



Published in final edited form as:

AIDS. 2012 February 20; 26(4): 403–417. doi:10.1097/QAD.0b013e32834f19b6.

HIV infection and risk of overdose: a systematic review and meta-analysis

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Abstract

Drug overdose is a common cause of non-AIDS death among people with HIV and the leading cause of death for people who inject drugs. People with HIV are often exposed to opioid medications during their HIV care experience; others may continue to use illicit opioids despite their disease status. In either situation, there may be a heightened risk for nonfatal or fatal overdose. The potential mechanisms for this elevated risk remain controversial. We systematically reviewed the literature on the HIV–overdose association, meta-analyzed results, and investigated sources of heterogeneity, including study characteristics related to hypothesize biological, behavioral, and structural mechanisms of the association. Forty-six studies were reviewed, 24 of which measured HIV status serologically and provided data quantifying an association. Meta-analysis results showed that HIV seropositivity was associated with an increased risk of overdose mortality (pooled risk ratio 1.74, 95% confidence interval 1.45, 2.09), although the effect was heterogeneous ($Q = 80.3$, $P < 0.01$, $I^2 = 71\%$). The wide variability in study designs and aims limited our ability to detect potentially important sources of heterogeneity. Causal mechanisms considered in the literature focused primarily on biological and behavioral factors, although evidence suggests structural or environmental factors may help explain the greater risk of overdose among HIV-infected drug users. Gaps in the literature for future research and prevention efforts as well as recommendations that follow from these findings are discussed.

Keywords

fatal; HIV; mortality; opioid; overdose

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The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of NIH, NIDA, CDC, or CFAR.

Conflicts of interest

The authors declare no conflicts of interest.

Introduction

Drug overdose is a common cause of non-AIDS death among people with HIV and the leading cause of death for people who inject drugs [1–6]. People with HIV are often exposed to opioid medications during their HIV care experience; others may continue to use illicit opioids despite their disease status. Either scenario may present a heightened risk for fatal and nonfatal opioid overdose. Recently, both the US President’s Emergency Plan for AIDS Relief and the Global Fund to Fight AIDS, Tuberculosis and Malaria (<http://www.pepfar.gov/>) issued guidance that they will support overdose prevention activities, acknowledging the growing toll that overdose takes on people with HIV [7,8].

Opiates and synthetic and semisynthetic opioid drugs (hereafter referred to collectively as opioids) are important medications for the treatment of pain and end-stage disease. However, this class of drugs also has the potential for the development of physical dependence, abuse, and addiction. Opioids include oxycodone, hydrocodone, hydromorphone, fentanyl, morphine, and methadone. Indeed, heroin, an illegal opiate, is one of the most common drugs of abuse worldwide. The WHO reports that approximately 13.5 million people use opioids, including 9.2 million heroin users [9]. Many opioid users have a history of injection; similarly, many injectors report past opioid use. The global number of IDUs is estimated at 11–22 million people [10].

Injection drug use represents a major route of infection for HIV, accounting for up to 80% of new HIV infections in eastern Europe and central Asia [9]. Additionally, HIV-infected IDUs can act as a bridge population for transmission of HIV to the larger population. Injection-related HIV-epidemics exist in countries throughout the world, with incidence ranging from 1.5% in Australia and New Zealand to 17% in east/south-east Asia, 27% in eastern Europe, and 29% in Latin America [11].

Although the association between HIV infection and injection drug use has been well documented, the potential association between HIV and overdose has received less attention. In addition to the high rates of opioid mortality among IDUs [2,12,13], nonfatal overdose events are also common. Lifetime nonfatal overdose rates among heroin users range from 29 to 68% [14–17], and among illicit users of prescription opioids in the USA ranges from 28 [18] to 38% [19]. Nonfatal overdose is associated with significant morbidity, including pneumonia, renal failure, mental impairment, and cardiac arrhythmia [20]. The strongest predictor of experiencing an overdose is prior overdose [20,21], with most users reporting multiple overdose experiences in their lifetime [18,21,22].

Over the past two decades, investigators have considered a biological connection between HIV seropositivity and an elevated risk of overdose, whereas others dismiss detected associations as uncontrolled residual confounding [23]. Proposed biological mechanisms include underlying disorder (due to HIV infection) [3,24], abnormal liver function or pulmonary problems [13,25], poor physical health [26], medical complications from injecting [27], and reduction in CD4⁺ cell counts [28]. Additionally, some authors suggest a behavioral connection between HIV seropositivity and an elevated risk of overdose, namely drug use and risk-taking behaviors [1,25,29,30]. There may also be other important structural and environmental influences that have not been thoroughly considered.

Recent research pertaining to HIV [31–34], drug use [34,35], and overdose [21,36] describe elements of the ‘risk environment’ that can affect these health outcomes. For example, an opioid overdose is more likely to be fatal if the user is alone rather than in the presence of others. Injury epidemiology draws upon the Haddon matrix [37] to guide risk factor identification, prevention, and control that relate not only to host (patient), agent (the opioid), and environment (setting/context) factors but also to the timing of the injury: pre-

event, during event, and postevent. Although few investigators have critically examined the shared biological, behavioral, and structural risks associated with HIV infection and overdose, a comprehensive understanding of this nexus could hold enormous promise for public health interventions and could also provide potentially lifesaving information to healthcare professionals, who prescribe opioid medications to patients with HIV or who interact with HIV-infected opioid users.

This study aimed to systematically review the literature on the putative association of HIV infection with overdose, meta-analyze results, explore sources of heterogeneity, and investigate biological, behavioral, and structural causal mechanisms of association.

Methods

We performed a search of the *PubMed* database, conducted from July to September 2010, using combinations of the terms: HIV, drug, overdose, heroin, naloxone, naran, buprenorphine, methadone, opiate/opioid, fatal, fatality, death, mortality, morbidity, and nonfatal. We identified 251 unique articles that fitted our search criteria. All abstracts were read to identify potentially suitable manuscripts; 69 were identified as possibly relevant and were read completely. Of these, 23 were identified as irrelevant, and data were extracted from the remaining 46 studies using a standardized format. Inclusion criteria for articles were as follows: those presenting original research, being written in English, and being published in a peer-reviewed journal. There were no limitations on publication date or geography.

Extracted data were entered in a database with 28 distinct fields corresponding broadly to study details [design, period, population, HIV status (serological evidence, self-report)]; exposure and outcome definition and measurement; quantification of an association between HIV infection and overdose (or lack thereof); discussed causal mechanisms (biological, behavioral, environmental, none); and study limitations. Double data extraction was performed, with consensus on the extracted content reached by discussion, and final review of material by the first author.

To be eligible for the meta-analysis, studies must have reported measures of association [odds ratio (OR), relative risk (RR), hazard ratio] or sufficient data to calculate an unadjusted RR (i.e., overdose incidence by HIV status in a cohort design; OR and prevalence of overdose among HIV-uninfected in a cross-sectional or case-control design) with upper and lower confidence interval (CI) limits or standard errors. Adjusted effect measures were used in the analysis when included in the studies. Studies were pooled for analysis; ORs were transformed into RRs following standard methods [38–40].

When detected, we explored sources of variability extracted from the systematic review, including crude vs. adjusted analysis; cross-sectional vs. cohort design; US study location vs. outside of the USA; clinic-based population (yes/no); IDU only vs. mixed/unknown IDU status population; pre-HAART, post-HAART, and both pre-HAART and post-HAART era; year of study; calculated vs. reported measure of association; and fatal vs. nonfatal/both overdose outcomes. The Q -statistic and I^2 -statistic evaluated heterogeneity of effects [38]. Categorical data on potential sources of heterogeneity were assessed with Q -statistics comparing categories; continuous data were assessed using mixed-effects meta-regression. We used Comprehensive Meta-Analysis version 2 software (Biostat, Englewood, New Jersey, USA, 2005) [39] to generate summary estimates of the effects of HIV infection on overdose risk. Random effects models were employed to more accurately account for differences in sampling, methods, and aims among the reviewed studies [40]. To assess for publication bias, we checked for asymmetry in funnel plots of effects against standard errors

and applied Egger's test [41]. We first present the meta-analysis findings, and then summarize causal mechanisms of the HIV–overdose association from the systematic review.

Results

Of the 46 studies reviewed, six were case series or chart reviews, seven were cross sectional, and 33 were prospective or retrospective cohort studies. Studies spanned 15 countries, were published from 1988 to 2010, and reported data collected retrospectively or prospectively over a 29-year period (1977–2006). Table 1 [1–4,13,23–30,42–74] details reviewed studies.

Meta-analysis

A total of 27 studies were eligible for inclusion in the meta-analysis [1,2,13,25,29,30,42–60,75]. Of these, 22 were prospective or retrospective cohort designs, five were cross-sectional designs; 17 were conducted outside of the USA; and 16 used clinic-based samples. Participants were mostly IDUs ($n = 16$), or a mixture of participants of injecting and noninjecting or of unknown injecting status ($n = 11$). Overdose outcomes tended to pertain to fatal ($n = 21$) rather than nonfatal ($n = 6$) events. All but three studies [26,44,52] employed HIV serological testing to verify HIV status. Examination of funnel plots of effects showed no evidence of publication bias (data not shown); an Egger's test was not significant ($t = 1.07$, $P = 0.29$).

The pooled RR across the 27 studies was 1.60 (CI 1.16, 2.21); the Q -statistic was statistically significant and the I^2 -statistic was 94%. Figure 1a reports the forest plot. Covariates tested for sources of variation showed that only one factor was significant at the P value less than 0.10 level: study population type (IDU only vs. mixed or unknown IDU status).

HIV biologically tested

Three large studies did not collect HIV status biologically [26,44,52] and may have fundamentally underestimated the HIV–overdose association by 'missing' a large number of truly HIV-infected people who may not have known their status or underreported their HIV infection status. Pooling effects across the 24 studies reporting HIV status biologically returned an overall RR of 1.74 (CI 1.45, 2.09); the Q -statistic was statistically significant ($Q = 80.3$, $P < 0.01$) and the I^2 -statistic was 71%. Figure 1b reports the forest plot. Testing for heterogeneity showed a statistically significant source was study population type ($Q = 4.57$, $P = 0.03$). Studies with IDU only population types ($n = 14$) had pooled RR of 1.48 (CI 1.17, 1.86), but heterogeneity remained high (Q -statistic significant, $I^2 = 73\%$). Studies with a mixed (IDU, non-IDU) or unknown IDU status population ($n = 10$) had pooled RR of 2.18 (CI 1.66, 2.87); the Q -statistic was not statistically significant and the I^2 -statistic was 40%. A trend indicated study design as an additional source of heterogeneity across the 24 studies ($Q = 3.71$, $P = 0.05$) in which cross-sectional designs ($n = 4$) had a pooled RR of 2.41 (CI 1.65, 3.51); the Q -statistic was not significant and the I^2 -statistic was 44%. Cohort studies ($n = 20$) had a pooled RR of 1.59 (CI 1.32, 1.92); the Q -statistic was significant and the I^2 -statistic was 65%. Other potential sources of heterogeneity were not significant by Q -statistic or meta-regression.

Causal mechanisms considered in studies with positive associations

Proposed causal mechanisms for observed associations between HIV infection and overdose risk encompassed biological and behavioral factors and considered HIV as a potential confounder as well as a mediator of the association. Still, some authors dismissed a detected association as speculative. Biological explanations considered how aspects of HIV itself could elevate this risk through clinical status, immunosuppression, opportunistic infections,

and poorer physical health [1,24–26,30, 46,59]. Some authors named more specific mechanisms of action, focusing on pulmonary conditions or infections more common in people with HIV that are likely to exacerbate the respiratory depression that causes death from overdose [13,25]. Several studies posited that conditions that affect the body's ability to metabolize [e.g. liver disorder, co-infection with hepatitis B virus or hepatitis C virus (HCV)], which are also more common in people with HIV, could explain the observed association between HIV and overdose [13,24,25,46,58]. Wang *et al.* [25] systematically tested the mediating impact of some of these biological factors on the observed HIV–overdose association, determining that HIV immunosuppression and associated multisystem disorder (respiratory/pulmonary) accounted for a 20% reduction in effect. Abnormal liver functioning reduced the association by 12–35% [25].

Few studies examined patient HIV treatment status or HIV treatment adherence, although treatment was raised as a mediator of overdose risk. Assessing this association was impossible because investigators used population-level mortality data that indicated HIV status, but not treatment history. Oftentimes, even if HIV treatment status and adherence were assessed, direct comparisons between these variables and rates of overdose were not considered. In some instances, CD4 cell counts, which may serve as a proxy for HIV disease state, were assessed. Among this limited number of studies, findings varied, with some suggesting greater risk [24,61,76] and others no association [28,50] between lower CD4 cell counts and heightened overdose risk.

Behavioral factors that could explain the observed association of HIV infection and overdose risk were also raised. Authors discussed how high-risk lifestyle and psychiatric comorbidities could simultaneously explain overdose events and HIV status [1,26,29,30,48,59,62]. Although several studies raised whether HIV-infected drug users have more suicidal tendencies and, therefore, may engage in riskier drug use [30,58], research has not found such evidence [59]. Indeed, residual confounding from high-risk behaviors of HIV-infected drug users, frequent injectors, shooting gallery use, syringe sharing, or other 'risk-taking personality' traits appeared to produce small (15%) reductions in observed HIV–overdose effects [25]. Other authors suggest that drug users tend to reduce injecting behaviors after HIV diagnosis and also as HIV infection advances [46]. One study [63] found that people who knew their HIV status were more likely to reduce opioid consumption, rather than engage in other overdose preventive behaviors.

Structural factors as causal mechanisms

Seven studies measured structural and environmental risks for overdose. Factors considered in these studies included access to medication-assisted therapy (MAT) for opioid dependence, homelessness, neighborhood poverty and socioeconomic status, incarceration, and isolation or using drugs alone. Of the studies reviewed, several found that access to and enrollment in methadone treatment greatly reduced HIV-infected IDUs' risk of overdose [42,51,57]. Research has shown homeless and poor drug users to be at increased risk of overdose and that receiving government welfare payments were associated with lower overdose risk [43,45,57]. Tardiff *et al.* [45] found that high neighborhood poverty was associated with an increased risk of being HIV-positive, and that opioid overdose was more likely to occur among HIV-positive than HIV-negative decedents in New York City. Prison time, including lifetime incarceration and recent prison release, was another significant structural contributor to overdose risk [4,43]. Seaman *et al.* [4] observed that the risk of death from an overdose was eight times higher within 2 weeks of being released in an HIV-infected IDU cohort [43]. A case series of HIV-infected hospital patients, who died a non-AIDS death, found that 38 of 64 deaths were drug-involved intoxications (59%), 15 of which (39%) had recently been released from prison [24]. Surprisingly, the authors do not remark on history of incarceration among the decedents, although a contemporaneous

analysis on the same population mentions alterations to tolerance due to abstinence, such as recent return from prison, as an explanation for overdose risk in the predominantly injection-transmitted HIV cohort [76]. An intriguing study by Neira-León *et al.* [63] showed that HIV-infected IDUs were no more likely than HIV-uninfected IDUs to use drugs alone, and that this environmental overdose risk factor was responsive to intervention, either medical care or overdose prevention education.

Discussion

This article is the first to systematically review and meta-analyze the literature on the putative association between HIV infection and overdose risk. Among 46 studies extracted and reviewed in this undertaking, 24 reported data sufficient for inclusion in a meta-analysis and tested for HIV-infection biologically. Despite the heterogeneous pool of studies, the meta-analysis results suggest that people who use drugs have a 74% greater risk of overdose if they are HIV-infected compared with their counterparts who are not HIV-infected.

Causal mechanisms discussed in the literature to explain the increased risk tended to consider biological and behavioral factors, but other factors may also influence this association, including environmental and structural factors. Only seven studies (15%) systematically reviewed and considered environmental or structural factors in the analysis of overdose risk factors. Data from these studies suggest that environmental and structural risk factors shown previously to increase overdose risk also affect HIV-infected populations and, to the extent that they are more pronounced in people with HIV, could help explain some of the higher overdose risk associated with HIV status. The limited number of studies indicates a need for future research to consider the role these factors may play in overdose risk for HIV-infected and uninfected persons.

Similarities in risk and protective factors for HIV and overdose suggest an opportunity to reduce HIV transmission and overdose mortality by scaling-up established prevention interventions and extending existing legal and policy tools, most notably HAART, MAT, and prescribed naloxone.

HAART

Too few studies examined HIV treatment status or adherence to quantify its mediation of overdose risk. Wang *et al.* [25] provided the most compelling evidence of a biological component, particularly immunosuppression and multisystem disorder, to the HIV-overdose association. It is, therefore, biologically plausible that HAART's benefits for HIV-infected patients could also extend to protection against overdose for people who use drugs. Yet, even when HIV treatment is received, potential medication interactions with continued street drug use may contribute to persistent overdose risk. For instance, several antiretroviral medications are known to increase or decrease methadone and other street drug blood levels or have known interactions with benzodiazepines and marijuana [77,78], both of which may be used therapeutically and abused. As people with a substance use disorder are often excluded from randomized clinical trials, it may be challenging to anticipate many of the side-effects and consequences of new antiretroviral medications in this population. Several published reviews offer basic clinical guidance on these topics [77–80]. Further research is needed to better understand specific HIV medication interactions and how to reduce risk of overdose in substance using patients.

Access to HAART medications, prescribed by providers prepared to prevent and manage potential interactions between antiretrovirals and drugs with abuse potential, may be viewed as a protective factor against overdose for HIV-infected drug users. Efforts to ensure that all

HIV-infected drug users have adequate and stable access to HAART have the potential to reduce mortality due to AIDS and to overdose.

Medication-assisted therapy

Numerous studies including several examined in this systematic review [30,51,57] have established receipt of MAT, particularly methadone and buprenorphine therapies, as protective against fatal overdose. MAT reduces illicit drug use, decreases HIV risk behavior, and decreases drug-associated crime [81–86]. Access to adequate MAT also increases compliance for antiretroviral therapy among HIV-infected patients [87–90]. On a community level, providing both MAT and HAART can reduce the transmission of HIV from opioid users to others, helping to reduce the overall incidence and prevalence of HIV [81,85,86,90,91]. The Joint United Nations Programme on HIV/AIDS estimates that there are only eight people receiving MAT for every 100 people who inject drugs globally [92]. We note that studies have found increased overdose risk immediately following dropout or cessation across a variety of treatment types, although the risk is lowest with MAT [93], so relapse and overdose prevention are important while in treatment.

Naloxone

One public health intervention to decrease overdose-associated morbidity and mortality is the distribution of naloxone to at-risk drug users, their families, and friends. Naloxone is a prescription medication with no abuse potential that reverses an opioid overdose and is part of the standard emergency medical response to an opioid overdose [94,95]. Such programs train people in overdose prevention, response, and naloxone administration. Between 1996 and 2010, US programs, at more than 155 sites located in 16 states, have documented over 10 000 overdose reversals with naloxone by over 50 000 trained bystanders [96–101], with mounting evidence linking program enrollment to reductions in community opioid overdose mortality [97,102,103].

Targeting naloxone provision to HIV-infected opioid users has the potential to reduce fatal overdose in this population. Physicians who care for HIV-infected opioid users could prescribe naloxone to at-risk patients, including patients who are opioid injectors, who illicitly use prescription opioids, who are prescribed long-acting opioids, or who are diagnosed with other conditions or illnesses known to increase overdose risk. Programs that provide care and support to HIV-infected people could also distribute naloxone, given sufficient medical oversight of the prescribing practices. Syringe exchange programs are a common mechanism for distributing naloxone and, in places with high HIV prevalence among injectors, provide a means of reaching people at high overdose risk. Countries (or states) with formularies for HIV-related medications could consider adding naloxone to these lists; it is already on WHO's Model List of Essential Medicines [104].

Limitations of reviewed studies

We detected important methodological limitations in the reviewed studies, which warrant mention. First, studies varied immensely in their definition of 'overdose', more often failing to define it. In some cases, intentionality was not addressed, which may have increased outcome measurement variability. Fatal drug overdose as cause of death was sometimes defined by a committee of study investigators; others employed standard disease classification [105]. Nonfatal overdose may have been ascertained by self-report – typically without defining or describing symptoms of overdose – or by administrative record of the victim's admittance to a hospital or response by emergency medical services. Both approaches may be severely flawed. Self-reported overdose may be subject to response bias: if HIV-infected persons are more likely to report nonfatal overdoses because of heightened awareness of their health status, associations could be biased away from the null.

Furthermore, for studies conducted in places where police also attend emergency calls and may arrest those at the injury scene on drug-related charges, relying upon administratively defined nonfatal overdoses may severely underestimate the total number of events and introduce selection bias if certain types of drug users are less likely to call for help. It is also likely that nondifferential error in self-reported overdose occurred, but would likely have resulted in a bias toward the null hypothesis for these studies. Another challenge to this review was verification of drug treatment status and HIV adherence, as they were poorly cataloged. Employing more systematic definitions of overdose, expanding the use of computer-assisted technology to improve validity of responses, better tracking treatment attendance and exposure; also, cataloging disease progression and adherence to HIV medication regimens would greatly facilitate comparisons across studies for future meta-analyses and could better inform readers of these important details.

Study strengths and limitations

This study has several strengths. First, we comprehensively searched the available literature, including a broad range of study types, populations, and outcomes, and pooled available evidence to investigate and quantify the association of HIV with overdose risk. Second, this study applied theories relevant to the exposure and outcome from infectious disease epidemiology and injury epidemiology. In doing so, our review extends previous discussions in single studies that limited the putative causal association between HIV and overdose risk to only biological factors. As with many findings from the HIV field [106–108], considering the effects of extra-medical interventions and influences can be revealing, clinically significant, and can point the way toward approaches that may have larger public health impact.

This study has some potential limitations that suggest avenues of future research. First, the meta-analyzed results reflected a high degree of variability across studies, but we were unable to determine many statistically significant sources of heterogeneity from the tested covariates. The relatively small number of studies, especially those providing covariates such as MAT, HCV, and HIV treatment status and adherence, limited our ability to test heterogeneity sources. To accommodate heterogeneity levels, we report pooled effects from random effects models, as recommended [40]. Second, we were unable to adequately review studies on structural and environmental risk factors that may differentially augment the risk of or constitute causal mechanisms of overdose in people with HIV. The topic of structural risk is an active area of inquiry in overdose [21,36], other injury health outcomes such as motor vehicle accidents [109,110] as well as in HIV transmission [31,33]. A third limitation was the sparse literature on behavioral factors, especially one's social network composition, size, and supportiveness that may exert causal influences on overdose risk that differ by HIV status. Fourth, few reviewed articles were identified in resource-poor countries, or in locations with current injection-driven epidemics. To address all of these significant limitations, there is a clear indication for future research. Longitudinal studies of health outcomes for participants with HIV should consider including nonfatal overdose as a sentinel health event and exploring fatal overdose as a primary outcome, especially for observational and treatment intervention studies with people using opioids. In places where opioids are increasingly being prescribed to treat chronic pain (e.g. USA, Canada), the population at risk, and that should be considered in longitudinal studies of overdose, may extend beyond those with a history of substance use disorder or infected by injection drug use. Finally, the reviewed articles included those published only in English and studies conducted in humans. Although English-language articles represent the majority of research published on this subject, roughly 10% of the 317 database search results were not in English, making it possible that we overlooked important non-English language contributions.

Conclusion

This systematic review and meta-analysis found evidence of a positive association between HIV status and overdose risk. There may be biological, behavioral, and structural mechanisms influencing the greater risk of overdose for people with HIV. Future research to explore these mechanisms is indicated. Expanded access to existing effective interventions to reduce overdose risk is warranted for drug users infected with or at risk of HIV. Healthcare providers who treat HIV-infected patients with a history of substance use disorder and/or who prescribe opioid medications should consider counseling patients on how to reduce their risk of overdose. Healthcare providers may also consider prescribing naloxone to patients, discussing the option of initiating buprenorphine therapy, or offering a referral to another MAT, as appropriate.

Acknowledgments

T.C.G. conceived of the study, reviewed articles, performed analysis, and participated in manuscript writing. S.K.M. and M.A.Y. reviewed articles, assisted with analysis, and participated in manuscript writing. E.R.P. performed the meta-analysis and participated in manuscript writing. J.D.R. provided feedback on the study approach, interpretation of data, and reviewed manuscript drafts.

The authors are grateful to Nickolas Zaller, Sarah Bowman, Roxanne Saucier, Nabarun Dasgupta, and R. Douglas Bruce for their thoughtful comments and edits to earlier drafts of this manuscript.

This work was supported in part by a grant from the Centers for Disease Control and Prevention (CDC) (R21CE001846-01 to T.C.G.); award number K24DA022112 from the National Institutes of Health, National Institute on Drug Abuse (NIH/NIDA); and by grant number P30-AI-42853 from the National Institutes of Health, Center for AIDS Research (NIH/CFAR).

This work was also made possible in part through the support of training grant number 5T32DA013911 from the National Institutes of Health, National Institute on Drug Abuse (NIH/NIDA).

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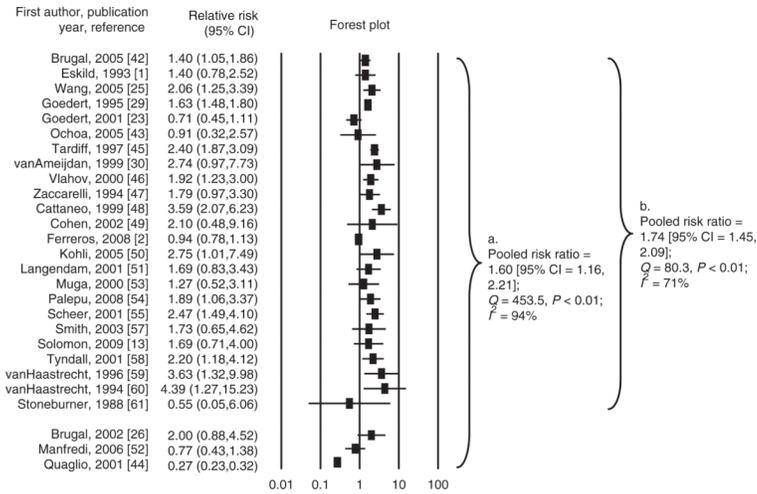


Fig. 1. Meta-analyses of the effect of HIV infection on overdose risk among drug users (a) All 27 studies and (b) all 24 studies in which HIV status was reported biologically. CI, confidence interval.

Detailed summary of the 46 systematically reviewed studies.

Table 1

References	Data collection years	Study design	Study population (N, definition)	HIV status	HIV treatment status/ARV adherence?	Fatal or nonfatal	Number of overdose deaths	Number of all deaths
Bargagli <i>et al.</i> [100]	1990–1998	Retrospective cohort	N = 35 935; opiate users recruited from drug treatment centers	Not assessed	Assessed/not assessed	Fatal	13 per 1 000 in Barcelona; approximately seven per 1 000 in Denmark, London, Rome, Vienna	3221 total
Brette <i>et al.</i> [24]	1986–1995	Case series within a prospective cohort	N = all patients who were HIV-positive and died without an AIDS diagnosis (N = 64) examined for study; 720 HIV-positive at hospital (total cohort)	All HIV-positive	Not assessed/not assessed	Fatal	29	64 non-AIDS and 195 AIDS deaths
Brugal <i>et al.</i> [26]	1996	Data from cross-sectional surveys analyzed as case-control and case cross-over designs	N = 2556; patients entering treatment for heroin dependence in outpatient facilities (regardless of therapy employed)	19.4% HIV-positive	Not assessed/not assessed	Nonfatal	No deaths	No deaths
Brugal <i>et al.</i> [42]	1992–1997	Prospective cohort	N = 5049; heroin users in methadone treatment	Not assessed	Not assessed/not assessed	Fatal	349	1005 total
Carvajal <i>et al.</i> [101]	1988–1994	Retrospective case series	N = 442; HIV-positive patients referred to psychiatric program from infectious disease units in general hospitals	All HIV-positive	Yes: assessed stages of AIDS according to CDC definitions/ N/A- pre HAART	fatal	1	2 total
Cattaneo <i>et al.</i> [48]	1996–1997	Cross-sectional	N = 397; blood samples from	HIV-positive (N = 20); HIV-positive and	Not assessed/not assessed	Fatal	107 total; 33 HIV-positive, 74 HIV-negative	397 cadavers

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References	Data collection years	Study design	Study population (N, definition)	HIV status	HIV treatment status/ARV adherence?	Fatal or nonfatal	Number of overdose deaths	Number of all deaths
Cohen <i>et al.</i> [49]	enrolled in 1994–1995	Prospective cohort	397 decedents age 16–50 N = 2059, 596; 2059 HIV-positive women and 569 women at risk of HIV infection; all 13 years or older at enrollment	HCV- positive (n = 45) HIV-positive (n = 2059)	YES: article defines therapy regimens on pg 92 L. RR for women on combined antiretroviral therapy: AIDS-related deaths, RR 0.6 (95% CI 0.4–0.7) and aRR 0.97 (95% CI 0.69–1.4), non-AIDS-related deaths, RR 1.1 (0.7–1.7) and aRR 1.6 (0.96–2.7). After adjusting for viral load, combination therapy not independently associated with death due to AIDS; 50% of HIV-positive participants reported using combo therapy by 1998, with first use reported in 1996/not assessed	Fatal	16 HIV-positive and 2 HIV-negative	91 non-AIDS and 294 AIDS deaths among HIV-positive; 17 deaths among HIV-
De Palo <i>et al.</i> [63]	1991–1992	Case series	N = 65; ICU patients admitted to hospital with proven HIV infection or AIDS-defining opportunistic infection	HIV-positive or had AIDS-defining opportunistic infection	Prior antiretroviral treatment did not influence outcome; 18 patients had received antiretroviral treatment/not assessed	Both	2	33 total
Eskild <i>et al.</i> [1]	1985–1991	Prospective cohort	N = 1009; IDUs (defined as any injection in lifetime)	HIV-positive (n = 180) and HIV-negative (n = 829)	N/A pre-HAART	Fatal	58 (38 HIV-negative and 20 HIV-positive)	87 total (55 HIV-negative and 32 HIV-positive)
Eskild <i>et al.</i> [102]	1987–1991	Prospective cohort	N = 131; HIV-positive IDUs registered with department of health before 1987; IDU defined as any history of injecting drugs after 1979, sample represented 75% of all HIV-positive IDUs in Norway diagnosed before 1987	All HIV-positive	N/A pre-HAART	Fatal	17	21 nonnatural; total of 25 subjects died

References	Data collection years	Study design	Study population (N, definition)	HIV status	HIV treatment status/ARV adherence?	Fatal or nonfatal	Number of overdose deaths	Number of all deaths
Ferretos <i>et al.</i> [2]	1987–2004	Community-based prospective cohort	N = 7186; active IDUs recruited from any of three AIDS Prevention and information centers	HIV-positive (n = 3443) and HIV-negative (n = 3743)	Not assessed/not assessed	Fatal	89 HIV-positive deaths before 1997, 121 deaths after 1997 related to drug use (includes OD, suicide, and accidents); 112 HIV-deaths before 1997, 132 deaths after 1997 due to drug-related deaths	1589 (1209 HIV-positive and 380 HIV-)
Fingerhood <i>et al.</i> [27]	1994–2003	Prospective cohort	N = 175; consecutive patients at Baltimore clinical specializing in care for people with HIV and substance abuse; all participants were HIV-positive and current IDUs	All HIV-positive	HIV treatment was provided at the clinic [80 participants (45.7%) received HAART, 95 (54.2%) were exposed to NRTI, 36 (20.6%) were exposed to NNRTI, and 62 (35.4) were exposed to PI/not directly assessed but viral load may be indicator: overall 49 (28%) of participants achieved undetectable viral load, with 49 achieving it on HAART (61.3% of HAART patients)]	Fatal	6	53 total deaths
Goedert <i>et al.</i> [29]	1980–1990	Retrospective cohort	N = 4962; individuals enrolled in drug treatment program in the province	HIV-positive (n = 2040), HIV-negative (n = 1063), HIV-untested (n = 1859)	Not assessed/not assessed	Fatal	64 total; 4 among HIV-negative, 34 among HIV-untested; 26 among HIV-positive	281 total deaths; 9 among HIV-, 88 among HIV-untested, 184 among HIV-positive
Goedert <i>et al.</i> [23]	1987–1991	Prospective cohort	N = 6570; 18 or older and reported IDU within the preceding month	HIV-positive and HIV-	Not assessed; authors note that HAART therapy likely had little (if any) effect on the results because there was little use of the therapy among American drug users until at least 1997/not assessed	Fatal	186	1351 deaths
Kohli <i>et al.</i> [50]	1996–2001	Longitudinal study (prospective cohort)	N = 1054; HIV-infected and at-risk drug users recruited from methadone treatment programs in the Bronx; only patients who underwent 1 year or more of research during	38% HIV-positive (n = 398)	Among 293 HIV-positive with a CD4 cell count <350 cells/ μ l, 186 (63%) used HAART during the study period/not assessed	Fatal	10 HIV-positive and 6 HIV-negative	23 HIV-positive drug-related deaths and 21 HIV-negative drug-related deaths; overall: 104 HIV-positive deaths and 40 HIV-negative deaths

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References	Data collection years	Study design	Study population (N, definition)	HIV status	HIV treatment status/ARV adherence?	Fatal or nonfatal	Number of overdose deaths	Number of all deaths
Krentz <i>et al.</i> [103]	1984–2003	Retrospective chart review	the study period were included in COD analysis N = 1987; all HIV-positive individuals in southern Alberta	All HIV-positive	ARV-naive patients were defined as not having received any ARV drugs at any time during the course of their illness; 87% of HIV-positive patients who died from AIDS were extensively treated; crude mortality rate declined from 117 deaths per 1000 patient-years pre-HAART to 24 death per 1000 patient-years in current HAART period/adherence rates not reported but acknowledge noncompliance as persistent issue	Fatal	Non-AIDS deaths for the entire study period were 75; 22 from OD	Total deaths in pre-HAART were 436, total deaths in current HAART era were 124
Langendam <i>et al.</i> [51]	1985–1996	Prospective cohort	N = 1218; 827 selected for analysis, all patients at a methadone clinic who attended at least one F/U	27% HIV-positive	Not assessed/not assessed	Fatal	31 total; 14 deaths among HIV-positive; 17 among HIV-negative	150 total deaths
Laurichesse <i>et al.</i> [104]	1982–1996	Surveillance data analysis (case record review) on pre-AIDS and AIDS deaths reported to government	N = 9057; 485 pre-AIDS deaths and 8574 AIDS deaths	All HIV-positive	Not assessed/not assessed	Fatal	24	468 pre-AIDS deaths
Lyles <i>et al.</i> [28]	1988–1992	Prospective cohort	N = 605; HIV-1-infected IDUs	All HIV-positive	Not assessed but F/U occurred in an HIV outpatient study clinic/not assessed	Nonfatal	Nonfatal study	No deaths
Manfredi <i>et al.</i> [52]	1977–2002	Prospective cohort	N = 1214; IDUs attending outpatient service for treatment and prevention of substance abuse	HIV-positive (n = 426); HIV-negative (n = 433)	Not assessed, authors note a considerable drop in death rates due to AIDS around 1997, coinciding with the introduction of HAART/not assessed.	Fatal	60 total	271 total deaths
Mezzelani <i>et al.</i> [105]	1985–1994	Retrospective cohort	N = 1 022; deaths among IDUs attending/seeking medical care at 26 drug centers	49% HIV-positive (n = 500); 21% HIV-negative (n = 219); 20% unknown serologic status (n = 202)	Not assessed/N/A pre-HAART	Fatal	389 patients: 100 HIV-positive, 130 HIV-negative, 159 HIV unknown	1022 total deaths

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References	Data collection years	Study design	Study population (N, definition)	HIV status	HIV treatment status/ARV adherence?	Fatal or nonfatal	Number of overdose deaths	Number of all deaths
Miller <i>et al.</i> [106]	1996–2004	Prospective cohort	N = 572; active IDUs, aged 14–29 years and residents of the Vancouver area	16% HIV-positive	Not assessed/not assessed	Fatal	4	42 deaths, but 20 of these were after age 30 and were excluded from further analysis
Mirakbari <i>et al.</i> [107]	1997–1999	Prospective cohort	N = 1 155, patients of St. Paul's Hospital ED that received naloxone in prehospital or ED setting because of suspected opiate overdose	HIV-positive patients	Not assessed/not assessed	Both	Not reported	8 deaths in total for 24h period postassessment
Muga <i>et al.</i> [53]	1987–1991	Prospective cohort	N = 376; intravenous heroin users admitted to detoxification between February 1987 and January 1990	70.2% HIV-positive at entry	Not assessed/not assessed	Both	18 HIV-positive, 6 HIV-negative	82 total deaths
Neira-León <i>et al.</i> [65]	2001–2003	Prospective cohort	N = 991; 18–30-year-old males recruited in outdoor settings by chain-referral procedure, had used heroin in last 90 days, and on at least 12 days in last year	13.6% HIV-positive, 66.7% HIV-negative, 19.7% unknown	Not assessed/not assessed	Nonfatal	No deaths	No deaths
Ochoa <i>et al.</i> [43]	2000–2001	Prospective cohort	N = 795; IDUs under 30 years, had injected once or more in the prior month, recruited via street outreach, snowball technique	HIV-positive (n = 19), HIV-negative (n = 595)	Not assessed/not assessed	Nonfatal	No deaths	No deaths
Palepu <i>et al.</i> [54]	1999–2006	Prospective cohort	N = 7015; ICU database of prospectively	4.4% HIV-positive (n = 309)	N/A pre-HAART	Both	12 HIV-positive, 140 HIV-negative	297 HIV-positive, 6566 HIV-

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References	Data collection years	Study design	Study population (N, definition)	HIV status	HIV treatment status/ARV adherence?	Fatal or nonfatal	Number of overdose deaths	Number of all deaths
Penning <i>et al.</i> [3]	1981–1992	Retrospective cohort	collected data of patients admitted, diagnosed based on the ICNARC N = 638; autopsied drug death cases at the Munich Institute of Forensic Medicine	HIV-positive (n = 74), HIV-negative (n = 510), unknown Status (n = 54)	N/A pre-HAART	Fatal	638	638
Prins <i>et al.</i> [64]	1982–1988	Retrospective cohort	N = 664; IDUs with known HIV status and date of status determination who took part in one of eight European prospective cohort studies on seroconversion	HIV-positive at start (n = 331), HIV-negative at first and seroconverted during F/U (n = 351)	N/A pre-HAART	Both	24	108; 57 with AIDS, 50 without AIDS
Quaglio <i>et al.</i> [44]	1985–1998	Retrospective cohort	N = 2708, all IDUs who had sought medical care at least once in the PCUDs during study period	46.3% HIV-positive (n = 1254); 32.3% HIV-negative (n = 876); 21.4% unknown serological status (n = 578)	Not assessed/not assessed	Fatal	1001	2708 total deaths
Scheer <i>et al.</i> [55]	1995–1997	Cross-sectional	N = 1959; all 13–70-year-old patients examined by San Francisco Medical Examiner during study period, or individuals found through review of laboratory and pathology reports, death certificates, and medical records	9% HIV-positive (n = 176), and AIDS was diagnosed 60% of these (n = 105)	Not assessed/not assessed	Fatal	361; 329 with HIV diagnosis; 24 HIV-positive, 305 HIV-negative	1959 total deaths

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References	Data collection years	Study design	Study population (N, definition)	HIV status	HIV treatment status/ARV adherence?	Fatal or nonfatal	Number of overdose deaths	Number of all deaths
Seaman <i>et al.</i> [4]	1983–1994	Retrospective cohort	N = 316; male IDUs infected with HIV in the City Hospital HIV cohort	All HIV-positive	Not assessed/not assessed	Fatal	6 of 7 deaths overdose within 2 weeks, 14 of 26 deaths were overdoses after	33 total deaths
Selwyn <i>et al.</i> [108]	1985–1990	Prospective cohort	N = 731; former and current IDUs recruited from a methadone clinic in the Bronx	306 HIV-positive, 425 HIV-negative at study enrollment; 14 seroconverted during F/U; 2 HIV-positive excluded from analysis; total of 318 seropositive individuals in analysis	N/A pre-HAART	Fatal	3 HIV-positive and 5 HIV-negative	72 HIV-positive and 25 HIV-
Smith <i>et al.</i> [57]	1993–1999	Prospective cohort	N = 885; HIV-positive women (871 seroprevalent, 14 seroconverters), and 425 HIV-negative women at behavioral risk for HIV infection into the HIV Epidemiological Research Study	HIV-positive (n = 885), HIV-negative (n = 425)	Of women with study visits in the last 6 months of 1999 and CD4 ⁺ cell counts <200 cells/ μ l, 41.5% were taking HAART, 27.4% were on non-HAART combinations, 2.8% were on monotherapy, and 28.3% were taking no antiretrovirals/adherence with HAART evaluated in a substudy of 175 HIV-positive HERS participants. Mean monthly adherence was <60%; 2% had >95% adherence over 6 month F/U	Fatal	18 HIV-positive; 5 HIV-negative	234 deaths among HIV-positive and 8 deaths HIV-
Solomon <i>et al.</i> [13]	2005–2008	Prospective cohort	N = 1158; IDUs, recruited by field staff in zones known to have IDUs, and then snowball strategy employed. Eighteen and older, self-reported injection at least once in past 6 months	HIV-positive (n = 293), HIV-negative (n = 865)	Not assessed/not assessed	Fatal	22 total (14 HIV-negative, 8 HIV-positive)	85 deaths
Stoneburner <i>et al.</i> [61]	1978–1986	Prospective cohort	N = 7884; deaths reviewed; a subset of deaths were reviewed in more detail (497 IDUs)	HIV-positive (n = 230), HIV-negative (n = 255), and remaining had unknown COD in the HIV study subset	N/A pre-HAART	Fatal	Among a subset of 485 IDU non-AIDS death cases: 1 HIV-positive OD and 2 HIV-negative OD	230 HIV-positive and 255 HIV-negative in HIV study subset; total deaths in study = 7884

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References	Data collection years	Study design	Study population (N, definition)	HIV status	HIV treatment status/ARV adherence?	Fatal or nonfatal	Number of overdose deaths	Number of all deaths
Talaie <i>et al.</i> [109]	2004–2005	Cross-sectional	enrolled in an HIV study) N = 214; opium poisoned patients admitted to ICU and ward of poisoning center at hospital	HIV-positive (n = 3), HIV-negative (n = 208), Unchecked (n = 3)	Not assessed/not assessed	Nonfatal	Nonfatal	Nonfatal
Tardiff <i>et al.</i> [45]	1991–1993	Seroprevalence (cross-sectional) study	N = 2159; people 15 or older who died of accidental fatal drug overdoses in New York City	29.9% HIV-positive (n = 646)	Not assessed/not assessed	Fatal	2159	2159
Tyndall <i>et al.</i> [58]	1996–2000	Prospective cohort	N = 1416; individuals who injected drugs within the past month, 14 or older, recruited through posters, community organizations	303 HIV-positive and 1113 HIV-negative	Not assessed/not assessed	Both	40: 15 HIV-positive, 25 HIV-negative	125 total deaths
van Ameijden <i>et al.</i> [30]	1989–1995	Prospective cohort	N = 498; Dutch IDUs recruited from methadone and HIV treatment centers	29% HIV-positive	Not assessed/not assessed	Both	15	44 total deaths
van Asten <i>et al.</i> [110]	1982–2001	Prospective cohorts (cross-cohort analysis)	N = 790; IDUs with a known date of a seronegative and seropositive HIV test in eight cohorts spanning six countries	790 HIV-positive	Of the 530 IDU in F/U in the HAART era, 227 IDU received HAART/not assessed	Both	31	276 total deaths
van Haastrecht <i>et al.</i> [60]	1985–1992	Prospective cohort	N = 338; Dutch nationals recruited from 'low-threshold' methadone programs and through a sexually	HIV-positive (n = 86), HIV-negative (n = 252) at entry	N/A pre-HAART	Fatal	6 HIV-positive, 4 HIV-negative	Not reported

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References	Data collection years	Study design	Study population (N, definition)	HIV status	HIV treatment status/ARV adherence?	Fatal or nonfatal	Number of overdose deaths	Number of all deaths
van Haastrecht <i>et al.</i> [59]	1985–1993	Prospective cohort	transmitted disease clinic for drug-using prostitutes N = 632; Dutch nationals recruited from 'low-threshold' methadone programs and through a sexually transmitted disease clinic for drug-using prostitutes	HIV-positive at entry (n = 139), seroconverted over F/U. For IDUs HIV-positive (n = 32), for non-IDUs: HIV-positive (n = 4), seroconverts (n = 6)	Not assessed/not assessed	Both	6 HIV-negative, 10 HIV-positive	77 total deaths
Vlahov <i>et al.</i> [46]	1988–1995	Prospective cohort	N = 2960; systematic sample of 160 HIV-negative and all HIV-positive participants (704 at baseline) were analyzed, of 2960 who were enrolled and 2203 who appeared for at least one F/U; 271 seroconverted during the study	HIV-positive at baseline (n = 704) and seroconverted during F/U (n = 271)	N/A pre-HAART	Fatal	42 HIV-positive, 39 HIV-negative	416 total deaths
Wang <i>et al.</i> [25]	1988–2001	Prospective cohort	N = 1927; active (within past 6 months) IDUs	All HIV-negative at baseline, seroconverted during study (n = 308)	IDUs were censored at initiation of HAART for this analysis/not assessed due to censoring	Fatal	92 (67 HIV-positive)	92
Zaccarelli <i>et al.</i> [47]	1985–1991	Prospective cohort	N = 2431; IDUs attending two drug treatment centers in Rome who underwent HIV testing between 1985 and 1991	HIV-positive (n = 770); HIV-negative at enrollment (n = 1661), seroconverted (n = 82)	N/A pre-HAART	Fatal	89 HIV-positive, 18 HIV-negative	181 total deaths (89 due to AIDS and 92 due to other causes)

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aRR, adjusted relative risk; ARV, antiretroviral; COD, cause of death; ED, emergency department; F/U, follow-up; HCV, hepatitis C virus; ICNARC, Intensive Care National Audit and Research Council; IDU, injection drug user; OD, overdose; OR, odds ratio; PCUDs, public health authority centers for drug users; RR, relative risk.