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BRIEF REPORT

Beyond Overdose: Drug-Related Deaths in People With and Without HIV in San Francisco, 2007–2018

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Despite elevated mortality in people with HIV (PWH) using drugs, drug-related deaths are poorly characterized. Among 6764 drug-related deaths, methamphetamine was more common in PWH than others. One in 4 deaths in PWH involved acute infection. Combatting mortality in PWH who use drugs should include stimulant-specific and infection prevention efforts.

Keywords. cause of death; drug overdose; HIV infections; infections.

Amidst a national crisis related to soaring rates of drug use and overdose, reducing mortality among people with HIV (PWH) in the United States remains a challenge. In San Francisco, PWH who have a history of injecting drugs have nearly double the 3-year mortality compared with all PWH in San Francisco (21% vs 11%) [1]. In the general US population, the incidence rates of drug overdose and invasive bacterial infections related to drug use have risen in the last decade [2]. However, our understanding of causes of death among PWH who use drugs (including alcohol) has been limited, and few studies have investigated specific causes of drug-related death beyond overdose [3]. We are unaware of investigations designed to compare drug-related causes of death in people with and without HIV. We sought to compare drug-related deaths and associated causes of death in those with and without HIV in order to inform targeted interventions to reduce mortality among PWH who use drugs.

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METHODS

Study Design and Population

This was a cross-sectional study of decedents who died from drug-related causes (including alcohol) in San Francisco from January 1, 2007, through December 31, 2018. Decedents aged 14 years or older were identified by obtaining all San Francisco drug-related death records from the California Electronic Death Reporting System (CA-EDRS). Demographic data, causes of death, significant conditions contributing to death, and substances involved in death were obtained. These methods, as well as the San Francisco Chief Medical Examiner's Forensic Laboratory Division toxicology screening processes, have previously been described [4]. Using a computational search of causes of death and/or significant condition fields for recreational drugs excluding tobacco (eg, alcohol, heroin, fentanyl, methamphetamine, cocaine, and others) (Supplementary Appendix A), a total of 7056 drug-related deaths were identified. After physician review (A.A.), 292 decedents were excluded because the death was not due to illicit drugs, yielding a final sample size of 6764 decedents.

To identify decedents who had HIV, we next performed a computational search of death certificate fields for the following terms: "HIV," "human immunodeficiency virus," "AIDS," and "acquired immunodeficiency syndrome," and 223 decedents were identified. To address the possibility that this method of identification led to an underascertainment of deaths among PWH, we compared the number of deaths among people who had HIV noted on the death certificate with that in the San Francisco Department of Public Health HIV surveillance database. Among this database of all individuals diagnosed with HIV in San Francisco, there was a similar number of San Francisco deaths that listed drug overdose as a cause of death among PWH between 2007 and 2018 [1], suggesting that our approach was sufficient.

Classification of Drug-Related Deaths

All drug-related deaths were further classified based on their proximal cause of death, and each death could have multiple classifications. After manual review of a random sample of 100 records weighted by death year, the following categories were established for coding deaths: overdose, acute infection, noninfectious medical complication, trauma or violence, or other miscellaneous cause. The cause of death and significant condition fields were computationally searched for a list of terms corresponding with each category (Supplementary Appendix B). Each decedent record was then manually reviewed by A.A. to

ensure classification accuracy, and a subset was secondarily reviewed for internal consistency by P.C.

Statistical Analysis

We performed chi-square and Fisher exact tests to compare demographic characteristics and substances involved in death between decedents with and without HIV. A separate multivariable logistic regression model evaluated the relationship between HIV status of the decedent (independent variable) and each cause of death category described above (overdose, acute infection, a noninfectious medical cause, trauma or violence, or other; dependent variables), adjusting for the following independent variables; decedent age, biological sex, and race/ethnicity. All analyses were performed using Stata 16 (College Station, TX, USA).

Patient Consent Statement

Patient consent was not obtained, as all data were de-identified before use, and this study was deemed exempt by the University of California, San Francisco, Institutional Review Board (IRB #: 19-27119).

RESULTS

Between 2007 and 2018 in San Francisco, 6764 individuals died related to drug use, and 223 of these decedents had HIV noted on their death certificate. The median age was younger among PWH than those without HIV (50 vs 53 years, respectively) (Table 1). Stimulants, including cocaine, amphetamine, methamphetamine, and methylphenidate, were involved in 40% (n = 90) of drug-related deaths among PWH compared with 29% (n = 1919) of those without HIV ($P < .01$). Similarly, methamphetamine-related deaths were more common among PWH than those without HIV (21% vs 13%; $P < .01$). In contrast, alcohol-related deaths were less common among PWH (26%) than those without HIV (26% vs 46%; $P < .01$).

Table 1. Characteristics of Drug-Related Deaths in San Francisco Between 2007 and 2018, by HIV Status

	Decedents With HIV (n = 223)	Decedents Without HIV (n = 6541)	*P* Value
Age, median (IQR), y	50 (45–56)	53 (42–61)	.02
Male sex	80 (178)	77 (5020)	.33
Race/ethnicity, % (No.)			
White	59 (130)	54 (3518)	.19
Black/African American	26 (58)	21 (1379)	.08
Hispanic/Latinx	8 (17)	15 (978)	<.01
Asian/Pacific Islander	3 (7)	6 (391)	.08
Other/unknown	4 (8)	3 (189)	.54
Drugs involved, % (No.)			
Any opioid	26 (58)	26 (1696)	.98
Heroin	2 (5)	6 (373)	.03
Fentanyl	2 (4)	3 (215)	.22
Any stimulant[a]	40 (90)	29 (1919)	<.01
Cocaine/crack	22 (48)	19 (1211)	.26
Methamphetamine	21 (46)	13 (878)	<.01
Alcohol	26 (57)	46 (3029)	<.01
Any benzodiazepines	6 (13)	7 (466)	.55
Proximal cause of drug-related death, % (No.)			
Overdose	38 (84)	37 (2444)	.93
Acute infection	26 (58)	8 (523)	<.01
Noninfectious medical cause of death	37 (83)	38 (2500)	.76
Trauma/violence	3 (7)	14 (934)	<.01
Other	6 (14)	9 (609)	.12
Infections listed as cause of death,[b] % (No.)			
Sepsis and septic shock	31 (20/65)	49 (256/523)	
Pneumonia	29 (19/65)	41 (213/523)	
Endocarditis	8 (5/65)	8 (42/523)	
Skin and soft tissue infection	2 (1/65)	7 (36/523)	
Bacteremia	3 (2/65)	5 (25/523)	
Other[c]	49 (32/65)	15 (78/523)	

Abbreviation: IQR, interquartile range.

[a]Search terms included *co*caine, amphetamine, methamphetamine, and methylphenidate.

[b]Not mutually exclusive. Specific infections with >5% prevalence in at least 1 category of decedents are listed as separate line items.

[c]Other infections excluded those listed above and included any of the following: necrotizing soft tissue infection, empyema, peritonitis, *Clostridium difficile* colitis, other abdominal infection, urinary tract infection, meningitis, and other infections listed in Supplementary Appendix B.

Acute infection was more commonly involved in drug-related deaths among PWH than decedents without HIV (26%, n = 58; vs 8%, n = 523; $P < .01$), while drug-related deaths involving trauma or violence were less common (3%, n = 7; vs 14%, n = 934; $P < .01$). Compared with those without HIV, PWH had a >5-fold increased adjusted odds of acute infection involved in drug-related death (adjusted odds ratio, 5.58; 95% CI, 4.02–7.74) (Supplementary Figure 1). The manner of reporting the specific infection that led to death is not standardized on death certificates, but the most commonly described specific infections reported as a cause of death included sepsis or septic shock (31% of PWH with an infection-related death vs 49% without HIV with an infection-related death), pneumonia (29% vs 41%), endocarditis (8% vs 8%), skin and soft tissue infection (2% vs 7%), and bacteremia (3% vs 5%). The remainder of infections were either <5% prevalent in either category of decedents or nonspecific (ie, listed as "bacterial infection," "infectious complication of drug use," etc.) (Table 1; Supplementary Appendix B).

DISCUSSION

In this cross-sectional study of drug-related deaths among persons with and without HIV, we observed that stimulants, in particular methamphetamine, were more commonly implicated in drug-related death in PWH and that acute infection contributed more to drug-related death among PWH compared with those without HIV.

Methamphetamine and other stimulants are known to cause disproportionately higher morbidity among PWH compared with those without HIV, including potentiated HIV neurotoxicity, HIV viremia, and progression to AIDS [5], although few studies have addressed mortality and quantified the burden of specific drugs involved in death among PWH. Although a mortality-focused study reported that stimulant use was not associated with an increased odds of all-cause mortality among PWH [6], our finding that 1 in 5 drug-related deaths among PWH involves methamphetamine helps establish the importance of stimulant-specific programming in the world of drug-related death prevention, particularly for PWH. Many may consider overdose prevention synonymous with opioid overdose prevention, but this work suggests that nascent methamphetamine-focused efforts should be encouraged. Relatedly, prior work has identified a strong connection between methamphetamine use and sexual risk behaviors leading to HIV transmission [5–9], suggesting that future study should include not only mortality, but also nuanced understanding of patterns and motivations to use particular substances among specific epidemiologic groups, as this may also help mitigate harm.

In the last decade, over one-quarter of drug-related deaths among PWH in San Francisco involved an acute infection. We have long known that HIV and drug use are associated with increased risk of infection for many reasons, both independently and together. For example, multiple studies have demonstrated that PWH have an elevated risk of community-acquired pneumonia, although PWH who use drugs may have the highest risk of pneumonia [10]. Opioids have been associated with invasive pneumococcal disease, due in part to opioid-induced immunosuppression [11], and methamphetamine has been associated with impaired cellular immunity [12]. In addition to the mechanistic likelihood that drugs themselves confer increased risk of infection, drug use has been associated with infection related to nonsterile injection practices, skin picking, etc. Mitigating factors with evidence of clinical benefit include syringe services [13] and vaccination programs [10], but people who use drugs may be least likely to be successfully vaccinated for many common infections [14]. These findings warrant further investigation into the effectiveness of expanding the depth and breadth of current harm reduction programming, safe consumption services (eg, safer injection services and services for noninjection practices), and vaccination efforts.

Our study was subject to a number of important limitations. Chief among them is recognizing the subjective nature of medical examiner determinations of cause of death and significant contributing conditions, which may be vulnerable to bias and inconsistent documentation. However, these data remain the most valuable source to understand drug-related deaths. Second, the cross-sectional nature of these data limits our ability to understand or comment on substance use patterns before death. That said, prior work has noted consistency between patterns of drug use before and at death [15].

In conclusion, among drug-related deaths in San Francisco from 2007 to 2018, methamphetamine was more commonly implicated in deaths among PWH compared with those without HIV, and over one-quarter of drug-related deaths among PWH involved an acute infection. In addition to opioid overdose prevention, health care providers serving PWH who use drugs should consider incorporating stimulant-specific efforts into drug-related death prevention, as well as enhanced efforts to prevent infection, such as expansion of harm reduction services and vaccination promotion.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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