OR longitudinal OR cohort) AND ("substance abuse" OR "drug abuse" OR "drug use" OR marijuana OR heroin OR amphetamine OR cocaine OR crack OR opioid OR opiate) AND ("HIV OR AIDS") AND ("disease progression" OR "AIDS-defining illness" OR "AIDS-defining event" OR death).

2.3. Selection criteria and data extraction

All abstracts were independently reviewed by two of the authors (AMK and HQ) to determine which studies should be selected for more detailed review. When there was disagreement about whether to further review a study, the authors reviewed the abstract together and came to a consensus. Studies that met the following criteria were selected for inclusion in this review: non-injection drug use and disease progression as defined above, all or part of the follow-up occurring in 1996 or later, and published in English. References from included studies were reviewed to identify additional studies.

A secondary purpose of this review was to characterize the specific mechanisms of HIV disease progression, including immune-modulating effects of illicit drugs, utilization of and adherence to cART, and possible pharmacological interactions between antiretrovirals (ARVs) and illicit drugs. Published studies on these topics were not identified in a systematic fashion.

3. Results

3.1. Study selection and study characteristics

Abstracts from 315 publications were reviewed. Twenty-two papers were not in English and 5 were concluded prior to 1996. An additional 279 papers were excluded due to one or more of the following reasons: (1) study was conducted among IDUs only; (2) study did not use AIDS-defining even (ADE) or AIDS-related mortality as study endpoints (e.g., using CD+ cell count or HIV viral load); (3) study did not use drug use as the primary or confounding risk factor; and (4) study was not a prospective cohort design. Cross-sectional studies were

not included because they could not ascertain temporal relationship of exposure (drug use) and outcome (ADE), and some used history data which could not determine the frequency and/or activity of drug use. A total of 9 publications met the inclusion criteria and were included in this review of the relationship of NIDU and HIV progression to ADE or AIDS-related mortality (Anastos, et al., 2005; Cohen, et al., 2002; Cook, et al., 2008; Cook, et al., 2004; Hershow, et al., 2005; Ickovics, et al., 2001; Kapadia, et al., 2005; Lucas, et al., 2006; Thorpe, et al., 2004).

All of the studies were performed in the United States, and most were conducted between 1994 and 2004, except two that began in 1989 (Hershow, et al., 2005; Thorpe, et al., 2004). Of note is that 8 of the studies were done among women only, with 5 of these coming from the WIHS (Anastos, et al., 2005; Cohen, et al., 2002; Cook, et al., 2008; Cook, et al., 2004; Kapadia, et al., 2005). Two publications used pregnant women study subjects and both were from the Women and Infant Transmission Study (WITS) (Hershow, et al., 2005; Thorpe, et al., 2004).

3.2. Measurements of exposure and outcome variables

The proportion of study participants who used drugs during the study period ranged from 25.5% (Cohen, et al., 2002) to 58.6% (Kapadia, et al., 2005). Five of the studies had the primary purpose of assessing drug use on disease progression (Cohen, et al., 2002; Cook, et al., 2008; Kapadia, et al., 2005; Lucas, et al., 2006; Thorpe, et al., 2004), while the remaining studies were not specifically performed to assess for the effect of drug use, but they did report an effect of drug use as a covariate. Three studies had a measure of drug use that included frequency rather than use or non-use of a particular drug or drugs (Cook, et al., 2008; Kapadia, et al., 2005; Lucas, et al., 2006).

Three studies assessed time to AIDS-related mortality only (Cohen, et al., 2002; Cook, et al., 2004; Ickovics, et al., 2001), 2 assessed time to AIDS-defining event only (Lucas, et al., 2006; Thorpe, et al., 2004), 3 performed separate analyses for both AIDS-related mortality and AIDS-defining event (Anastos, et al., 2005; Cook, et al., 2008; Kapadia, et al., 2005), and 1 study combined AIDS-defining event and all-cause mortality as the outcome under study (Hershow, et al., 2005).

3.3. Association of NIDU and HIV disease progression

Among 6 studies estimating the effect of drug use on time to AIDS-related mortality (Table 1), the point estimates of hazard ratios ranged from 0.89 to 3.61. Of the 11 hazard ratios, 5 were equal to or just below 1.0 while the remaining 6 were ≥1.27. Only two of these, however, were statistically significant (Anastos, et al., 2005; Cook, et al., 2008). The study by Cook et al. is a good example of how measurement of drug use can impact the results: compared with non-users, persistent drug users had nearly 4 times the risk of death (HR=3.6) while intermittent drug users had nearly the same risk (HR=0.9) (Cook, et al., 2008). The other positive study showed that current crack, cocaine, or heroine users (route unspecified) had 2.35 times the hazard of mortality than non-users ($p < 0.05$) (Anastos, et al., 2005).

In contrast to studies assessing time to AIDS-related mortality, there was more consistency among studies assessing time to an AIDS-defining event. Hazard ratios ranged from 1.19 to 2.51 with 8 of the 14 estimates falling between 1.55 to 1.65 regardless of drug use definition, measurement of use or frequency, or whether drug use was of primary or secondary interest. Eleven of 14 estimates were statistically significant (Table 2). Nearly all studies adjusted for age, race, cART use, CD4 count or percent, and viral load, but beyond this there was great heterogeneity in the covariates of the multivariable models.

3.4. Mediators of drug use and disease progression

Drug use, either non-injection or injection, may affect HIV disease progression to AIDS or AIDS-related mortality through multiple mechanisms (Figure 1). Compared with HIV-infected people who do not use drugs, HIV-infected drug users may have poorer general health due to malnutrition and co-morbidities such as sexually transmitted infections, tuberculosis, and hepatitis (Girardi, et al., 2005; Hendricks, Erzen, Wanke, & Tang, 2010; Kuyper, et al., 2005; Lelutiu-Weinberger, et al., 2009; Mitchell & Latimer, 2009; Quach, et al., 2008). Poorer nutrition and co-morbidities have been associated with suboptimal immune reconstitution or HIV virologic failure (Hermans, et al., 2010; Modjarrad & Vermund, 2010; Quach, et al., 2008; Smit, et al., 2008).

In vitro studies with animal models have shown that illicit drugs such as amphetamines, cocaine, marijuana, and opiates may affect HIV disease outcomes by altering immune function and increasing susceptibility to infection. This immunomodulatory effect is mainly receptor-mediated, either directly by interaction with specific receptors on immune cells or indirectly by reaction with similar receptors on cells of the nervous system (Friedman, Newton, & Klein, 2003). However, there is a paucity of controlled epidemiological studies that definitively correlate immunosuppressive effects with increased incidence of infections or immune disorders in humans, including disease progression to AIDS (Cabral, 2006; Friedman, Pross, & Klein, 2006).

However, the primary effect of drugs on HIV disease progression might be mediated via factors that may limit access and/or adherence to cART (Celentano & Lucas, 2007). In addition, the pharmacokinetic interactions between ARVs and drugs of abuse may also reduce the effectiveness of cART.

NIDU and access to cART—Drug use is associated with delayed initiation of cART (starting cART when meeting treatment guidelines) (Rodriguez-Arenas, et al., 2006; Tegger, et al., 2008), and deferred initiation of combination therapy is associated with a higher risk of mortality (Sterne, et al., 2009). While there are few studies assessing NIDU and cART initiation, several studies have investigated NIDU and cART utilization (currently being prescribed ART). A study assessing the relationship between current cART use and abuse of heroin, cocaine, sedative, amphetamine, and marijuana in the last 12 months found that the odds ratios for each drug ranged from 0.40 to 0.75 while controlling for CD4 count, AIDS, and other sociodemographic variables (Turner, et al., 2001). Among patients with CD4 cell counts ≤350 who warranted treatment per the current guidelines, NIDU (including heavy alcohol use) in the past year was associated with not having been on ARVs in the previous 6 months (OR 0.35; 95% CI: 0.21 – 0.57 (Sohler, et al., 2007). Another study also showed that active crack/cocaine users with an AIDS diagnosis were less likely to have been prescribed cART than non-users who also had an AIDS diagnosis (OR 0.40; 95% CI: 0.19 – 0.85) (Cofrancesco, et al., 2008).

Of the 9 studies we reviewed for effects of NIDU on HIV disease progression, only two reported descriptive data on cART use and both showed that a lower proportion of drug users were on cART, though they had lower CD4 cell counts at baseline compared with non-users (Cook, et al., 2008; Lucas, et al., 2006).

NIDU and adherence to cART—Illicit drug use is a consistently reported barrier to cART adherence (Hinkin, et al., 2007; Howard, et al., 2002; Mills, et al., 2006; Tucker, et al., 2003; Wilson, et al., 2002). Cocaine, marijuana, amphetamine, or sedative use in the prior month were associated with nonadherence with odds ratios ranging from 1.6 to 2.3 for each drug type (Tucker, et al., 2003). Another study reported that NIDU in the prior 6 months was associated with an overall adherence of <90% during the study period (OR 4.1;

95% CI: 1.8 – 9.3), with stimulant users having seven times the odds of non-adherence compared to those who didn't use any drugs (Hinkin, et al., 2007). In the WIHS study, use of crack, cocaine or heroin was associated with a lower level of adherence to treatment regimens (<95%) (OR 2.27; 95% CI: 1.32 – 3.91) (Wilson, et al., 2002). Drug use is frequently co-morbid with depression, anxiety and severe mental illness (Chander, Himelhoch, & Moore, 2006; Pence, Miller, Gaynes, & Eron, 2007; Torrens, Gilchrist, & Domingo-Salvany, 2010), which are well-established barriers to adherence.

Of the 9 studies we reviewed, only one provided descriptive information on adherence and showed that persistent and inconsistent users were less likely to report >=95% adherence at every study visit compared with non-users (7% and 16% vs. 29%; p<0.001) (Cook, et al., 2008). Another study reported that adherence did not differ between NIDU and non-users but did not provide the data (Kapadia, et al., 2005). Two studies adjusted for adherence in the analyses of disease progression, but did not provide descriptive data on adherence by drug use category (Anastos, et al., 2005; Lucas, et al., 2006).

NIDU and ARV drug interactions—Several commonly abused drugs, including cocaine, marijuana, ecstasy and amphetamines as well as opioid agonist medications such as methadone and buprenorphine, are metabolized by the cytochrome P450 (CYP) enzymes (Gruber & McCance-Katz, 2010; Lakhman, Ma, & Morse, 2009; Pasanen, et al., 1995; Wynn, Cozza, Zapor, Wortmann, & Armstrong, 2005), as are antiretrovirals (ARVs), particularly non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) (Kakuda, Scholler-Gyure, & Hoetelmans, 2010; Seden, Back, & Khoo, 2009; Slish, et al., 2007; Wynn, et al., 2004; Zapor, Cozza, Wynn, Wortmann, & Armstrong, 2004). In addition, both abused drugs and ARVs may induce and inhibit specific CYP450 enzymes (Antoniou & Tseng, 2002; Hariparsad, et al., 2004; Harrington, Woodward, Hooton, & Horn, 1999; Ma, et al., 2005; Zhou, Xue, Yu, Li, & Wang, 2007). The pharmacokinetic interactions can result in increased toxicity or reduced effectiveness (Altice, Kamarulzaman, Soriano, Schechter, & Friedland, 2010; Baker, et al., 2010; Clarke, et al., 2001; Iribarne, et al., 1998; Khalsa & Elkashef, 2010; McCance-Katz, Moody, et al., 2006; McCance-Katz, et al., 2007; McCance-Katz, Rainey, et al., 2006; Wynn, et al., 2005). For example, amphetamines are metabolized by CYP2D6, and amphetamine abusers are likely to have an increased serum concentration level and increased risk of toxicity when using CYP inhibitors, e.g., ritonavir, nelfinavir or efavirenz (Lin, et al., 1997; Lin, et al., 1995). NNRTIs and several PIs may induce methadone metabolism and decrease methadone plasma concentrations in methadone maintenance patients, and cause withdrawal symptoms (Gruber & McCance-Katz, 2010). Therefore, patients should have a higher dose to avoid withdrawal symptoms when they start AVRs and have a lower dose to avoid toxicity when they stop ARVs. On the other hand, methadone can reduce absorption of ARV (e.g., stavudine) in the gastrointestinal (GI) tract,(Rainey, et al., 2000) which may result in failure of ARV treatment and development of HIV drug resistance; methadone can also inhibit glocuronidation of zidovudine (McCance-Katz, Rainey, Jatlow, & Friedland, 1998), which may lead to toxicity.

4. Discussion

4.1. Summary of findings

This is the first review to specifically address the effect of NIDU on clinical HIV disease progression in the new cART era. Among the studies included in this review, there is considerable agreement about the effect of NIDU on increased progression to AIDS, regardless of whether NIDU duration or frequency was measured. The effects seem to be moderate, as 8 of the 14 hazard ratios in the 6 papers were between 1.55 and 1.65. It should

be noted that 7 papers came from either the WIHS or the WITS parent study; therefore, some agreement is to be expected. However, the reviewed studies had inconsistent results for the association of NIDU and AIDS-related mortality, and the hazard ratios were both above and below the null value of 1.0. One possible explanation is that there is truly no significant effect that can be detected with the available sample sizes in the reviewed studies. An alternative explanation is due to inaccurate measurement of death, as death was ascertained using multiple data sources instead of solely being based on clinical evaluation.

It should be noted that the collective findings from this review may have limited generalizability given that 8 of the 9 studies were conducted exclusively among women in the WIHS and WITS studies, with only one study in both men and women (Lucas, et al., 2006). More studies on this topic are highly recommended considering high prevalence of NIDU among HIV-infected patients.

4.2. Methodological concerns and challenges

A number of methodological concerns and challenges remain both in measurement and analysis in the studies assessing drug use and HIV disease progression. The type of drugs abused, route of administration, dose and frequency, and polydrug use may have different effects on HIV disease progression. The challenge of collecting information on all aspects of drug use is daunting, as a drug user may use multiple drugs, change dose, frequency and administration route of drugs over time, and even stop and resume using drugs in different periods of his lifetime. The vague definitions of IDU or NIDU, active drug use versus history of drug use, and heroin use opposed to cocaine use in data analysis are likely to lead to misclassification of drug use groups.

There is a similar challenge for measurement of outcome variables, particularly death. It is often difficult to differentiate AIDS-related causes from non-AIDS-related causes particularly for drug users who also have high risks of non-AIDS mortality. In addition, death is often assessed based on secondary databases, e.g., National Death Index, and the misclassification of AIDS-related and non-AIDS-related mortality is likely and may lead to biased analysis results.

Adherence to ARV regimens is a crucial determinant of treatment outcome that is also affected by drug use. Measurement of treatment adherence is challenging, and there is currently no readily available measure used in routine clinical practice. Patient self-report is easy to implement but is subjected to bias and poor accuracy; microelectronic monitoring systems (MEMS) are accurate but expensive; therapeutic monitoring of plasma drug concentrations is infeasible for routine use at every clinic visit; use of pharmacy data on drug pick-up is more reliable than self-reporting but may not elucidate actual patterns of suboptimal adherence or short-term changes in adherence. Even if data on treatment adherence are properly collected, it remains a question of over-adjustment in the data analysis of NIDU and HIV disease progression. Poor adherence might be one mechanism by which NIDU impacts HIV disease progression. Meanwhile, there may be other biologic mechanisms by which NIDU hastens disease progression. Differentiating the biologic effects of drug use from the behavioral effects of adherence is critical in data analysis. Some studies have addressed this issue by adjusting for adherence during the study, but it is generally not advised to adjust for variables that lie on the causal pathway from exposure (NIDU) to outcome (AIDS) (Rothman, Greenland, & Lash, 2008) unless specific assumptions are made or complex analytic methods are used (Cole & Hernan, 2002; Kaufman, Maclehose, & Kaufman, 2004; Rothman, et al., 2008).

Another methodological issue is the time of entry to study cohort. The ideal time is at HIV infection,(Perez-Hoyos, et al., 2006) or prior to the availability of cART (Dorrucci, Pezzotti,

Phillips, Alliegro, & Rezza, 1997; Pezzotti, et al., 1996). If the time of infection is not considered in studies assessing HIV disease progression, study findings may be biased toward a positive association with disease progression, as drug users are more likely to enter care later than non-users and have later HIV disease stages at study entry. Though baseline immunologic and virologic data can be adjusted in data analysis, residual confounding of the impact of disease stage is still possible considering the length of the HIV latent period. An alternative time of entry to study is at initiation of cART. In this case, drug users may still have worse baseline immunologic and virologic status than non-users, but because both groups meet the criteria for initiating cART, the findings may be less biased.

4.3. Future perspectives

As few independent studies have been conducted to evaluate NIDU and HIV disease progression and had inconsistent findings, particularly on the effect on AIDS-related mortality, more studies are needed with sound research methodologies, namely prospective cohort study design, diversity of study population (e.g., both men and women), proper time of entry to study, and accurate assessments of drug use, disease progression outcomes, and ARV treatment adherence. It is suggested that injection and non-injection drug users may have different disease outcomes;(Collaboration, 2007; Cook, et al., 2008; Egger, et al., 2002; Krol, et al., 1999; May, et al., 2007; Nicastri, et al., 2005; Perez-Hoyos, et al., 2006) however, none of the 9 studies we reviewed compared the effect of route of drug use. Ideally, this question should be addressed in one study that includes both injection and non-injection drug users, as this study design may avoid confounding by study design and population. We did a retrospective study assessing both effects of IDU and NIDU, and found that HIV-infected IDUs had faster disease progression than NIDU patients [Qian et al, unpublished data]. Explanations for the difference are that IDUs might have a longer history of drug use and use a high dose of drugs than NIDUs.

The effect and mechanism of illicit drugs on ARV treatment outcomes remains unclear. While in vitro information has proved helpful, this is a topic that has received little attention in public health and epidemiologic AIDS literature and the clinical implications remain largely unknown. Further work is needed to identify the pharmacokinetics of various drugs on ARVs, as well as the clinical effects these drugs have on plasma concentrations, separate from the effects of adherence.

In conclusion, we propose a hypothesized mechanisms diagram which highlights the complex immunological, pharmacological, and behavioral effects that drug use has on HIV disease progression (Figure 1). Basic science, epidemiological and clinical research is needed to fully understand the link between NIDU and HIV outcomes. Knowledge of the complex mechanisms will help improve clinical service and outcomes for this increasingly common problem in HIV/AIDS treatment and care.

Acknowledgments

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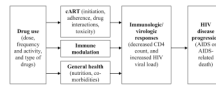
Figure 1.
Conceptual diagram for mediators of the association between drug use and HIV disease progression

Table 1

Cohort studies on the association between non-injection drug use and risk of AIDS-related mortality

Publication	Population	Sample size	Study purpose	Definition of drug use	Definition of AIDS-related mortality	Adjusted measure of effect [§]
Cohen, 2002[*]	Women	2,059	To examine the causes of AIDS and non-AIDS mortality	Non-injection cocaine or heroin use	Death due to AIDS-defining illness, or non-specific infection or organ failure with last CD4<200	Drug use vs. no use: IRR=1.3 (0.9, 1.8)
Cook, 2004[*],[¶]	Women	1,716	To examine associations between depressive symptoms and AIDS-related mortality	Use of crack, cocaine or heroin at anytime during the study	Same as above	Drug use vs. no use: HR=0.9 (0.6, 1.4)
Cook, 2008[*]	Women	1,686	To examine the association between patterns of crack use and AIDS mortality	Repeated measures of frequency of crack use in the past 6 months over study period	Same as above	Intermittent vs. no use: HR=0.93, p ≥0.05 Persistent vs. no use: HR=3.61, p<0.001
Anastos, 2005[*],[¶]	Women	961	To determine association between race and cART treatment effects	Current use of cocaine, heroin, or crack	Same as above	Current drug use vs. no use: HR=2.35, p<0.05
				Non-injection use of depressants (alcohol, marijuana, heroin), stimulants (crack, cocaine), or both (polydrug)		Depressant vs. no use: HR=0.95 (0.66, 1.37) Stimulant vs. no use: HR=1.65 (0.85, 3.20) Polydrug vs. no use: HR=0.89 (0.59, 1.31)
Kapadia, 2005[*]	Women	1,046	To evaluate association of NIDU and HIV disease progression	Frequency of any non-injection drug use	Same as above	Former vs. never use: HR=1.27 (0.82, 1.96) Inconsistent vs. never use: HR=0.99 (0.66, 1.50) Consistent vs. never use: HR=1.42 (0.87, 2.33)
Ickovics, 2001[¶]	Women	765	To determine association between depressive symptoms and HIV-related mortality	Non-injection use of crack or cocaine, injection drug use, or both during the study period	HIV-related deaths were identified via review of medical records, no other details provided	Both non-injection crack/cocaine use and injection drug use were unassociated with HIV-related mortality in univariate analyses (p<0.05).

[*]
Women's Interagency HIV Study (WIHS);

[**]
Women and Infant Transmission Study (WITS);

[¶]
Drug use was not primary exposure being assessed;

[§]
Variables included as covariates in the multivariable models:

Cohen 2002: age, alcohol, ART/cART, hepatitis B virus, hepatitis C virus, IDU (history), IDU (recent use), race, smoking, viral load.

Cook 2004: adherence, age, CD4 count, depression, education, employment, ART/cART use, income, marital status, mental health service utilization, race, residential status, study site, symptoms, viral load.

Cook 2008: age, CD4 count, education, income, race, study site, viral load, year of HIV diagnosis.

Anastos 2005: adherence, age, CD4 count, depression, ART/cART, HIV exposure, income, prior AIDS defining event, race, smoking, treatment naïve prior to cART initiation, viral load.

Kapadia 2005: age, CD4 count, emergency room visit in last 2 months, cART use, viral load.

Table 2

Cohort studies on the association between non-injection drug use and risk of AIDS-defining event (ADE)

Publication	Population	Sample size	Study purpose	Definition of drug use	Definition of AIDS-defining event (1993 CDC case definition)	Adjusted measure of effect[§]
Cook, 2008[*]	Women	1,686	To examine the association between patterns of crack use and HIV disease progression	Repeated measures of frequency of crack use in the past 6 months over study period	New ADE excluding CD4 count <200	Intermittent vs. no use: HR=1.57, p<0.001; Persistent vs. no use: HR=1.65, p<0.05
Anastos, 2005[*],[¶]	Women	961	To determine association between race and cART treatment effects	Current use of cocaine, heroin, or crack	Same as above	Current drug use vs. no use: HR=1.49, p<0.05
				Non-injection use of depressants (alcohol, marijuana, heroin), stimulants (crack, cocaine), or both (polydrug)		Depressant vs. no use: HR=1.19 (0.90, 1.58); Stimulant vs. no use: HR=2.04 (1.06, 3.94); Polydrug vs. no use: HR=1.65 (1.21, 2.25)
Kapadia, 2005[*]	Women	701	To evaluate association of NIDU and HIV disease progression	Frequency of any non-injection drug use	Same as above	Former vs. never use: HR=1.56 (1.05, 2.32); Inconsistent vs. never use: HR=1.63 (1.15, 2.30); Consistent vs. never use: HR=2.51 (1.60, 3.96)
Lucas, 2006	Men and women	1,851	To assess longitudinal association of drug use with HIV disease progression	Frequency of heroin or cocaine use (any route)	New/recurring ADE	Intermittent (abstinent period) vs. no use: HR=1.3 (0.9, 1.8); Intermittent. (active period) vs. no use: HR=1.6 (1.2, 2.3); Persistent vs. no use: HR=1.9 (1.2, 2.8)
Hershow, 2005[**],[¶]	Pregnant women	652	To examine association of HCV coinfection and HIV disease progression	Self-reported cocaine, crack, heroin, or other opiate (including methadone) use; or any IDU; or positive urine for drugs	First ADE or all-cause mortality	Drug use in past year: HR=1.62 (0.81, 3.24)
Thorpe, 2004[**]	Pregnant women	1,148	To examine association of drug use and HIV disease progression	Self-reported cocaine, crack, heroin, or other opiate (including methadone) use; or any IDU; or positive urine for drugs	First ADE excluding CD4 count <200	Drug use vs. no use: HR=1.65 (1.00, 2.72)

[*] Women's Interagency HIV Study (WIHS);

[**] Women and Infant Transmission Study (WITS).

¶Drug use was not primary exposure being assessed

§Variables included as covariates in the multivariable models:

Cook 2008: age, CD4 count, education, income, race, study site, viral load, year of HIV diagnosis.

Anastos 2005: adherence, age, CD4 count, depression, ART/cART, HIV exposure, income, prior AIDS defining event, race, smoking, treatment naïve prior to cART initiation, viral load.

Kapadia 2005: CD4 count, emergency room visit in last 2 months, cART use, viral load.

Lucas 2006: adherence, age, alcohol, CD4 count, gender, race, viral load.

Hershow 2005: age, CD4 percent, ART/cART, hepatitis C virus, viral load.

Thorpe 2004: age, CD4 percent, ART/cART, smoking, subsequent pregnancies