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Social and structural factors associated with HIV disease progression among illicit drug users: A systematic review

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Abstract

Objective—To systematically review factors associated with HIV disease progression among illicit drug users, focusing on exposures exogenous to individuals that likely shape access and adherence to HIV treatment.

Design—A systematic review of peer-reviewed English-language studies among HIV-seropositive illicit drug users with at least one of these endpoint of interest: a diagnosis of AIDS; death; changes/differences in CD4 cell counts; or changes/differences in plasma HIV-1 RNA levels.

Methods—Articles were included if they reported factors associated with an outcome of interest among a group of illicit drug users. Studies were identified, screened and selected using systematic methods.

Results—Of 2,668 studies matching the search criteria, 58 (2%) met the inclusion criteria, all but one from North America or Western Europe. Overall, 41 (71%) studies contained significant individual-level clinical characteristics or behaviours (e.g., illicit drug use) associated with disease progression. Fifteen studies (26%) identified significant social, physical, economic or policy-level exposures, including incarceration, housing status or lack of legal income.

Conclusion—While past studies demonstrate important environmental exposures that appear to shape access to care and subsequent disease progression, the limited literature to examine these factors demonstrates the need for future research to consider risk environment characteristics and the role they may play in shaping health outcomes from HIV infection among drug users through determining access and adherence to evidence-based care. (198 words)

Keywords

Antiretroviral therapy; CD4; drug users; pathogenesis; progression; risk factors; viral load

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INTRODUCTION

Highly active antiretroviral therapy (HAART) has resulted in steep declines in HIV-related morbidity and mortality [1]. With appropriate levels of adherence to prescribed therapies, engagement in HAART has been shown to reliably suppress plasma HIV RNA, delay disease progression and dramatically improve survival [2, 3].

Unfortunately, the full clinical benefits of HAART have not been seen among all HIV-seropositive groups. Uptake of HAART is lower among individuals who use drugs [4, 5]; compared to individuals in other risk categories, they exhibit higher rates of sub-optimal treatment outcomes [1, 6, 7]. For example, in a multi-centre study of individuals beginning HAART, injection drug users (IDU) experienced mortality rates approximately five times higher than individuals infected through sexual contact [8]. A large multi-centre study including over 7500 seroconverters from Europe, Australia and Canada found worsening disparities in progression rates between illicit drug users and members of other exposure groups in the HAART era, suggesting inferior treatment uptake and adherence patterns [9]. As IDU can benefit from HAART at similar rates as non-IDU given adequate compliance to therapeutic regimens [10], investigations of sub-optimal outcomes have largely focused on individual-level barriers and facilitators of HAART access and adherence [11–14], including psychological co-morbidities and drug use patterns. Although proximate (i.e., behavioural and drug-related) patterns of exposure to HAART have been shown to be strongly associated with HIV disease outcomes [3], the relationships between external exposures and disease progression among drug users are unclear.

In recent years, efforts to model and address the negative sequelae of illicit drug use, including accidental overdose death, soft tissue damage and infection with blood-borne pathogens, have expanded beyond proximate causes to include contextual determinants [15–17]. Specifically, the risk environment conceptual framework describes how the interactions between social, political, economic and physical determinants at the macro- and micro-environmental levels facilitate or constrain individual behaviours and structure the risk of drug-related harms [15, 16]. In line with previous works [15, 16], we have chosen to define social- and structural-level exposures as those external to individuals which interact with individual-level characteristics and behaviours to determine HIV-related vulnerabilities. While high-profile reviews have recently applied the risk environment framework to HIV transmission patterns [17], we are unaware of the framework being applied to an examination of factors associated with HIV disease progression. In light of this, and recent high-profile calls for analyses of HIV treatment outcomes among drug users that include broader social- and structural-level exposures [11, 18], we sought to conduct a systematic review explicitly informed by the risk environment framework of the scientific literature on HIV disease progression among illicit drug users.

METHODS

Search strategy

We used an *a priori*-defined search strategy based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [19]. We searched the EBM, EMBASE, MEDLINE, PubMed and Science Citation Index electronic databases to identify relevant studies published in peer-reviewed journals between 1 January 1996 and 1 November 2010. Articles were selected for further review if they had at least one match in each of three sets of keywords or search terms: Illicit drug use (i.e., “heroin”, “crack”, “amphetamines”, “cocaine”, “injection drug user”, “illicit drug user”); disease progression (i.e., “viral suppression”, “viral load”, “cd4”, “death”); and HIV/AIDS. When possible, filters were used to exclude case reports, case series, reviews and other non-eligible study

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types. Only studies among human subjects were included. We also reviewed the citation lists of included studies for eligible studies.

Inclusion and exclusion criteria

Studies were included if they were conducted among HIV-seropositive individuals who were current or former illicit drug users or contained eligible analyses among strata of current or former drug users. Eligible study endpoints were: Change or difference in CD4 cell count or percentage; change or difference in plasma HIV-1 RNA viral load (PVL); incidence or prevalence of AIDS, as defined by the United States Centers for Disease Control diagnostic guidelines; and death, including all-cause, pre-AIDS, HIV-related and infectious disease-related mortality. To be included, studies had to include analyses of factors associated with these outcomes of interest, with significance assessed through appropriate statistical tests or the estimation of effect measures and confidence intervals. Studies were ineligible if they were written in a language other than English or were not published in a peer-reviewed journal.

Search protocol

One author (M-JSM) conducted the database search and entered study abstracts matching the keywords and criteria into a search database. After removing duplicates, studies clearly not meeting the criteria were excluded from further review. Full text versions of all remaining potentially eligible articles were retrieved and independently reviewed by two authors (M-JSM and BDM). Each author marked each remaining study “included” or “excluded”; any discrepancies were discussed by the authors until a consensus was reached.

RESULTS

Four thousand one hundred twenty-two records matched all search criteria and were retrieved from electronic databases; 10 articles were identified following manual searching of reference lists. Following removal of duplicate records, 2668 studies remained eligible for review. After screening citation data and abstracts, the full-text version of 182 reports (6.8%) were assessed by both M-JSM and BDM. Of these, 56 (2.1%) are included in this report [20–77]. Figure 1 presents the results of the acquisition, screening and selection process.

Table 1 presents details of the included studies stratified by endpoint, setting and sample type. Of the 56 articles, 16 (29%) included an analysis of factors associated with time to AIDS diagnosis among HIV-seropositive drug users. Death was an outcome of interest in 23 (41%) studies. Changes or differences in CD4 cell count was an endpoint in 16 (29%) studies. In 15 (27%) studies, changes or differences in PVL was an endpoint. All but one study (in Thailand [51]) was conducted among HIV-seropositive drug users in Western settings. The plurality (27, 48%) occurred in the United States or Canada; 21 (38%) in Western Europe countries; and 7 (13.8%) in multi-national settings. The mean study sample size was 363 individuals (inter-quartile range [IQR]: 125 – 524) and the median follow-up time was 44 months (IQR: 30 – 61). Twenty-one studies (38%), all from North America, recruited participants from community settings; of the remainder, 14 (25%) recruited individuals from hospital settings; 12 (21%) from drug treatment settings; two (4%) used population-based data; and seven (13%) employed analytic samples constituted using multiple recruitment strategies.

Progression to AIDS

The associations identified in this review, stratified by clinical endpoint and the risk environment framework, are presented in Table 2. Sixteen studies compared rates of disease

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progression among IDU by modeling the time to a diagnosis of AIDS. In the period preceding the widespread availability of HAART among drug-using populations, several studies [39, 57, 62, 63, 67] used samples of individuals with well-estimated HIV seroconversion dates to assess factors possibly associated with the natural history of HIV infection. Studies confirmed the well-established prognostic value of host immunologic [32, 36, 49, 63, 73–75] and virologic characteristics [32, 73] observed in other risk categories. In the pre-HAART era, no study found strong evidence of an effect of illicit drug use on clinical progression [58, 75]. For example, in a multi-centre study of IDU in Italy and the United States [58], participants in Baltimore, Maryland, who were mostly poly-drug injectors, and participants in Italy, who were mostly cocaine injectors, did not exhibit different rates of AIDS, as might be expected if drug use accelerated disease progression. In addition, neither age at first injection nor length of injection career was associated with time to AIDS in a pooled analysis of all participants [58]. Although no study could be found assessing the direct effect of access and adherence to HAART on time to AIDS among IDU, studies using calendar time as a proxy measure of the general availability of HAART provide weak evidence of the benefit of HAART on progression to AIDS [57, 69–71].

Mortality

Survival of HIV-seropositive IDU was investigated in 23 studies, in which 11 (20%) [20, 22, 26, 27, 37, 48, 53, 57, 67, 68, 70] modeled all-cause mortality, 6 (11%) [24, 34, 39, 59, 62, 72] modeled HIV- or AIDS-related mortality, 2 (4%) [58, 73] modeled infectious disease-related mortality and 3 (5%) [63, 64, 71] modeled time to pre-AIDS mortality. Unsurprisingly, both HIV-related and all-cause mortality rates were high in studies of untreated IDU populations, approximating 50 per 1000 person-years [24, 27, 42, 53, 59, 62, 63, 72, 73]. Studies among HAART-naïve samples [20, 24, 26, 27, 37, 39, 53, 58, 59, 62–64, 67, 68, 73] found little evidence of unique clinical or biological correlates of survival among IDU. As with analyses of time to AIDS, studies of the relationship between patterns of illicit drug use and HIV-related death were contradictory. In two studies of community-recruited injection drug users in Baltimore [34, 72], cocaine use was associated with lower rates of death; drug use was not associated with survival in other analyses [42, 53]. More recently, studies conducted in the wake of HAART uptake among IDU [34, 42, 52, 57, 70–72] have confirmed its beneficial impact on survival. Although based on self-reported data on exposure to medication, individuals treated with HAART had sharply reduced relative hazards of death compared to antiretroviral-naïve participants in a study of 665 community-recruited IDU followed from 1988 to 2002 [72]. In contrast to the well-described relationships between endogenous factors and survival, few associations with social- or structural-level factors were observed. In an early study of the relationship between HIV treatment and opioid substitution therapy, engagement in MMT at baseline was predictive of survival among IDU in Germany [37]. Lack of legal income at baseline was the strongest predictor of shortened survival in a small study among Parisian IDU after adjustment for age, CD4 cell count, p24 antigenemia, age and baseline drug use [59].

Immunologic changes

Immunologic status as measured by changes or differences in counts of circulating CD4 cells was a focus of 16 studies. Only weak evidence was found for a relationship between illicit drug use patterns and immunologic progression [43, 45, 47, 61, 65]. Only one study identified an association between immunosuppression and social- or structural-level factors [47]. In Mehta *et al.*'s study of HAART initiators in Baltimore, individuals reporting recent incarceration had significantly lower adjusted odds of CD4 cell count improvements [47].

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Virologic changes

Differences or changes in plasma viral load were assessed in fifteen studies. In studies of drug-using individuals on HAART [21, 31, 41, 55, 66], drug use was not a major predictor of elevated viral loads or treatment failure in four of five studies [31, 41, 55, 66]. Conversely, access to substitution therapy was strongly associated with optimal virologic response in studies of community-recruited drug users in France [66] and Canada [55]. Five studies [29, 44, 47, 50, 76] observed virologic trajectories following the initiation of HAART. Notably, in three [44, 47, 50] of four studies assessing them [44, 47, 50, 76], drug use patterns were not associated with lower relative hazards of suppression. A number of social and structural factors emerged as determinants of PVL [40, 41, 44, 56, 66]. Two studies by Knowlton *et al*. identified microsocial factors, such as social support and the quality of communication with medical care-givers, as positively associated with PVL suppression [40, 41]. In Vancouver, Canada, Palepu *et al*. found that being incarcerated in the six months prior to follow-up was a barrier to virologic suppression among drug users in a setting of universal access to HIV care [56]. Similarly, in a multi-centre study in the United States [40], individuals reporting stable housing environments had over three times higher odds of suppression after adjustment for a range of individuals and inter-personal factors.

DISCUSSION

Consistent with existing critiques of the scientific literature on HIV among drug users [11, 18], the major finding of this review is that few studies of disease progression among illicit drug users included measures of exposures at the social and structural levels. While a strong majority of these studies confirmed endogenous host and viral characteristics associated with the natural history of HIV infection as well as treatment outcomes, only a minority of studies identified associations between physical, social, political or economic factors and disease progression. In this group, Knowlton *et al*.'s studies [40, 41] are a notable example. In their study of individual-, social- and structural-level exposures on the likelihood of viral suppression among drug users on HAART [40], high social support, good communication with healthcare providers and stable housing were independent predictors of suppression. In two studies, incarceration was associated with poorer immunologic [47] and virologic [56] response following HAART initiation. This result stands in contrast to many prison-based trials of ART delivery, which have produced high levels of adherence to treatment [78, 79]. However, the inferior responses to ART identified in this review likely stem from treatment interruptions caused by movement between correctional and community environments [80, 81].

Notably, many of the social and structural risk factors for disease progression in this review — specifically incarceration [47, 56], poor housing status [40] and lack of legal income [59] — have been identified as important determinants of vulnerability to HIV infection in past descriptions of the risk environment framework [16, 17]. Thus, future analyses of HIV treatment outcomes might consider using this conceptual framework to model the disease progression process in drug users. More specifically, the evidence gathered in this review suggests that broader social and structural forces produce HIV disease outcomes through the mechanisms of access and adherence to antiretroviral therapy and related evidence-based treatments for individuals who use illicit drugs. Thus, future research could be informed by the risk environment framework to investigate the setting-specific social and structural determinants of treatment access and adherence.

This review found only weak evidence of a direct relationship between illicit drug use and disease progression. It is noteworthy that all studies reporting this association among groups of ART-treated participants did not include robust measures of patient adherence. Our

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finding stands in sharp contrast to numerous laboratory studies that have found important associations between illicit drugs and relevant virologic or immunologic functioning [82–86]. For example, exposure to morphine has been shown to up-regulate HIV replication *in vitro* [83]; cocaine use has been shown to impair immunologic performance in both murine and human subjects [84, 85]. However, these molecular-level effects were not clearly reproduced in studies of untreated human subjects in this review. In groups of drug users surveyed before the widespread use of HAART, illicit drug use was associated with disease progression in some [28, 43, 75] but not other [27, 43, 45, 58] studies. In addition, it is possible that the effect of illicit drug use is over-estimated if confounding by factors common to both drug use and HAART adherence is not considered. For example, while Weber *et al*. estimated that crack cocaine users had a faster time to AIDS diagnosis, their multivariate model did not include information on exposures likely to be associated with crack cocaine use and HIV-related morbidity, such as poorer access to healthcare, unstable housing or nutritional deficiencies. Among HAART-treated groups of drug users, the effect of illicit drugs on disease progression is thought to be mediated through lower levels of adherence to therapy. Although many studies are limited by poor or incomparable measures of drug use [23], stronger support for this hypothesis was found in this review [21, 24, 55, 76]. For example, frequent heroin use was univariately associated with lower odds of viral suppression in Palepu *et al*.'s 2006 study [55] of HIV-seropositive drug users in Vancouver; in a multivariate model including ART adherence, this association was not statistically significant, suggesting a mediating relationship. Nevertheless, it should be remembered that these studies largely fail to include any measurement of social or structural factors which might account for some of the effect of illicit drug use on non-adherence, such as higher levels of incarceration, poor housing status and physical and psychological co-morbidities. Among these studies, only Baum *et al*. [23] reported an independent effect for crack cocaine use on both CD4 cell decline and PVL after accounting for exposure to ART. In their short-term longitudinal study of 222 active illicit drug users in Miami, Florida, ongoing crack cocaine use was marginally associated with a faster rate of progression to CD4 < 200 cells in a multivariate model including baseline CD4+ cell count and HAART exposure but no measure of social or structural vulnerability [23]. However, it is unlikely their self-reported measure of HAART use adequately captured exposure to treatment as it did not predict PVL suppression in a univariate analysis. Also of note is a recent analysis using data from a long-running community-recruited cohort of HIV-seropositive IDU which failed to find a relationship between patterns of ongoing illicit drug use and viral suppression following HAART initiation [44].

The two main findings of this review — the strong focus, to date, on individual-level factors and the moderate and likely mediated associations between patterns of illicit drug use and disease progression — should be considered in light of the urgent need for interventions to improve HIV treatment outcomes among drug users. While the medical management of HIV-seropositive drug users in the clinical setting can be complex [87], clinical trials have proven directly administered antiretroviral therapy (DAART) twinned with opioid substitution therapy is effective at improving treatment outcomes [88–93]. This review suggests that the emerging evidence of relationships between exogenous factors and disease progression might provide useful new targets for clinical and community-based interventions, for example among drug users at risk of incarceration or homelessness, to support required levels of adherence among marginalized, drug-using individuals.

Limitations common to many of these studies should be mentioned in order to contextualize the findings. Most notably, although the most recent estimates suggest that close to 100 countries in the Americas, Europe, Africa and Asia are home to HIV-seropositive illicit drug users [94], these studies only drew from seropositive groups in a small minority of countries in western Europe, the United States and Canada. Notably, the only study including non-

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Western HIV-seropositive illicit drug users identified a novel host genotype associated with swifter CD4+ cell decline among untreated drug users. While this review has focused on social- and structural-level factors, the presence of immunologic polymorphisms among drug users has not been well evaluated. More generally, the patterns of disease progression among HIV-seropositive drug users in the countries with the largest ongoing HIV outbreaks outside sub-Saharan Africa [18] — Russia, China, Ukraine, Vietnam and Malaysia — have not been evaluated. A future study could investigate if this deficit is a result of our reliance on English-language studies or reflects a gap in the scientific literature. A further limitation is the dependence on samples of drug users drawn from treatment settings (25, 45%).

To conclude, this review of disease progression among illicit drug users found that most studies concentrated on individual-level host and viral characteristics. Although few considered the broader physical, social, political and economic determinants of disease production or treatment outcomes, some studies did identify important associations with factors including incarceration, housing status and engagement in opioid substitution therapies. Although many studies focused on the effect of drug use patterns, weak and contradictory evidence was observed to support the hypothesis that drug use is directly related to disease progression. In light of this review, future research and interventions should consider the risk environment framework when seeking to reduce HIV-related morbidity and mortality among drug users.

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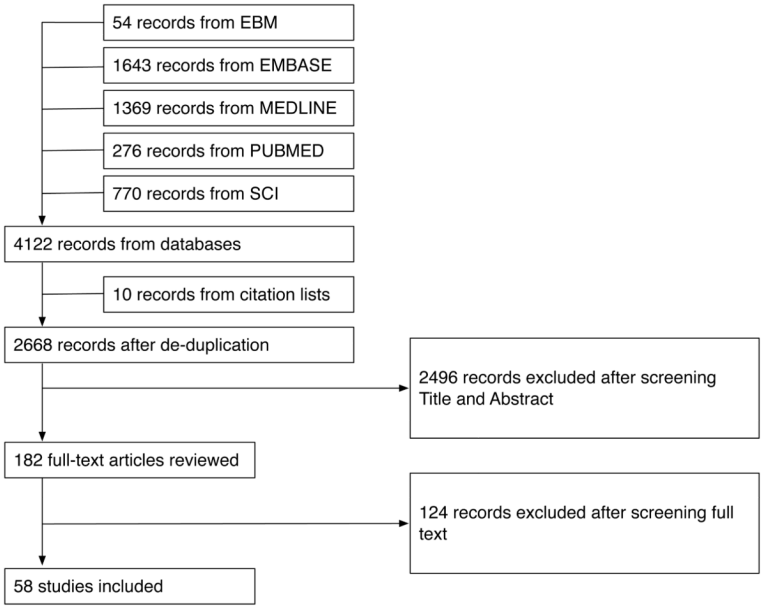

Figure 1.
Flowchart of study acquisition, screening and selection process

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Table 1

Descriptive summary of reviewed studies on HIV disease progression among illicit drug users

	AIDS	Mortality	CD4	PVL	All
All	16 (100%) [32, 35, 36, 39, 49, 57, 58, 62, 63, 67, 69–71, 73–75]	23 (100%) [20, 24, 26, 27, 34, 37, 39, 42, 48, 52, 53, 57–59, 62–64, 67, 68, 70–73]	16 (100%) [23, 25, 26, 30, 33, 38, 43, 45, 47, 51, 61, 62, 65, 67, 69, 77]	15 (100%) [21, 28, 29, 31, 40, 41, 44, 47, 50, 54–56, 60, 66, 76]	58 (100%) [20–77]
Setting					
North America	6 (38%) [32, 36, 39, 73–75]	9 (39%) [24, 27, 34, 39, 42, 53, 68, 72, 73]	6 (38%) [23, 30, 33, 45, 47, 77]	9 (60%) [21, 31, 40, 41, 44, 47, 54–56]	27 (47%) [21, 23, 24, 27, 30–34, 36, 39–42, 44, 45, 47, 53–56, 68, 72–75, 77]
Western Europe	4 (25%) [35, 49, 62, 67]	10 (43%) [20, 22, 26, 37, 48, 52, 59, 62, 63, 67]	6 (38%) [25, 26, 38, 61, 62, 67]	6 (40%) [28, 29, 50, 60, 66, 76]	21 (36%) [20, 22, 25, 26, 28, 29, 35, 37, 38, 48–50, 52, 59–62, 64, 66, 67, 76]
Asia	0 (0%)	0 (0%)	1 (6%) [51]	0 (0%)	1 (2%) [51]
Multi-centre	6 (38%) [57, 58, 63, 69–71]	5 (22%) [57, 58, 63, 70, 71]	2 (13%) [43, 69]	0 (0%)	7 (12%) [43, 57, 58, 63, 69–71]
Sample					
Community	4 (25%) [32, 36, 39, 73]	7 (30%) [24, 34, 39, 53, 68, 72, 73]	6 (38%) [23, 30, 43, 45, 47, 77]	7 (47%) [31, 40, 41, 44, 47, 55, 56]	21 (36%) [23, 24, 30–32, 34, 36, 39–41, 43–45, 47, 53, 55, 56, 68, 72, 73, 77]
Clinical/Treatment	4 (25%) [49, 67, 74, 75]	10 (43%) [20, 22, 26, 27, 37, 42, 48, 59, 64, 67]	7 (44%) [25, 26, 33, 38, 51, 61, 67]	7 (47%) [21, 28, 29, 50, 60, 66, 76]	25 (43%) [20–22, 25–29, 33, 37, 38, 42, 48–51, 59–61, 64, 66, 67, 74–76]
Other	8 (50%) [35, 57, 58, 62, 63, 69–71]	7 (30%) [52, 57, 58, 62, 63, 70, 71]	2 (13%) [62, 69]	1 (7%) [54]	10 (17%) [35, 52, 54, 57, 58, 62, 63, 69–71]
Sample size, median (IQR)	600 (504 – 761)	487 (126 – 686)	238 (128 – 259)	189 (106 – 246)	363 (125 – 524)
Follow-up months, median (IQR)	61 (48 – 84)	56 (41 – 81)	45 (30 – 57)	12 (12 – 24)	44 (30 – 61)

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TABLE 2

Summary of reviewed studies

Article	Location	Cohort	Recruitment and follow-up	Sample	Drug use	HIV treatment	Outcome
Page et al., 1996 [53]	Miami, Florida, United States		Community-recruited from non-treatment settings, 1987–1988; followed-up until 1995	116 current IDU, 32 (28%) female, 108 (93%) black, 80 (69%) aged 30–40 years	48 (41%) at least daily heroin	14 (12%) exposed to AZT	Time to death (all-cause)
Brown et al., 1996 [27]	New York City, New York, United States		Recruited from 6 methadone maintenance clinics, 1988 – 1991; followed-up until 1993	328 heterosexuals with history of IDU, 202 (62%) male, 191 (58%) African American, 186 (57%) age 30–39	165 (50%) injection drugs in previous 3 months, 122 (37%) injection heroin in last three month	Proportion exposed to zidovudine and PCP prophylaxis not reported	Time to death (all-cause)
German AIDS Study Group [37]	Germany		Recruited from 20 HIV/AIDS treatment centres, 1982 – 1993	1554 IDU, 59% male, average age 31 years	Not reported	All exposed to antiretrovirals, 88% zidovudine	Time to death (all-cause)
Brettle et al., 1996 [26]	Edinburgh, Scotland	Edinburgh City Hospital cohort	Recruited from hospital, 1985 – 1994	260 IDU estimated to have seroconverted between 1983 and 1985, 180 (69%) male, 188 (72%) < 25 years	Not reported	Proportion exposed to zidovudine not reported	Time to death (all-cause); time to AIDS [CDC 1987 definition]; time to CDC IV [CDC 1986 definition]
Crum et al., 1996 [30]	Baltimore, Maryland, United States	AIDS Link to the Intravenous Experience (ALIVE)	Recruited from community settings, 1988 – 1989	188 IDU seroconverting ± 1 year from November 1993, 74% men, 92% African-American	35% > 10 years injection history at baseline; 16% no injection in last six months	29% zidovudine use	Change in CD4+%, change in CD8+%
Hershow et al., 1996 [39]	Chicago, Illinois; Baltimore, Maryland; Bronx, New York; Rome, Italy	AIDS Outreach Intervention Project (Chicago); ALIVE (Baltimore); Bronx HERO (Bronx); Italian Seroconversion Study (Rome)	Recruited from community and treatment settings	370 IDU with incident HIV infection, 27% female, mean age 32 years at seroconversion	Not reported	23% ever exposed to zidovudine	Time to death from AIDS-defining condition; time to AIDS [CDC 1987]
Ferrando et al., 1996 [33]	San Francisco, California, United States		Recruited at MMT clinic in 1991	57 IDU on MMT and zidovudine treatment, 42%	60% cocaine dependence, 36% alcohol dependence,	100% exposed to zidovudine	CD4+ cell count change

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Article	Location	Cohort	Recruitment and follow-up	Sample	Drug use	HIV treatment	Outcome
				female, 52% Caucasian	11% amphetamine dependence		
Montella et al., 1997 [49]	Rome, Italy	Italian Seroconversion Study	Recruited from hospital setting, 1985 – 1991; followed prospectively to 1993	549 IDU seroconverting 1985 – 1991, 140 female,	100% history of heroin injection	Not reported	Time to AIDS [CDC 1987]
Prins et al., 1997 [63]	Spain, Scotland, Netherlands, Switzerland, France, Austria	European Seroconverter Study	Recruited from community and treatment settings, 1982 – 1988;	664 IDU with documented seroconversion, 221 (33%) female, mean age 25 years at seroconversion	Not reported	Not reported	Time to death, pre-AIDS
Radkowski et al., 1997 [65]	Poland		Recruited from methadone clinic (cases) and detoxification ward (controls)	56 IDU, 73% female	Not reported	Not reported	Change in CD4+ cell counts
Lyles et al., 1997 [45]	Baltimore, Maryland, United States	ALIVE	Recruited from community settings, 1988 – 1989	605 IDU recruited before 1993, 78% male, 97% African American	71% current user, 33% inject < 1 day	Not reported	Difference in CD4+ cell count pairs
Baum et al., 1997 [24]	Miami, Florida, United States		Community recruited from non-treatment settings, 1987–1988; followed-up until 1995	125 IDU, 34% women, 88% African American	77% positive urine screen for cocaine use during study	Proportion exposed to zidovudine not reported	Time to death, HIV-related causes
Marmor et al., 1997 [46]	New York City, New York, United States		Recruited from hospital-based methadone programme, 1990 –1991, followed until 1993	133 IDU, 78% male, 47% Hispanic	11 (9%) = 1 injection/day; 78 (61%) < 1 injection/day	Not reported	Time to death (all-cause)
Vlahov et al., 1998 [73]	Baltimore, Maryland, United States	ALIVE	Recruited from community settings, 1988 – 1989; followed until 1996	522 IDU with incidence seroconversion, 80% male, 96% African-American	Not reported	6% on zidovudine at baseline; 47% exposed to monotherapy during follow-up	Time to death (infectious disease-related); time to AIDS diagnosis
Haydon et al., 1998 [38]	Edinburgh, Scotland	Edinburgh IDU cohort	Recruitment from clinical settings, 1985 onwards	240 IDU with known HCV serostatus, 163 (68%) male,	Not reported	Not reported	Time to death (all-cause); time to CDC Stage IV [undefined definition date] and time to AIDS [CDC 1997 definition]
Zhang et al., 1998 [77]	Baltimore, Maryland, United States	ALIVE	Recruited from community settings, 1988 – 1989	170 IDU, 31 (17%) women, 6 (3%)	156 (89%) current IDU	Not reported	CD4+ cell count

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Article	Location	Cohort	Recruitment and follow-up	Sample	Drug use	HIV treatment	Outcome
Webber et al., 1998 [74]	New York City, New York, United States	Bronx HERO	Recruited from clinic-based methadone treatment programme, 1985, followed until 1997	524 IDU, 42% female, 64% Hispanic	Approximately 77% reported any injection at each follow-up	Approximately 60% exposed to zidovudine; 80% exposed to PCP prophylaxis	Time to AIDS-defining condition [CDC 1993 definition]
Farzadegan et al., 1998 [32]	Baltimore, Maryland, United States	ALIVE	Recruited from community settings, 1988 – 1989 and 1992 – 1993, followed until 1996	812 IDU, 24% female, 96% African American	80% current drug use at baseline	10% zidovudine use in the previous six months at baseline	Time to AIDS [CDC 1993 definition]
Webber et al., 1999 [75]	New York City, New York, United States	Bronx HERO	Recruited from clinic-based methadone treatment programme, 1985, followed until 1997	524 IDU, 302 (58%) male, 63% Hispanic	93% self-reported illicit drug use during follow-up, 77% self-reported injection	Proportion exposed to zidovudine at baseline and during follow-up not reported	Time to AIDS [CDC 1993 definition]
Pezzotti et al., 1999 [58]	Baltimore, Maryland, United States and Italy	ALIVE and ISS	Community and hospital recruitment	1003 IDU with estimated seroconversion 1988 – 1996, 28% female, 77% non-black	21% > 10 years injection career;	Not reported	Time to AIDS [CDC 1993 definition], time to death (infectious-disease related)
Krol et al., 1999 [43]	Baltimore, Maryland, United States and Amsterdam, Netherland	ALIVE and the Amsterdam Cohort Study among Drug Users	Community-recruited	287 IDU with estimated seroconversion date, 72% male, 73% non-White	81% self-report injection drug use; 37% cocaine injectors	Not reported	Decline in CD4+ cell counts
Schinkel et al., 1999 [67]	Amsterdam, Netherlands	Amsterdam Cohort Study Among Drug Users	Recruited from 1985 until 1997	108 IDU with incidence seroconversions, 60% male, 89% White race	Not reported	Not reported	Time to AIDS [CDC 1987 and 1993 definitions], time to death (all-cause), time to CD4+ cell count < 200
Carrieri et al., 1999 [28]	Marseille, Nice and Paris, France	MANIF	Recruited from clinical settings, October 1995 – October 1996	108 IDU, 34% female, average 33 years old	39% injected morphine/heroin in previous six months at baseline, 25% in maintenance therapy	Not reported	HIV-1 RNA viral load
Prazuck et al., 1999 [61]	Villeneuve-Saint-Georges, France		Recruited from HIV clinical service, 1991 – 1996; followed for 481 months	12 IDU, 100% male	100% active IDU	4 (33%) ever exposed to zidovudine	Differences in CD4+ cell count
Prins et al., 1999 [62]	Spain, Scotland, Netherlands, Switzerland, France, Austria	European Seroconverter Study	Recruitment from community and clinical settings, 1982 – 1988; followed until 1995	664 IDU, 221 (33%) female	Not reported	Not reported	Time to death (AIDS-related); time to immunosuppression;

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Article	Location	Cohort	Recruitment and follow-up	Sample	Drug use	HIV treatment	Outcome
							time to AIDS [CDC 1987 definition
Piketty et al., 1999 [59]	Paris, France		Recruited from clinic setting, 1989 – 1992; followed until 1996	124 IDU, 91 (73%) male	68% reported daily injection at baseline; 57% reported daily injecting at study end	35% received antiretroviral therapy during follow-up	Time to AIDS-defining event [CDC, 1992]; time to death (all-cause)
Shor-Posner et al., 2000 [68]	Miami, Florida, United States	Miami HIV-1-Infected Drug Abusers Cohorts (MIDAS)	Recruited from community clinic and followed from 1992 – 1996	125 IDU, 66% male, 89% African-American	50% positive for poly-drug use by urine toxicology; 55% self-report daily use of illicit drugs	8% ART-exposed	Time to death (all-cause)
Ajello et al., 2000 [20]	Unreported		Recruitment setting and method unreported; study period 1993 – 1995	21 non-IDU non-HIV; 47 HIV-seronegative IDU and 101 HIV-seropositive IDU	Not reported	Not reported	Difference in CD4+ cell count
Carrieri et al., 2000 [29]	Paris, Nice and Marseille, France	MANIF	Recruited from clinical settings, October 1995 – October 1996, followed until 1998	103 HAART-treated patients, 20 on buprenorphine and 83 ex-IDU	Not reported	All participants initiated HAART at baseline; adherence not reported	Difference in plasma HIV RNA load
Prins et al., 2000 [64]	Amsterdam, Netherlands and London, England	Amsterdam Cohort Studies on HIV Infection and AIDS; Royal Free Hospital cohort	Recruited from clinical settings prior to December, 1985; followed until January 1, 1998	111 men with haemophilia; 118 IDU; 158 men who have sex with men; all with well-estimated seroconversion date	Not reported	Not reported	Time to death (pre-AIDS); time to AIDS
Pradier et al., 2001 [60]	Paris, Nice and Marseille, France	MANIF	Recruited from clinical settings, October 1995 – October 1996, followed until 1998	119 IDU prescribed HAART with complete adherence evaluation, 65% male	5.9% active IDU at baseline	All prescribed HAART; 28.6% < 100% adherence during follow-up	Change in plasma HIV RNA load; change in CD4+ cell count
Moreno et al., 2001 [50]	Madrid, Spain		Recruited from specialist clinical setting and followed-up from October 1996 – October 1998	54 (26.0%) IDU on methadone and 154 (74%) IDU not on methadone; all	10 (18%) in methadone group reported illicit drug use during follow-up	All prescribed HAART; 63% had > 90% adherence during study	Changes in plasma HI RNA load; change in CD4+ cell count

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				prescribe HAART			
Barber et al., 2001 [22]	Lleida, Catalonia, Spain	Lleida AIDS Cohort	Recruited from specialist clinical setting and followed-up until March 1999	185 IDU with seroconversion date between 1982 and 1991; 100% Caucasian, 75% male	Not reported	154 (74.0%) received ART at some point during study	Time to AIDS [CDC 1987] and time to AIDS [CDC 1993]
Zaccarelli et al., 2002 [76]	Rome, Italy		Recruited from outpatient clinic and followed-up from October 1998 – December 1999	80 IDU; 58 (72.5%) male, mean age 37	20% reported active injection drug use	100% treated with combination antiretroviral therapy	Time to virologic failure defined as two observations > 500 copies/mL
Arnsten et al., 2002 [21]	Bronx, New York City, New York	HERO	Recruited from substance abuse treatment clinic and followed-up from July 1998 to April 2000	80 IDU on antiretroviral therapy 51 (60%) male, 19 (23%) African American	32 (38%) self-reported heroin or cocaine use during study	100% on ART; 59 (69%) had regimens including a protease inhibitor	Plasma HIV RNA suppression
Perez-Hoyos et al., 2003 [57]	Valencia and Barcelona, Spain	GEMES	Recruited from clinical settings and followed until January 2000	830 IDU with well-estimated seroconversion dates in the 1980s	Not reported	Approximately one-third accessed ART during study period	Time to AIDS; time to death (all-cause)
Golub et al., 2003 [36]	Baltimore, Maryland, United States	ALIVE	Recruited from community settings; followed-up until December, 1999	451 IDU without AIDS diagnosis [CDC 1993]; 76.3% men, 95.8% African-American	Not reported	Not reported	Time to AIDS [CDC 1993]; time to death (all-cause)
Palepu et al., 2003a [56]	Vancouver, Canada	Drug Treatment Programme	Recruited from treatment registry and followed-up until December, 2000	174 IDU on HAART	Not reported	Not reported	Likelihood of plasma HIV RNA suppression
Palepu et al., 2003b [54]	Vancouver, Canada	Barriers to antiretroviral therapy (BART)	Recruited from community settings and followed-up from May 1996 to July 2001	234 IDU on HAART; 38.0% female	65% injected heroin and/or cocaine daily over study period	100% initiated HAART at baseline	Likelihood of plasma HIV RNA suppression
van Asten et al., 2003 [71]	Valencia, Spain; Edinburgh, Scotland; Amsterdam, Netherlands; Geneva, Switzerland; Glasgow, Scotland; Paris, France; Innsbruck, Austria	European Seroconverter Study	Recruited from clinical settings from 1982 to 1988 and followed until January 1998	751 IDU with well-estimated date of seroconversion; 33% female, median age 26 years at seroconversion	Not reported	Not reported	Time to AIDS [CDC 1993 definition]

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Nguyen et al., 2004 [51]	Bangkok, Thailand		Recruited from drug treatment settings between 1995 – 1998	130 IDU with incident seroconversion; mean age 31 years, 89.2% male	Not reported	Not reported	Time to CD4+ cell count < 200 cells
de la Hera et al., 2004 [35]	Valencia and Barcelona, Spain	GEMES	Recruited from clinical settings and followed until March 2001	929 IDU with well-estimated seroconversion dates; 24.7% women	Not reported	337 (36.3%) prescribed HAART during study	Time to AIDS; time to death (all-cause)
van Asten and Prins, 2004 [69]	Valencia, Spain; Edinburgh, Scotland; Amsterdam, Netherlands; Geneva, Switzerland; Glasgow, Scotland; Paris, France; Innsbruck, Austria	European Seroconverter Study and Italian Seroconverter Study	Recruited from clinical settings from 1982 to 1988 and followed until January 1998	126 IDU co-infected with hepatitis C; 40 (32%) female	Not reported	75% had exposure to HAART by the end of the study period	Time to AIDS; time to death (pre-AIDS)
van Asten et al., 2005 [70]	Valencia, Spain; Edinburgh, Scotland; Amsterdam, Netherlands; Geneva, Switzerland; Glasgow, Scotland; Paris, France; Innsbruck, Austria	European Seroconverter Study	Recruited from clinical settings from 1982 to 1988 and followed until January 2002	790 IDU with well-estimated date of seroconversion, 68% male	Not reported	227 (42.8%) in the HAART era exposed to HAART	Time to AIDS; time to all-cause death
Galai et al., 2005 [34]	Baltimore, Maryland, United States	ALIVE	Recruited from community settings and followed-up until December, 2000	1030 IDU with CD4+ cell counts < 500 cells	Approximately 30% inject > 1 time/day	Approximately 5% exposed to HAART	Time to death (HIV related)
Bouhnik et al., 2005 [25]	Paris, Nice and Marseille, France	MANIF 2000	Recruited from clinical settings and followed until 2000	243 IDU initiating HAART with CD4+ cell count > 200 cells	17% active injectors at baseline	All initiated HAART	Time to death (AIDS-related) or CD4+ cell count < 200 cells
Vlahov et al., 2005 [72]	Baltimore, Maryland, United States	ALIVE	Recruited from community settings and followed until December 2002	665 IDU with CD4+ cell count < 200 cells; 94.6% Black, 74.6% male	63.7% injected illicit drugs during study	62.1% ever exposed to HAART during study	Time to death (HIV-related)
Kohli et al., 2005 [42]	Bronx, New York City, New York, United States	HERO	Recruited from methadone treatment clinics from 1996 to 2001	398 IDU, 237 (59.5%) male, 267 (67.1%) Hispanic	185 (46.5%) any illicit drug use in previous six months at baseline	165 (46.4%) exposed to HAART at baseline	Time to death (all-cause)
Knowlton et al., 2006 [40]	Baltimore, Maryland; Miami, Florida; New York City, New York; San Francisco, California, United States	Interventions for Seropositive Injectors — Research and Evaluation (INSPIRE)	Recruited from community settings and followed up from 2000 to 2004	1113 IDU on HAART; 156 (34%) female, 315 (69%) non-Hispanic black	432 (91%) self-report illicit drug use	All on HAART; 42% self-reported taking prescribed medications	Likelihood of HIV RNA viral load suppression

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Palepu et al., 2006 [55]	Vancouver, Canada	BART	Recruited from community settings and followed-up from May 1996 to November 2004	278 IDU on HAART; 160 (57.6%) male	Approximately 50% self-reported daily cocaine injection at baseline	All on HAART; 129 (46.4%) =95% adherent by pharmacy refill at baseline	Likelihood of HIV RNA viral load suppression
Duncan et al., 2007 [31]	Miami, Florida, United States		Recruited from community settings	80 individuals, 100% self-reported crack cocaine smoking; 100% African-American women	Participants self-reported approximately 22 days of crack use in previous month	None exposed to treatment at recruitment	Change in CD4+ cell counts
Mehta et al., 2007 [47]	Baltimore, Maryland, United States	ALIVE	Recruited from community settings and followed until 2004	258 IDU initiating HAART between 1996 and 2002; 29% female and 95% African American	42.6% any injection drug use at HAART initiation	All individuals initiated HAART; 101 “consistent use”	Change in CD4+ cell count; change in plasma HIV RNA load
Knowlton et al., 2007 [41]	Baltimore, Maryland; Miami, Florida; New York City, New York; San Francisco, California, United States	INSPIRE	Recruited from community settings and followed from 2001 to 2005	133 IDU on HAART for at least 12 months with viral load improvements since initiation	109 (82%) any injection drug use during study period	104% adherence = 90%	Likelihood of achieving or remaining undetectable HIV RNA load
Michel et al., 2009 [48]	Paris, Nice and Marseille, France	MANIF 2000	Recruited from clinical settings between 1995 and 1997 and followed until January 2005	294 IDU on HAART with at least two study interviews	100 (34%) reported being in opioid substitution; 179 (60.9%) reported no heroin use in previous six months	All on HAART	Time to death
Baum et al., 2009 [23]	Miami, Florida, United States		Recruited from homeless shelter between 2002 and 2005	222 IDU, 77% black, 73% male	50% crack cocaine use at baseline, 6% heroin use	Approximately 65% on ART during study	Time to CD4+ cell count = 200 cells
Roux et al., 2009 [66]	Paris, Nice and Marseille, France	MANIF 2000	Recruited from clinical settings between 1995 – 1996	113 IDU, 30 (26.5%) women	30 (26.5%) heroin, 26 (23.0%) cocaine during previous six months	59 (52.2) 100% adherence to HAART by self-report	Likelihood of plasma HIV RNA load suppression
Krusi et al., 2010 [44]	Vancouver, Canada	AIDS Care Cohort to evaluate Exposure to Survival Services	Recruited from community settings and followed up from 1996 to 2007	381 participants initiating ART, 157 (41.2%) women	323 (84.8%) self-report injection drug use during previous six	135 (39.6%) < 95% adherent to ART by pharmacy refill first six months after baseline	Likelihood of plasma HIV RNA load suppression

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					months at baseline		
Omland et al., 2010 [52]	Denmark	Danish HIV Cohort Study	Recruited from specialized clinical settings and followed from January 1995 to December 2006	392 IDU with HCV co-infection, 245 (62.5%) male	Not reported	160 (40.8%) on HAART	Time to death (all-cause)

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Table 3

Factors associated with HIV disease progression among illicit drug users

		AIDS	Mortality	CD4+ cell count	HIV RNA viral load
EXOGENOUS					
Macro-	Physical	Study site [39, 62, 63, 70], study year [35, 70, 74]	HAART[1] era [34, 72], study year [57, 70], study site [39, 62, 70]		
	Social				
	Policy				
	Economic				
Micro	Physical			Incarceration [47]	Housing [40], incarceration [56]
	Social				Social support [40, 41], patient-provider communication [40]
	Policy		MMT[2] [37]		MMT[2] [44, 66], Retention in OST[3] [66]
	Economic		Lack of legal income [59]		
ENDOGENOUS					
Co-morbidities		Crack use [75], psychological distress [36]	Anemia [72], cocaine use [72], selenium deficiency [24, 68], withdrawal symptoms [48], STD [34], recent hospitalization [34, 72], serum thiol [46]	CES-D[4] score [25], HCV[5] genotype [69], Syringe borrowing [43], Active injection drug use [47, 61], Injection heroin use [43], Injection drug use duration [43], Illicit drug use duration [45], illicit drug use [65]	Alcohol use [56], cocaine use [21], crack use [31], illicit drug use [76], injection drug use [28]
Pharmacotherapies			HAART[1] use [34, 42, 72], ART[6] use[37], PCP[7] prophylaxis,[34]	HAART[1] non-adherence [25]	ART[6] regimen [54, 56, 60], HAART[1] adherence [50, 55, 56, 60, 66, 76], time since ART[6] initiation [21, 54–56]
HIV-related morbidity		Thrush [36, 49], HIV symptoms [75]	Thrush [72], AIDS diagnosis [34, 46]		AIDS diagnosis [50]
Virologic characteristics		Viral load [32, 73]	Viral load [48, 73]	Viral load [77]	Viral load [54, 56, 60, 76]
Immunologic characteristics		CD4+ cell count [32, 36, 49, 63, 73–75], IgA[8] level [49]	CD4+ cell count [27, 37, 42, 53, 63, 64, 68, 72, 73], IgA[8] level [53], IgG[9] level [53], sTNFR-II[10] level [20]	CD4+ cell count [25]	CD4+ cell count [28, 40, 41, 44, 60]
Genetic characteristics			HLA[11] genotype [26]	CCR5[12] haplotype [51], HLA[11] haplotype [26]	
Host characteristics		Age [49, 74], age at seroconversion [62], time since seroconversion [62], gender [57]	Age [37, 48], BMI [68], gender [37, 57], time since seroconversion [59, 63], age at seroconversion [59]		Age [28, 47, 55], race [41], gender [21]

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[1] Highly active antiretroviral therapy;

[2] Methadone maintenance therapy;

[3] Opioid substitution therapy;

[4] Centre for Epidemiologic Studies Depression Scale;

[5] Hepatitis C virus;

[6] Antiretroviral therapy;

[7] Pneumocsystis carinii pneumonia;

[8] Immunoglobulin A;

[9] Immunoglobulin G;

[10] Soluble tumour necrosis factor;

[11] Human leukocyte antigen;

[12] CC Chemokine receptor 5