Impact of Abstinence and of Reducing Illicit Drug Use Without Abstinence on Human Immunodeficiency Virus Viral Load

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Background. Substance use is common among people living with human immunodeficiency virus (PLWH) and a barrier to achieving viral suppression. Among PLWH who report illicit drug use, we evaluated associations between HIV viral load (VL) and reduced use of illicit opioids, methamphetamine/crystal, cocaine/crack, and marijuana, regardless of whether or not abstinence was achieved.

Methods. This was a longitudinal cohort study of PLWH from 7 HIV clinics or 4 clinical studies. We used joint longitudinal and survival models to examine the impact of decreasing drug use and of abstinence for each drug on viral suppression. We repeated analyses using linear mixed models to examine associations between change in frequency of drug use and VL.

Results. The number of PLWH who were using each drug at baseline ranged from n = 568 (illicit opioids) to n = 4272 (marijuana). Abstinence was associated with higher odds of viral suppression (odds ratio [OR], 1.4–2.2) and lower relative VL (ranging from 21% to 42% by drug) for all 4 drug categories. Reducing frequency of illicit opioid or methamphetamine/crystal use without abstinence was associated with VL suppression (OR, 2.2, 1.6, respectively). Reducing frequency of illicit opioid or methamphetamine/crystal use without abstinence was associated with lower relative VL (47%, 38%, respectively).

Conclusions. Abstinence was associated with viral suppression. In addition, reducing use of illicit opioids or methamphetamine/crystal, even without abstinence, was also associated with viral suppression. Our findings highlight the impact of reducing substance use, even when abstinence is not achieved, and the potential benefits of medications, behavioral interventions, and harm-reduction interventions.

Keywords. substance use; drug use; heroin; viral suppression; abstinence.

There are approximately 1.1 million people living with human immunodeficiency virus (PLWH) in the United States, and substance use rates are high [1–3]. An early study found that approximately 40% of PLWH reported illicit drug use in the prior year [2]. A more recent study found that rates varied by drug, with current use (3 months) ranging from 2% (illicit heroin) to 24% (marijuana) [4]. Illegal and legal (eg, alcohol) substance use is associated with detrimental health outcomes, acting as a barrier to the HIV care continuum, including poor engagement in care [5], a lower likelihood of receiving antiretroviral therapy (ART) [6], decreased ART adherence [7–9], and increased mortality [10]. Substance use disorders have been associated with poor viral suppression rates [7–9, 11] and, thus, morbidity, mortality, and potential HIV transmission [12, 13].

The inverse association between substance use and HIV viral load (VL) has been noted in several studies. However, studies have often examined only 1 drug such as stimulants [7] or opioids [14] or examined injection drug use [9, 11]. Studies have typically not evaluated the independent contributions of

Received 22 October 2018; editorial decision 4 April 2019; accepted 11 April 2019; published online April 17, 2019.

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each substance used by PLWH let alone the frequency of use by drug. This is an important gap given differences in impact of individual substances on outcomes such as adherence and depression among PLWH [4, 15–17].

Furthermore, many substance use and HIV treatment outcome studies have been cross-sectional or only focused on baseline substance use [4, 5, 9], limiting the ability to evaluate longitudinal associations, particularly among those whose substance use severity changes over time. Substance use interventions often lead to a reduction in frequency of use even if abstinence is not achieved [18, 19]; however, the impact of reduced substance use frequency on VL has not been well studied.

Our purpose in this study was to examine relationships between changes in drug use over time and VL. We examined the associations of reduced use of illicit opioids, methamphetamine/crystal, cocaine/crack, and marijuana, regardless of whether those reductions resulted in abstinence. We hypothesized that successful reduction in drug use frequency even if abstinence was not achieved, would have beneficial effects on VL. We hypothesized this effect would vary by type of drug.

METHODS

Study Population

This study was conducted among PLWH from the Centers for AIDS Research Network of Integrated Clinical Sites (CNICS) cohort. CNICS is a longitudinal, observational study of PLWH who received primary care at CNICS sites from 1 January 1995 to the present [20]. We conducted additional analyses adding PLWH from the Criminal Justice Seek, Test, Treat, and Retain (STTR) collaboration to maximize diversity. STTR was initiated by the National Institute on Drug Abuse and combines data from observational studies and trials intended to improve outcomes along the HIV care continuum for people involved in the criminal justice system, many of whom have substance use disorders [21, 22]. Four STTR studies were included to enhance demographic, clinical, and geographic diversity.

Study Participants

These analyses included PLWH aged ≥18 years who completed longitudinal assessments of substance use frequency, including illicit opioids, methamphetamines/crystal, cocaine/crack, and marijuana. Only individuals who used 1 of the drugs of interest at baseline were included in analyses for that particular drug. Participants had to have 2 or more VL measurements taken after 2010 to be eligible. CNICS participants were PLWH who received clinical care at 1 of 7 participating sites to ensure geographic and racial/ethnic diversity. The STTR studies were STTCOIP: an Illinois study targeting PLWH leaving jail or prison [23]; STRIDE2: a study of opioid users with HIV around the District of Columbia [24]; CARE+RCT: a study of PLWH in jail or recently released from jail around the District of Columbia metropolitan area [25]; and VISTA, a Vietnam-based study of male PLWH who injected drugs [26].

Data Sources

Both CNICS and STTR have data repositories that harmonize and integrate demographic, clinical, laboratory, and other data such as patient-reported substance use assessments [20, 22].

Drug and Alcohol Use

PLWH complete a 10–12 minute clinical assessment with touch-screen tablets approximately every 6 months as part of routine care in CNICS [27, 28]. The CNICS clinical assessment includes measures of drug use (modified Alcohol, Smoking, and Substance Involvement Screening Test [ASSIST]) [29, 30], alcohol use (Alcohol Use Disorders Identification Test [AUDIT-C] [31, 32]), and other domains. While the approach and drug use instruments varied for STTR studies, each one had instruments with similar items (eg, How many times did you use marijuana during the last 30 days?). Follow-up assessment timing varied; however, all studies assessed substance use longitudinally.

For these analyses, we focused on drug use frequency. Drugs of interest included heroin and other illicit opioids including prescription opioids not taken as prescribed, methamphetamine/crystal including noncocaine stimulants, cocaine/crack, and marijuana. We defined drug use frequency among those using a drug at baseline as the number of days during the last 30 days that a drug was used. We also categorized frequency of use as less than weekly, 1–3 times per week, and daily/almost daily to enhance ease of interpretation of figures. To analyze the impact of changes in drug use, we categorized each drug at follow-up assessments as abstinence (no use in the prior 30 days for an individual who used that drug at baseline), reduction without abstinence (the number of days used in the prior 30 days was fewer than number of days used at baseline [18]), and nondecreasing (the number of days used in the prior 30 days was the same or greater than baseline). In addition, we explored polydrug use, defined as currently using drugs from 2 or more of the 4 categories (ie, heroin and other illicit opioids, methamphetamine/crystal, cocaine/crack, and marijuana).

Outcome

The primary outcome of interest was viral suppression, defined as an undetectable VL (≤400 copies/mL). We also evaluated VL (copies/mL) at each time point, which was log transformed (base$_{10}$) due to skew ($\log_{10}$VL). We then back-transformed VL coefficients by raising them to the power of 10. We calculated relative VL values, which were defined as the ratio of VL of PLWH with abstinence or reduction for each drug divided by the VL of PLWH who had nondecreasing drug use.

Statistical Models

We calculated descriptive statistics including mean, median, frequency, and standard deviation.

We conducted analyses using joint longitudinal and survival models [33] to examine the impact of decreasing drug use and abstinence on viral suppression using a separate model for each drug category (heroin and other illicit opioids, methamphetamine/crystal, cocaine/crack, and marijuana) due to known limitations with less complex models [34]. These models were limited to CNICS as they have convergence issues in small datasets [35]. We censored individuals who died, dropped out of clinical care, or did not have VL measured for 18 months.

We also conducted sensitivity analyses using separate linear mixed models for each drug category and for each study (CNICS and each STTR study) to examine the impact of decreasing drug use and abstinence on VL over time. We used linear mixed models since they inherently handle unbalanced numbers and times of observations between individuals and clustering by participant [36].

For both types of models, PLWH reporting current use of a given drug at the first time point were included in the model for that drug. We modeled change in drug use frequency as a time-updated categorical variable: abstinence, reduction without abstinence, or nondecreasing frequency of drug use compared to baseline. Models were adjusted for age, sex, cohort entry year, and follow-up time, although there were exceptions. For example, VISTA participants were all male; therefore, these models did not adjust for sex. Due to differences in how models handle time, the linear mixed models adjusted for calendar time not entry and follow-up time. All models adjusted for concomitant frequency of other drugs and frequency of any alcohol use and binge alcohol use in a 30-day period. We did not adjust for ART use or adherence as these are potentially mediators on the pathway between substance use and VL. Studies with <15 participants using a given drug at baseline were excluded from that analysis. Substance use assessments taken while incarcerated were excluded as baseline values.

Due to heterogeneity across studies, we calculated pooled estimates via traditional fixed-effects meta-analysis statistical models [37] for both decreasing use and abstinence for each drug. Fixed-effects meta-analysis modeling was used because the individual studies can be regarded as mutually independent [38]. This allowed us to include heterogeneous studies such as VISTA, which is set in an international context, without losing internal validity of estimates. This approach allows impact to be measured taking into account a much larger and more diverse population. We also repeated analyses without the VISTA study.

Finally, we used joint longitudinal and survival models to examine the impact of switching from polydrug use to single or no drug use on viral suppression over time. This analysis was conducted with CNICS only due to insufficient numbers of polydrug users in the other studies. These models were adjusted for age, sex, cohort entry year, follow-up time, frequency of alcohol use, and frequency of binge alcohol use.

RESULTS

Baseline demographic and clinical characteristics of 12 492 PLWH in CNICS are listed in Table 1 overall and by baseline drug use. The mean age was 44, and 47% were white. Marijuana was the most widely used drug at baseline followed by methamphetamine/crystal. Mean follow-up was 3.9 years (standard deviation, 2.6), and mean number of VL values were 10.

Drug use frequency in the last 30 days among those in CNICS using each drug at baseline is shown in Figure 1, with illicit opioids and marijuana having the largest percentage of daily or almost daily users. Changes in use over time from baseline to the most recent assessment are shown in Figure 2. Marijuana users had the lowest percentage achieving abstinence and the highest percentage with nondecreasing frequency.

Overall, among users of the 4 drug classes with baseline detectable VL, the proportions by drug class who achieved viral suppression were higher among those who reduced (56%–72%) or quit (68–73%) vs those who did not decrease (41%–54%) drug use for all 4 drug classes.

We examined the likelihood of viral suppression (binary outcome) among 12 492 PLWH in the CNICS cohort using joint longitudinal and survival models. Abstinence was associated with viral suppression for all 4 groups of drugs (Figure 3) with odds ratios (ORs) ranging from 1.42 (95% confidence interval [CI], 1.24–1.63) for PLWH who became abstinent from marijuana up to 2.18 (95% CI, 1.56–3.04) for PLWH who became abstinent from illicit opioids. For people who reduced use without abstinence, reducing the frequency of methamphetamine/crystal use (OR, 1.65; 95% CI, 1.25–2.16) and reducing the frequency of illicit opioids (OR, 2.72; 95% CI, 1.47–5.04) were associated with VL suppression (Figure 3; survival model component, Supplementary Table 3).

We conducted sensitivity analyses to examine relative VL among CNICS and STTR studies. Supplementary Table 1 describes demographic and clinical characteristics of participants in CNICS and STTR studies. The number of participants per study varied from 82 to 12 492 PLWH. As described above, we limited analyses to studies with ≥15 individuals using a particular drug at baseline to be included in analyses for that drug. Four studies were used for illicit opioids and marijuana; fewer studies were used for the other drugs (Supplementary Table 2). The number of individuals included who were using each drug at baseline ranged from n = 568 (illicit opioids) to n = 4272 (marijuana).

Abstinence was associated with lower VL in pooled analyses for all 4 drug classes (Figure 4). Abstinence from illicit opioid use was associated with a $\log_{10}$VL difference of –0.218 ($P < .001$), resulting in a relative VL of 0.61 or 39% lower VL compared to

Table 1. Baseline Demographic and Clinical Characteristics of People Living With Human Immunodeficiency Virus at the Centers for AIDS Research Network of Integrated Clinical Systems Sites Across the United States by Baseline Substance Use

Characteristic	Everyone N (%)[a]	Illicit Opioid Users N (%)[a]	Methamphetamine Users N (%)[a]	Cocaine/Crack Users N (%)[a]	Marijuana Users N (%)[a]
N	12 492	403	1329	1072	4167
Age mean (SD), y	44 (11)	43 (10)	41 (10)	44 (10)	42 (11)
Female	1979 (16)	66 (16)	61 (5)	218 (20)	407 (10)
Race/Ethnicity					
White	5875 (47)	200 (50)	833 (63)	367 (34)	2185 (52)
Black	4110 (33)	143 (35)	172 (13)	506 (47)	1231 (30)
Hispanic	1881 (15)	44 (11)	244 (18)	140 (13)	536 (13)
Other	626 (5)	16 (4)	80 (6)	59 (6)	215 (5)
Current use					
Heroin/other illicit opioids	403 (3)	403 (100)	159 (12)	144 (13)	242 (6)
Methamphetamine/crystal	1329 (11)	159 (39)	1329 (100)	295 (28)	800 (19)
Cocaine/crack	1072 (9)	144 (36)	295 (22)	1072 (100)	634 (15)
Marijuana	4167 (33)	242 (60)	800 (60)	634 (59)	4167 (100)
Frequency of drug use (in prior 30 days) among those with current use, mean number of days (SD)					
Heroin/other illicit opioids	7 (12)	7 (12)	6 (11)	8 (12)	7 (12)
Methamphetamine/crystal	6 (11)	9 (13)	6 (11)	5 (10)	6 (10)
Cocaine/crack	3 (8)	6 (11)	3 (8)	3 (8)	3 (7)
Marijuana	12 (14)	14 (14)	10 (13)	11 (13)	12 (14)
Current alcohol use (any use)	8330 (67)	290 (72)	964 (73)	872 (81)	3368 (81)
Frequency of alcohol use among those currently drinking					
Days of use out of 30 days, mean (SD)	5 (6)	7 (7)	5 (6)	7 (7)	6 (7)
Binge alcohol use	4367 (35)	181 (45)	559 (42)	622 (58)	2034 (49)
Frequency of binge alcohol use among those with binge drinking					
Days of binge use out of 30 days, mean (SD)	2 (6)	5 (9)	3 (7)	4 (8)	2 (6)
Number of substances used					
0	7350 (59)	0	0	0	0
1	3698 (30)	94 (23)	419 (32)	319 (30)	2866 (69)
≥2	1444 (12)	309 (77)	910 (68)	753 (70)	1301 (31)
Viral load, copies/mL	UD	UD	UD	UD	UD
Median (IQR)	(UD–UD)	(UD–961)	(UD–4627)	(UD–1244)	(UD–UD)
CD4 count cells/mm^3	506	480	495	479	521
Median (IQR)	(320–709)	(281–707)	(311–697)	(289–689)	(333–726)

Abbreviations: IQR, interquartile range; SD, standard deviation; UD, undetectable.

[a]Unless otherwise specified.

those who continued illicit opioid use without decreasing frequency. Abstinence from methamphetamine/crystal was associated with a $\log_{10}$VL difference of –0.239 ($P < .001$), resulting in a relative VL of 0.58 or 42% lower VL. Abstinence from cocaine/crack was associated with a $\log_{10}$VL difference of –0.160 ($P < .001$), resulting in a relative VL of 0.69 or 31% lower VL compared to those who continued cocaine/crack use. Abstinence from marijuana among those using marijuana at baseline was associated with a $\log_{10}$VL difference of –0.105 ($P < .001$), resulting in a relative VL of 0.79 or 21% lower VL compared to those who continued marijuana use without decreasing frequency.

We also examined the impact of reducing use frequency of all 4 drugs without abstinence (Figure 4). Reducing use without abstinence for cocaine/crack and marijuana was not associated with significant VL differences. Reducing use without abstinence of illicit opioids and methamphetamine/crystal was associated with significantly lower VL. In the pooled analyses, decreasing methamphetamine/crystal use without abstinence was associated with a $\log_{10}$VL difference of –0.159 ($P = .005$), resulting in a relative VL of 0.69 or 31% lower VL compared to those who did not reduce use. Decreasing illicit opioid use without abstinence was associated with a $\log_{10}$VL difference of –0.366 ($P < .001$), resulting in a relative VL of 0.43 or 57% lower VL. Repeating relative VL analyses excluding the VISTA study or limited to CNICS only yielded similar results.

We examined change in polydrug use among 1445 participants who were using 2 or more drugs at baseline. Changing from polysubstance use to no drug use was associated with an increased odds of viral suppression (OR, 2.33; 95% CI,

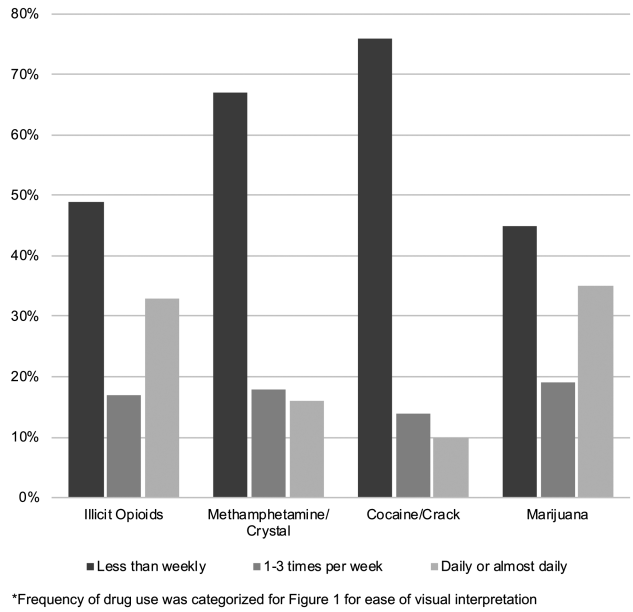


Figure 1. Frequency of drug use at baseline among people living with human immunodeficiency virus who are current users of each drug.

1.80–3.01) as was reducing from polydrug use to a single drug (OR, 1.60; 95% CI, 1.32–1.93).

DISCUSSION

In this study, we examined associations between reducing drug use frequency and drug abstinence with viral suppression and VL changes over time. It included PLWH from 7 CNICS clinics and 4 STTR studies to ensure geographic and clinical diversity. Abstinence from illicit opioids, methamphetamines/crystal, cocaine/crack, and marijuana among baselines users was associated with higher odds of viral suppression and lower VL. Reducing frequency without abstinence for illicit opioids or methamphetamines/crystal was associated with higher odds of viral suppression and significantly lower VL over time.

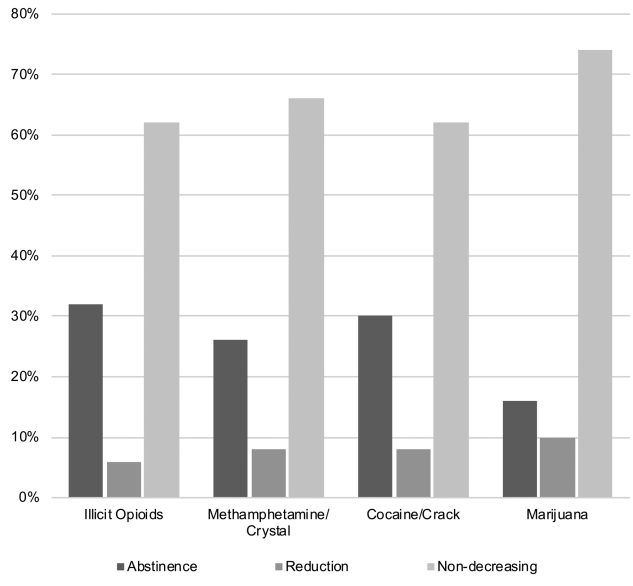


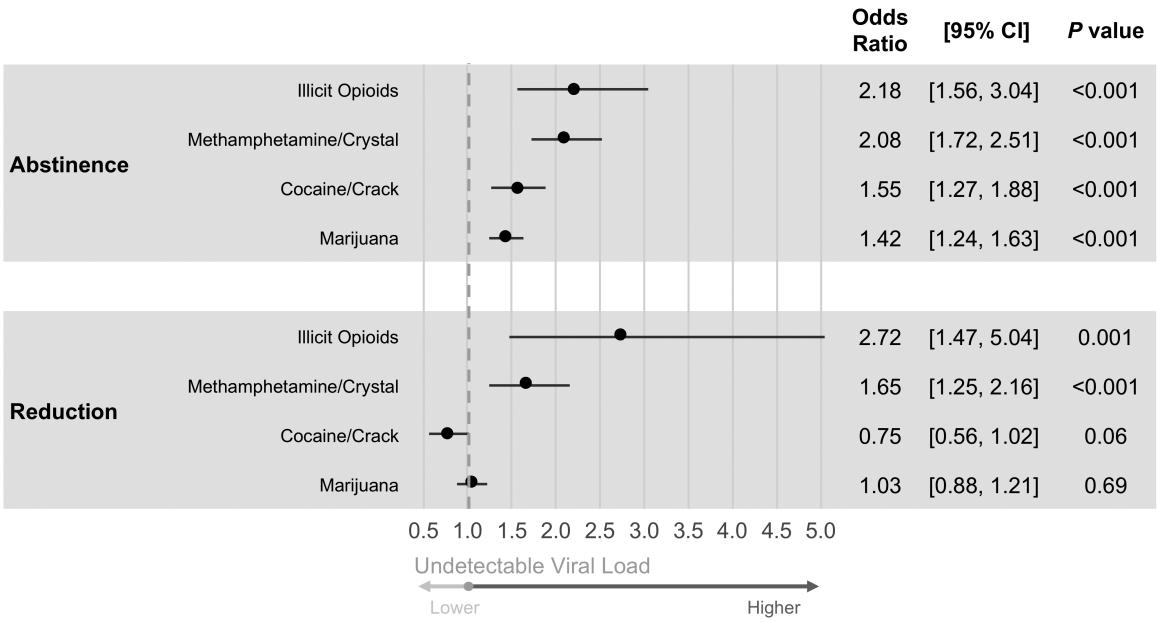
Figure 2. Observed changes in frequency among people living with human immunodeficiency virus who are current users of each drug at baseline.

The results demonstrate a positive association between abstinence and higher likelihood of viral suppression or lower relative VL, consistent with prior studies. Marijuana abstinence was associated with the smallest reduction in VL and odds of viral suppression, while abstinence from illicit opioids and cocaine/crystal was associated with the largest. One prior study found that current injection drug users (IDU) were less likely to achieve VL suppression than former or non-IDU, although changes in use over time were not examined [9]. Mimiaga et al found that current drug use (excluding marijuana) was associated with poorer ART adherence [4]. Chitsaz et al found that current drug use and severity of use were negatively associated with receiving and adhering to ART [5]. Springer et al found that treating opioid use disorder with extended-release naltrexone led to more viral suppression after release among prisoners and jail detainees [14]. These studies suggest 2 of the mechanisms by which drug use may impact VL, that is, receipt of and adherence to ART. While compelling, most studies have been cross-sectional and therefore unable to look at the longitudinal associations of abstinence with VL as examined in this study.

The more novel analyses are those that examine the impact of reducing drug use frequency without abstinence on VL. The impact of reducing frequency on VL has not been well studied, despite substance use interventions that focus on reducing frequency even if abstinence is not achieved [18, 19]. Findings support the benefits of a harm reduction substance use treatment model even when abstinence is not achieved [39–41]. We found that decreasing the frequency of illicit opioid and methamphetamine/crystal use was associated with increased odds of VL suppression and significantly lower VL.

These results suggest that medication-assisted treatments to reduce opioid use may be beneficial for decreasing VL and improving outcomes, consistent with a recent meta-analysis [42]. These interventions may also have public health benefits since decreasing VL decreases HIV transmissibility to others. VL reduction associated with reducing methamphetamine/crystal use highlights the importance of providing drug treatment even if abstinence is not achieved. The VL improvement associated with changing from use of multiple drugs to a single drug also highlights the importance of intervening even if abstinence is not achieved.

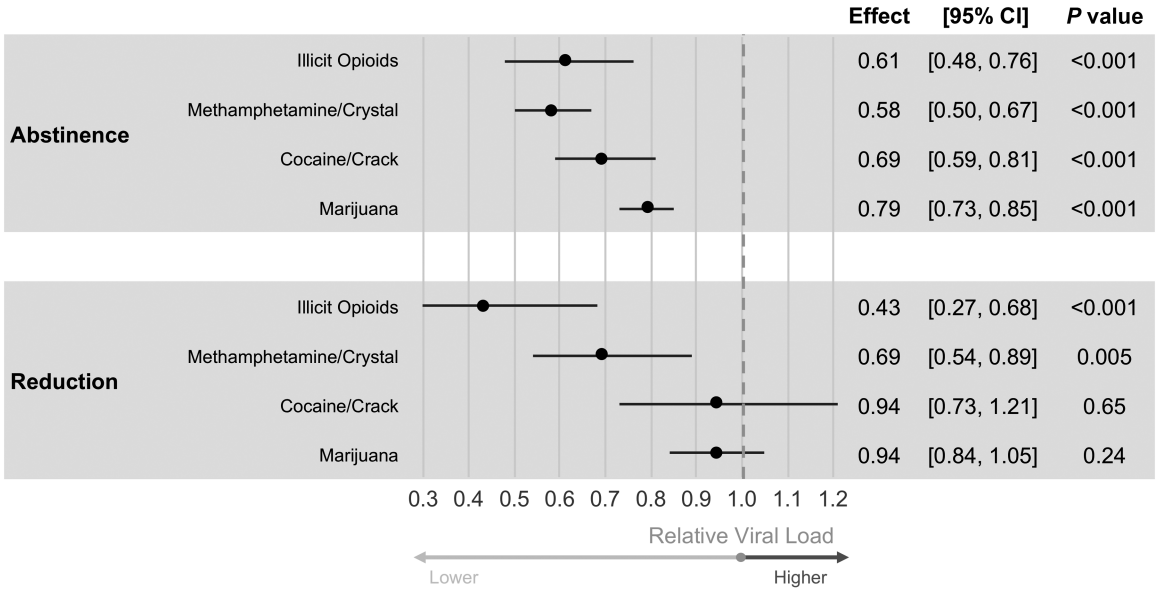
Study strengths include the large sample size; the longitudinal approach, which allowed associations between change in drug use and VL to be examined rather than only cross-sectional associations; and the ability to quantify drug use frequency in order to examine not only current use vs abstinence



Models adjusted for age, sex, and year of cohort entry and years of follow-up. Models also adjusted for concomitant use of other substances including other drugs, alcohol frequency, and binge alcohol use.

Figure 3. The association of decreasing or abstinence of 4 classes of drug use with undetectable viral load. Abbreviation: CI, confidence interval.

but also reductions in use. Including multiple sites addressed a limitation of studies that lacked geographic diversity, a problem given known variations in drug use patterns across the United States [43]. The use of joint longitudinal and survival models allowed us to focus on viral suppression with repeated measures while also properly accounting for differential loss to follow-up. These models greatly improve the statistical estimation for viral suppression, which is arguably the more clinically meaningful endpoint. In addition, we examined VL as a continuous outcome, which provided more power and avoided



Models adjusted for age, sex, and calendar time. Models also adjusted for concomitant use of other substances including other drugs, alcohol frequency, and binge alcohol use.

Figure 4. The associations of decreasing or abstinence of 4 classes of drug use with relative viral load using fixed-effects meta-analysis to pool drug-specific estimates across studies. Abbreviation: CI, confidence interval.

the known limitations of dichotomizing continuous data [44], focusing on relative VL to avoid interpretation difficulties with $\log_{10}$VL.

Limitations include the observational nature of the study. We focused on frequency rather than drug use disorder diagnoses. While reducing and stopping drug use was clearly associated with better VL, this does not necessarily indicate causality nor are all statistically significant changes in VL necessarily clinically significant. Furthermore, we did not evaluate reasons why PLWH may have reduced frequency, such as medication-assisted therapy for opioids and other types of interventions or mechanisms such as via adherence. We did not examine increased use separately; however, decreased use was the more clinically relevant goal. The large sample size from PLWH in care caused CNICS to dominate the pooled meta-analysis modeled estimate when estimating the continuous relative VL outcome. The heterogeneity of the population included in analyses examining relative VL may be a limitation; however, findings were similar in analyses limited to CNICS.

In future work, we will examine mediation analyses to better address such questions as how much of these impacts are being driven by adherence or other pathways. While benefits of medication-assisted therapy have been demonstrated for opioid use [42], studies that better address other drugs such as methamphetamine or polydrug use would be beneficial.

In conclusion, we demonstrated associations over time with abstinence from illicit opioids, methamphetamines/crystal, cocaine/crack, and marijuana and viral suppression or lower VL. In addition, the impact on VL of reducing use of illicit opioid and methamphetamine/crystal without abstinence highlights the potential benefits of harm-reduction substance use interventions that are able to successfully reduce use even when abstinence is not achieved.

Supplementary Data

Supplementary materials are available at *Clinical 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.

Notes

Acknowledgments. The authors thank the other investigators, staff, and particularly the participants at the Centers for AIDS Research Network of Integrated Clinical Sites sites and individual Criminal Justice Seek, Test, Treat, and Retain (STTR) studies for their valuable contributions. A list of CNICS and STTR investigators and institutions can be found at https://www.uab.edu/cnics/ and http://www.sttr-hiv.org.

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Financial support. Research presented in this article is the result of secondary data analysis and was supported by 5U01DA037702 from the National Institute on Drug Abuse (NIDA). In addition, this work was supported by the National Institutes of Alcohol Abuse and Alcoholism at the NIH (U24AA020801, U01AA020793, and U01AA020802). Additional support came from the National Institute of Allergy and Infectious Diseases (NIAID) at the NIH (CNICS R24 AI067039, UW CFAR NIAID grant P30 AI027757; UNC CFAR grant P30 AI50410, JHU CFAR grant P30 AI094189, and UAB CFAR grant P30 AI027767). Additional support came from the NIDA (U01DA036935 and R01DA047045). Primary data collection for STTR studies was supported by grants R01DA030768, R01DA030747, R01DA030781, R01DA030771, R01MH094090, R01DA030778, R01DA030766, R01DA030770, R01DA030762, R01DA030776, R01DA030793, R01DA032059, R01DA032083, R01DA032106, R01DA032061, R01DA032110, R01DA032080, R01DA032082, R01DA032057, R01DA032098, R34DA035728, and R01DA032100.

Potential conflicts of interest. The following have served as a consultant, advisor, or received research funding: M. S. S. from Gilead, Merck, Proteus, and ViiV Healthcare; M. J. M. from Gilead; R. D. M. from Medscape; J. J. E. from ViiV Healthcare, Janssen, Gilead, and Merck; C. G. B. from Gilead; K. C. from Gilead and Roche; and H. M. C. from ViiV Healthcare. F. A. reports grants to his institution from NIH, NIDA, Substance Abuse and Mental Health Services Administration, Health Resources and Services Administration, Gilead Foundation, and Merck; serves on the speakers' bureaus of Simply Speaking HIV, Clinical Care Options, and Gilead Sciences; and serves on the advisory boards of Merck and Gilead. C. C. reports owning stock and stock options in Quest Diagnostics. All other authors report no potential conflicts. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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