Longitudinal associations of substance use severity and antiretroviral therapy adherence among people with HIV

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Abstract

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Purpose: Substance use is associated with lower antiretroviral therapy (ART) adherence and subsequent negative effects on HIV suppression. We examined longitudinal associations of substance use severity and number of substances used with ART adherence in the current ART era.

Setting/Methods: We evaluated all adult people with HIV (PWH) in the Centers for AIDS Research Network of Integrated Clinical Sites cohort with ≥2 self-reported ART adherence measurements in 2010-2021. Participants completed longitudinal assessments for substance use severity (modified AUDIT-C [alcohol]; modified ASSIST [marijuana, illicit drugs including methamphetamine, cocaine/crack, illicit opioids]) and ART adherence (visual analog scale). Adjusted linear mixed models were used to examine longitudinal associations of ART adherence with time-varying substance use severity and number of substances used.

Results: Among 10557 PWH in care, alcohol (68%) and marijuana (33%) were the most reported substances; methamphetamine (9%) was the most reported illicit drug; and polysubstance use was common (32% ≥2 substances). More severe substance use across all substances and higher self-reported number of substances used were associated with lower ART adherence. Methamphetamine use was associated with the greatest declines in adherence ranging from 3.05% with low severity use (95% confidence interval [CI] -4.23, -1.87) to 10.77% with high severity use (95% CI -12.76, -8.78).

Conclusion: Severe substance use among PWH, especially methamphetamine, was associated with meaningful declines in adherence in the modern era of ART. Our findings warrant expansion of multidisciplinary, integrated care models and further research into new therapies, especially for methamphetamine, to improve ART adherence and downstream HIV outcomes.

Introduction

Substance use is common among people with human immunodeficiency virus (HIV) (PWH) in the United States (US) with almost a third affected by substance use or substance use disorder.[1,2] Substance use has been associated with lower antiretroviral therapy (ART) adherence[3] which can therefore lead to multiple negative HIV-related individual and public health outcomes including higher risk for detectable HIV,[4,5] reduced immune recovery and reconstitution,[6] higher mortality,[3] and greater HIV transmission risk.[3,7] Addressing substance use is difficult but an important part of improving ART adherence[3,8–10] given many associated direct (e.g., cognitive impairment) and downstream interactions (e.g., health, socioeconomic, justice system, among others) that also impact adherence.[10–13] In the setting of rapidly changing substance use epidemiology with higher prevalence of methamphetamine use[14–16] and decriminalization or legalization of medical and recreational marijuana use, as well as recent advancements in ART,[17] an updated, closer understanding of substance use, substance use severity, and ART adherence is needed to better clarify potential mechanisms and improve interventions and implementation strategies for adherence.

Substance use and addiction are dynamic, long-term conditions often involving use of multiple substances with varying severity over time.[1,3,8] Although earlier studies found associations of substance use and ART adherence differed by substance,[1,3,18] many studies did not fully capture complexities of the substance use-adherence relationship due to limitations from cross-sectional design or focusing only on baseline substance use,[1,3,18–21] examining only single substances,[3,21] and/or lacking severity data.[1,18]

We sought to address earlier limitations by conducting a longitudinal study examining the independent associations of substance use severity for alcohol, marijuana, cocaine/crack, illicit

opioids, and methamphetamine with ART adherence. We also examined associations of number of substances used with ART adherence over time given high prevalence of polysubstance use. We hypothesized that more severe substance use would be associated with lower ART adherence over time with variation by substance.

Methods

Study Setting and Data Collection:

The Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) is a prospective observational cohort study of adult PWH in routine care at 8 academic sites across the US.[22] Patient-reported outcome (PRO) measures and comprehensive clinical data from electronic health records and institutional sources are verified and harmonized in a central repository. PRO measures are collected every 4-6 months in routine care and include a variety of clinically relevant outcomes such as ART adherence, substance use, and depressive symptoms, among others. Institutional review boards at each site approved the CNICS study protocol.

Participants, Study Design, and Measures:

We evaluated self-reported severity of alcohol, marijuana, cocaine/crack, illicit opioids, and methamphetamine use and ART adherence longitudinally among all PWH in CNICS with ≥2 self-reported ART adherence measurements between January 1, 2010 and July 31, 2021. For this study, we considered illicit drugs to include cocaine/crack, illicit opioids, and methamphetamine but not marijuana given its decriminalization and/or legalization in many areas in the US during the timeframe of this study. Substance use severity was measured by 2 well-validated instruments: modified Alcohol Use Disorders Identification Test-Consumption (AUDIT-C)[23,24] (alcohol) and modified Alcohol, Smoking and Substance Involvement Screening Test

(ASSIST)[25–27] (other drugs). Substance use severity was parameterized on a continuous scale (modified AUDIT-C: range 0-12, modified ASSIST: range 0-39) and categorically. Alcohol use severity was categorized into non-risky use (AUDIT-C 1-4 men, 1-3 women) and unhealthy use (>4 men, >3 women). Substance use severity for other drugs were grouped into low (ASSIST 1-3), moderate (4-26), and high (>26) severity categories. ART adherence was measured by self-reported 30-day visual analog scale (range 0-100%).[28,29] We based the number of substances or illicit drugs used on the total number of different substances or illicit drugs, respectively, reported on a specific PRO assessment. We measured baseline depressive symptoms using PHQ-9[30–32] (range 0-27) and based heavy episodic drinking frequency on a numerical transformation of the third AUDIT-C question (frequency of ≥5 drinks on one occasion in the past year: never, less than monthly, monthly, weekly, daily or almost daily).

Data Analysis:

We completed descriptive analyses of baseline demographic, clinical, and ART adherence characteristics by baseline substance use. In the primary analysis, we evaluated associations of time-varying substance use severity and ART adherence longitudinally using linear mixed models with exchangeable correlation structure, robust standard errors, random intercepts, and random slopes for time in study. Time-varying substance use severity was separately modeled in continuous and categorical parameterizations. All substances were modeled jointly in a single regression model for each parameterization to allow for conditional association of each substance given known overlap in use of multiple substances by participants. In sensitivity analyses, we adjusted for time-varying frequency of heavy episodic drinking in previous 30 days as well as stratified models and included interaction terms for baseline HIV detectability (HIV RNA <200 copies/mL vs ≥200 copies/mL), baseline ART adherence (≥90% vs <90%), and baseline

substance use severity (categorical) given earlier evidence for differences in relationships for alcohol.[33,34] Stratified analyses were completed using generalized estimating equations (GEE) to allow variation in baseline values as linear mixed models inherently account for baseline variations in random intercepts. In stratified analyses, separate models were completed for each stratum of the baseline covariate (e.g., baseline ART adherence ≥90% vs <90%). Separate models were also completed for each substance using unstratified GEE models including interaction terms for the specific substance and baseline covariate (e.g., baseline ART adherence*alcohol use severity). All models in the primary analyses and sensitivity analyses were adjusted *a priori* for age, sex, race/ethnicity, baseline depressive symptoms, duration in study, and CNICS site based on literature,[1,3,21] clinical knowledge, or to account for variation from study time and location.

We also assessed the relationships of self-reported number of substances used, number of illicit drugs used, and ART adherence using linear mixed models. We separately modeled categorical and continuous parameterizations of time-varying number of substances used with ART adherence and repeated the analyses with number of illicit drugs used. All models were adjusted for time-varying substance use severity (continuous) and the same previously mentioned clinical, demographic, and study factors.

Results

Baseline demographic and clinical characteristics are described in Table 1. Among the 10557 PWH followed for a mean of 4.5 years (standard deviation [SD] 3.1) in our study, mean age was 44.1 years, 85% were male, and 52% identified as non-white.

Alcohol and marijuana were the most used substances at baseline, and methamphetamine was the most used illicit drug. Polysubstance use at baseline was common (32% used ≥2

substances) especially among those using illicit drugs with over half in each drug group using ≥3 substances (range 55-75%).

Overall baseline ART adherence was high (mean 93%, SD 16%) with 84% reporting ≥90% adherence. Compared to those who used alcohol and marijuana, PWH who used illicit drugs had lower ART adherence (mean 86-87% vs 91%) as well as lower proportions reporting ≥90% ART adherence (65-67% vs 80%) and undetectable HIV (75-80% vs 84-85%).

In our primary analysis, more severe substance use for every substance (categorical and continuous) was associated with lower ART adherence over time (Table 2). Methamphetamine use was associated with the greatest declines in ART adherence with each 5-point higher ASSIST score associated with a 1.86% estimated lower adherence (95% confidence interval [CI] -2.10, -1.62) and more severe categories of use corresponding with greater decreases in adherence (low: -3.05, 95% CI -4.23, -1.87; moderate: -6.20, 95% CI -7.08, -5.33; high -10.77, 95% CI -12.76, -8.78). For other drugs, estimated mean decrease in adherence for each 5-point higher ASSIST ranged from 0.40% (95% CI -0.89, 0.10) for illicit opioids to 1.49% (95% CI -1.84, -1.15) for cocaine/crack. Alcohol use was associated with 0.29% lower ART adherence for each 1-point higher AUDIT-C (95% CI -0.37, -0.20). Categories with more severe use for all other substances were also associated with greater decreases in ART adherence. Associations for illicit opioid use followed the general pattern of other substances, but several estimates did not reach significance due to small sample size.

In sensitivity analyses for the primary analysis, estimates did not substantially differ when also adjusting for time-varying frequency of heavy episodic drinking in the previous 30 days (Supplemental Table 1). We also included interaction terms and stratified models by baseline HIV detectability (HIV RNA <200 copies/mL vs ≥200 copies/mL) (Figure 1), baseline

ART adherence (≥90% vs <90%) (Supplemental Figure 1), and baseline substance use severity (categorical) using GEE (Supplemental Figure 2). When including interaction terms in models, alcohol was associated with statistically significant variation by baseline HIV detectability (P=0.01) and adherence (P=0.001) but not baseline severity. For other substances, we found statistically significant variation for cocaine/crack (P=0.003) and marijuana (P<0.001) by baseline adherence and illicit opioids (P=0.01) and methamphetamine use (P<0.001) by baseline severity category. Estimates in stratified analyses generally did not differ substantially in magnitude to those observed in the primary analysis. Across all stratified analyses, the small number of PWH using illicit opioids reduced statistical power and resulted in estimates with wider variation similar to the primary analysis.

We also examined associations of self-reported number of substances used and illicit drugs used with ART adherence over time (Table 3). Number of substances used was associated with 0.60% lower adherence (95% CI -0.88, -0.31) for each additional substance reported. Categorical parameterizations of number of substances used suggested substantially greater declines in adherence with use of ≥3 substances compared to use of fewer substances. We repeated the analysis with number of illicit drugs used and found each additional illicit drug was associated with an estimated 2.45% lower adherence (95% CI -3.11, -1.80). In categorical parameterizations, estimated lower adherence for use of 1 to 3 illicit drugs (range -2.87 to -6.94) were similar to those for use of 3 to 5 substances (range -2.09 to -6.97).

Discussion

In this longitudinal study of PWH in care in the current ART treatment era (2010-2021), we found more severe use of each of the 5 substances was independently associated with lower ART

adherence over time. The greatest declines in ART adherence were observed with methamphetamine use. We also demonstrated that higher self-reported number of substances used was associated with lower ART adherence over time even after accounting for severity of use for all substances. Severe substance use, especially with methamphetamine, was associated with meaningful declines in adherence even in the modern era of ART warranting continued investigation into mechanisms and new therapies and expansion of multidisciplinary, integrated approaches to improve adherence.

Our results make intuitive sense with regards to a temporal relationship between severity of substance use and ART adherence.[3,18,21] Combining multiple substances into the same models allows for comparison of independent contributions of different substances and severities to adherence. Methamphetamine use and severity were associated with the greatest reductions in adherence, and for the same severity level, methamphetamine was associated with approximately 3-fold lower adherence compared to marijuana. In fact, the lowest severity methamphetamine use group had a comparable estimated decrease in adherence as the highest severity marijuana use group. The time-varying nature of these associations are important mechanistically and for interventions as they could suggest potential benefits for ART adherence even with short-term improvements in lower severity substance use (even without abstinence) and changing to less disruptive substances (e.g., substituting marijuana for methamphetamine) as harm reduction strategies. Our group previously described higher odds of HIV suppression and lower HIV viral levels associated with reduced substance use frequency,[5] which could be mediated by improved ART adherence. Further research evaluating reductions or changes in substance use severity and ART adherence is needed to assess this relationship more completely.

The relatively smaller effect sizes of illicit opioid use on ART adherence were unexpected. We saw expected attenuation with adjustments for other substances but to much lower levels of association than anticipated. This differs from prior studies with multiple substances which found similar associations of illicit opioid use on ART adherence as those of stimulants and larger than those of marijuana.[18] One potential explanation for these differences is our limited ability to account for therapy or medications for opioid use disorder, which may enable adherence and other self-care behaviors for PWH who continue to concurrently use illicit opioids.[35] This could result in underestimated associations between illicit opioid use and adherence. Additional potential reasons for differences with other studies could be our cohort of PWH in routine clinical care is enriched for individuals with differing opioid use patterns or learned how to better manage long-term opioid use. For example, PWH in our study may use opioids in a less disruptive fashion for pain, anxiety/stress, and in the context of polysubstance use, to balance the effects of stimulants and other drugs.[36–38] Additional qualitative investigation will be helpful to understand if the patterns and culture of opioid use are different among our cohort of PWH in clinical care compared to other cohorts and communities within similar timeframe and geographic area. Generalizing these findings for illicit opioid use should be cautious until differences are better clarified.

We conducted several sensitivity analyses for alcohol use severity based on earlier literature.[33,34] Baseline HIV detectability and ART adherence modified the relationship between alcohol use severity and ART adherence, while baseline alcohol use severity did not. We found PWH with baseline detectable HIV or ART adherence <90% had on average lower levels of ART adherence at the same alcohol use severity level compared to baseline undetectable HIV or ART adherence ≥90%, respectively. This generally aligns with prior studies among women[34] and

veterans[33] with HIV which found all 3 factors were effect modifiers for alcohol use severity and ART adherence. However, these studies observed individuals with baseline undetectable HIV, high ART adherence, and low alcohol use severity were the most sensitive to changes in alcohol use with respect to changes in adherence. Our findings may differ from these studies due to joint modeling of other substances; potential variation in alcohol use behaviors among women and veterans compared to our cohort of PWH in clinical care from the general population; and our use of absolute severity and adherence vs their evaluation of changes in severity and adherence (i.e., PWH sensitive to changes in severity may differ from PWH sensitive to a specific level of severity, floor and ceiling effects).

We extended the sensitivity analyses to other substances for exploration and observed effect modification by baseline adherence for cocaine/crack and marijuana and by baseline severity for illicit opioids and methamphetamine. Baseline HIV detectability did not modify the relationships of any other substance with adherence. Although these exploratory findings could suggest potential adherence threshold effects for cocaine/crack and marijuana and differential trajectories in adherence by baseline severity for illicit opioids and methamphetamine, the stratified analyses did not point to substantially meaningful differences in magnitude of associations. Additionally, the wide confidence intervals for many of these strata, especially baseline low opioid use severity, call into question whether there is true variation across strata and potential influence of small sample size, especially at the extremes. Taken together, our sensitivity analyses point toward many nuanced pathways linking addiction and adherence in the context of polysubstance use. Understanding these pathways and the mediators and moderators that influence them will be helpful for better targeted interventions and implementation strategies.

We found higher self-reported number of substances used was associated with lower ART adherence which was expected based on our primary analysis. The one published study, to our knowledge, directly examining polysubstance use and ART adherence aligns with our study, observing an association between missed ART doses and use of several combinations of 2-4 substances.[39] Although sample size precluded deeper evaluation for interactions of specific substance combinations leading to use of count exposure variables, our findings of an independent association with lower adherence after accounting for substance use severity suggest use of multiple substances could have synergistic effects on ART adherence or signify greater vulnerability to substances. This is not surprising given many predisposing factors and downstream consequences of substance use that could influence adherence.[10–13] For example, simultaneous use of substances could result in greater cognitive impairment leading to missed ART doses; use of multiple substances could also reflect a more vulnerable, disrupted lifestyle that makes it difficult to access ART.[10–13] Given high prevalence of polysubstance use among PWH, understanding the influences of specific substance combinations on adherence will be a crucial next step to clarifying mechanisms and developing combination-specific interventions and harm reduction strategies to improve adherence.

Treating substance use is an important part of a program for improving ART adherence.[3,8,9] Given the many social, structural, and mental health/behavioral challenges that often coexist with substance use, it is not surprising that recent reviews on substance use and ART adherence suggested additional need for comprehensive approaches that integrate substance use therapies with adherence interventions and other support mechanisms for longer sustained improvements in ART adherence.[3,8–10] However, funding and access to substance use, mental health, and other support for PWH are uneven across regions and need expansion.[9,40] Additionally, there is a

significant need for new pharmacologic therapies for substance use beyond those for opioid and alcohol use disorders, especially for methamphetamine[41,42] given its rapidly increasing availability and many negative health consequences.[14–16] The COVID-19 pandemic has accelerated adoption of telehealth use in the US and enabled novel care models for substance use, adherence, and HIV care such as "tele-harm reduction" to bridge health disparities.[43,44] Our stratified sensitivity analyses highlight vulnerability is complex and multilayered. Continued development of new therapies and care models as well as expanding access to effective known interventions are key to providing targeted and tailored approaches to reach more vulnerable groups and meet individuals where they are.

Several key limitations should be noted to contextualize interpretations. Our design was intended to provide evidence for PWH actively engaged in care, and as a result, our findings may not fully generalize to PWH not in care, who may be better served by care retention studies and interventions. Relatively small sample size of illicit opioid use limited statistical power and therapy for opioid use disorder was not evaluated which may have resulted in underestimated associations. Statistical power also forced strong assumptions about the parametric form of the continuous substance use and adherence relationship that were not necessarily supported by the pattern of estimates in the categorical analysis. Data limitations precluded testing of interactions of specific combinations of substances or simultaneous use of multiple substances though our findings suggest use of multiple substances at different but close time periods (i.e., ASSIST or AUDIT-C recall or follow up periods) have significant negative associations with adherence. Limited data that we have during the COVID-19 era precluded inference on changes surrounding this timeframe.

Despite these limitations, our study has several notable strengths. CNICS is a geographically diverse cohort of PWH in routine care with demographic characteristics similar to those of PWH in care in the US. Our longitudinal approach using continuous measures and multiple substances in the same model enabled comparison of associations of different substances and more accurate representations of the dynamic, long-term nature of addiction. Linear mixed models allowed accounting for uneven data collection and loss to follow up. Using well-validated AUDIT-C and modified ASSIST scores highlights benefits of including PROs into routine care and permitted capture of high-quality data on multiple dimensions of severity.

Conclusion

More severe substance use and higher number of substances used were associated with lower ART adherence over time. Severe substance use, especially methamphetamine, was associated with meaningful declines in adherence even in the modern era of ART. Unexpectedly weak associations with illicit opioid use should be a future area of qualitative investigation. Addressing substance use severity even without abstinence may be part of a harm reduction approach to improve ART adherence. Given rising prevalence of methamphetamine use and high frequency of polysubstance use, expansion of multidisciplinary, integrated care models and further research into new therapies and harm reduction strategies, especially for methamphetamine, are needed to improve ART adherence and downstream HIV outcomes.

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Tables and Figures

Table 1. Baseline demographics and clinical characteristics of people with HIV in care at CNICS sites across the United States by baseline use of specific substances in 2010-2021.

Characteristics	Overall n (%)[a]	Unhealthy Alcohol n (%)[a]	Cocaine/Crack n (%)[a]	Illicit Opioid n (%)[a]	Marijuana n (%)[a]	Methamphetamine n (%)[a]
N	10557	1849	655	239	3444	918
Age, mean (SD)	44.1 (11.1)	41.3 (10.8)	42.6 (10.5)	41.6 (10.2)	41.7 (11.0)	41.9 (9.6)
Male	9009 (85%)	1613 (87%)	574 (88%)	215 (90%)	3146 (91%)	884 (96%)
Race/Ethnicity						
White	5029 (48%)	915 (49%)	233 (36%)	142 (59%)	1791 (52%)	577 (63%)
Black	3376 (32%)	523 (28%)	279 (43%)	58 (24%)	1052 (31%)	107 (12%)
Hispanic	1625 (15%)	324 (18%)	113 (17%)	28 (12%)	430 (12%)	170 (19%)
Other	527 (5%)	87 (5%)	30 (5%)	11 (5%)	171 (5%)	64 (7%)
ART adherence, mean (SD)	93% (16%)	91% (16%)	87% (20%)	87% (19%)	91% (17%)	86% (21%)
≥90% adherence	8880 (84%)	1483 (80%)	441 (67%)	161 (67%)	2739 (80%)	593 (65%)
Current use of substances						
Any alcohol	7193 (68%)	1849 (100%)	562 (86%)	176 (74%)	2860 (83%)	662 (72%)
Unhealthy alcohol	1849 (18%)	1849 (100%)	269 (41%)	68 (28%)	910 (26%)	188 (20%)
Cocaine/crack	655 (6%)	269 (15%)	655 (100%)	86 (36%)	435 (13%)	185 (20%)
Illicit opioids	239 (2%)	68 (4%)	86 (13%)	239 (100%)	162 (5%)	103 (11%)
Marijuana	3444 (33%)	910 (49%)	435 (66%)	162 (68%)	3444 (100%)	550 (60%)
Methamphetamine	918 (9%)	188 (10%)	185 (28%)	103 (43%)	550 (16%)	918 (100%)
Substance use severity among those with current use, mean (SD)						
Alcohol[b]	3.3 (2.3)	6.5 (1.8)	4.6 (2.8)	4.1 (3.0)	3.7 (2.4)	3.5 (2.7)
Cocaine/crack[c]	11.6 (9.9)	11.5 (10.2)	11.6 (9.9)	14.2 (10.7)	11.5 (10.0)	12.0 (10.8)
Illicit opioids[c]	11.1 (10.4)	11.0 (10.9)	15.1 (11.7)	11.1 (10.4)	11.2 (10.8)	13.6 (12.0)
Marijuana[c]	8.7 (6.5)	8.9 (6.8)	10.1 (7.4)	12.1 (8.1)	8.7 (6.5)	8.5 (6.7)
Methamphetamine[c]	16.0 (10.5)	15.4 (11.5)	17.9 (11.2)	22.2 (10.1)	16.2 (10.4)	16.0 (10.5)

Number of substances used, median (IQR)	1 (1-2)	2 (1-2)	3 (2-3)	3 (2-4)	2 (2-2)	3 (2-3)
0	2591 (25%)	-	-	-	-	-
1	4526 (43%)	811 (44%)	29 (4%)	17 (7%)	433 (13%)	123 (13%)
2	2620 (25%)	732 (40%)	172 (26%)	50 (21%)	2236 (65%)	293 (32%)
≥3	820 (7%)	306 (17%)	454 (69%)	172 (72%)	775 (23%)	502 (55%)
HIV RNA <200 copies/mL	8955 (85%)	1565 (85%)	527 (80%)	179 (75%)	2898 (84%)	693 (75%)
CD4 (cells/μL), median (IQR)	530 (343-736)	534 (361-726)	500 (332-719)	504 (297-726)	539 (349-751)	511 (331-731)
Depressive Symptoms (PHQ-9 ≥10)	2426 (23%)	485 (26%)	225 (34%)	99 (41%)	997 (29%)	353 (38%)

Abbreviations: ART: antiretroviral therapy; ASSIST: Alcohol, Smoking and Substance Involvement Screening Test; AUDIT-C: Alcohol Use Disorders Identification Test-Consumption; CI: confidence interval; CNICS: Centers for AIDS Research Network of Integrated Clinical Systems; HIV: human immunodeficiency virus; IQR: interquartile range; PHQ-9: Patient Health Questionnaire-9; RNA: ribonucleic acid; SD: standard deviation

[a]Unless otherwise specified

[b]Severity score defined by modified AUDIT-C: range 0-12, unhealthy use defined as >4 for men and >3 for women.

[c]Severity score defined by modified ASSIST: range 0-39.

Table 2. Associations between time-varying substance use severity and ART adherence among people with HIV in clinical care at CNICS sites in 2010-2021.

	ART Adherence[a]					
	Time-Varying Substance Use Severity (Categorical)			Time-Varying Substance Use Severity (Continuous)		
Covariate	Estimate	95% CI	P	Estimate	95% CI	P
Alcohol[b]						
Non-risky	**-0.36**	**-0.71, -0.001**	**0.049**	**-**	**-**	**-**
Unhealthy	**-1.57**	**-2.12, -1.02**	**<0.001**	**-**	**-**	**-**
Per 1-point higher AUDIT-C score	**-**	**-**	**-**	**-0.29**	**-0.37, -0.20**	**<0.001**
Cocaine/crack[c]						
Low	**-1.60**	**-2.64, -0.56**	**0.003**	**-**	**-**	**-**
Moderate	**-3.91**	**-4.97, -2.84**	**<0.001**	**-**	**-**	**-**
High	**-8.92**	**-11.99, -5.84**	**<0.001**	**-**	**-**	**-**
Per 5-point higher ASSIST score	**-**	**-**	**-**	**-1.49**	**-1.84, -1.15**	**<0.001**
Illicit opioids[c]						
Low	-0.80	-2.52, 0.92	0.36	**-**	**-**	**-**
Moderate	**-1.88**	**-3.55, -0.21**	**0.028**	**-**	**-**	**-**
High	-2.13	-6.37, 2.11	0.32	**-**	**-**	**-**
Per 5-point higher ASSIST score	**-**	**-**	**-**	-0.40	-0.89, 0.10	0.11
Marijuana[c]						
Low	**-0.59**	**-1.06, -0.11**	**0.015**	**-**	**-**	**-**
Moderate	**-1.16**	**-1.59, -0.73**	**<0.001**	**-**	**-**	**-**
High	**-3.61**	**-6.32, -0.90**	**0.009**	**-**	**-**	**-**
Per 5-point higher ASSIST score	**-**	**-**	**-**	**-0.58**	**-0.78, -0.39**	**<0.001**
Methamphetamine[c]						
Low	**-3.05**	**-4.23, -1.87**	**<0.001**	**-**	**-**	**-**
Moderate	**-6.20**	**-7.08, -5.33**	**<0.001**	**-**	**-**	**-**

High	**-10.77**	**-12.76, -8.78**	**<0.001**	**-**	**-**	**-**
Per 5-point higher ASSIST score	**-**	**-**	**-**	**-1.86**	**-2.10, -1.62**	**<0.001**

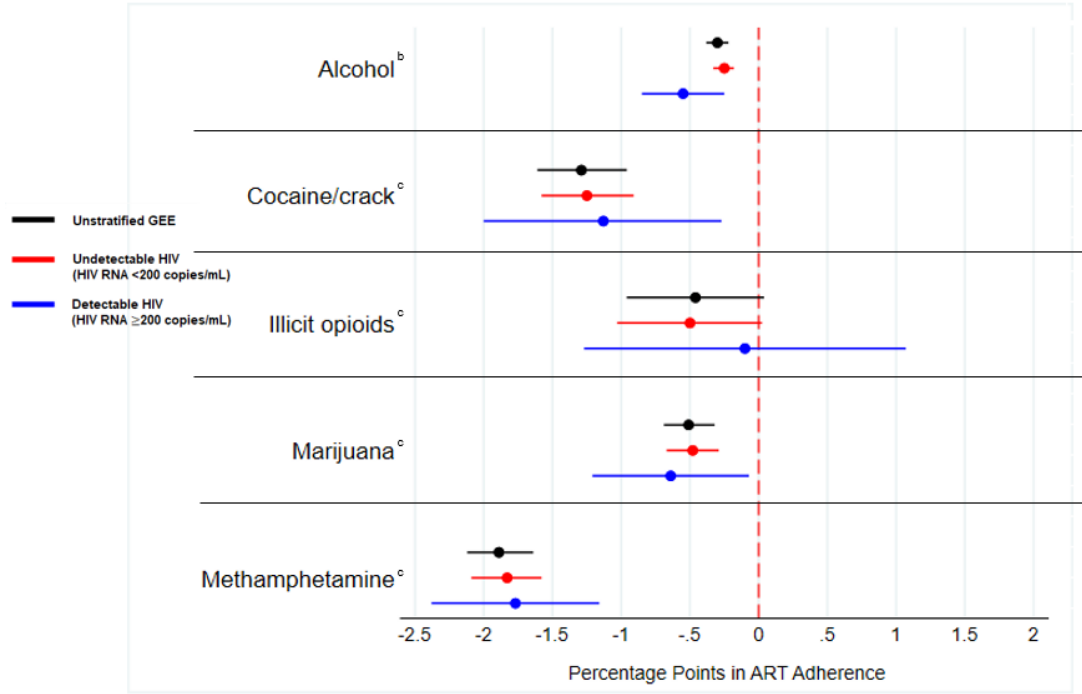
Abbreviations: ART: antiretroviral therapy; ASSIST: Alcohol, Smoking and Substance Involvement Screening Test; AUDIT-C: Alcohol Use Disorders Identification Test-Consumption; CI: confidence interval; CNICS: Centers for AIDS Research Network of Integrated Clinical Systems

[a]All substances were jointly modeled in linear mixed models adjusted for age, sex, race/ethnicity, CNICS site, duration in study, and baseline depressive symptoms. Referent group for all substances in categorical parameterization is no use.

[b]Severity score defined by modified AUDIT-C: range 0-12, non-risky use defined as 1-4 for men and 1-3 for women, unhealthy use defined as >4 for men and >3 for women.

[c]Severity score defined by modified ASSIST: range 0-39, low severity use defined as 1-3, moderate severity use defined as 4-26, and high severity use defined as >26.

Figure 1. Sensitivity analysis of substance use severity (continuous) and ART adherence stratified by baseline HIV detectability among people with HIV in clinical care at CNICS sites in 2010-2021 (N=10336, undetectable HIV n=8945, detectable HIV n=1391).



Baseline HIV Detectability	Estimate[a]	95% CI	P
Unstratified	-0.30	-0.38, -0.22	<0.001
Undetectable HIV	-0.25*	-0.33, -0.18	<0.001
Detectable HIV	-0.55*	-0.85, -0.25	<0.001
Unstratified	-1.29	-1.61, -0.96	<0.001
Undetectable HIV	-1.25	-1.58, -0.91	<0.001
Detectable HIV	-1.13	-2.00, -0.27	0.01
Unstratified	-0.46	-0.96, 0.039	0.071
Undetectable HIV	-0.10	-1.27, 1.07	0.86
Detectable HIV	-0.50	-1.03, 0.024	0.061
Unstratified	-0.51	-0.69, -0.32	<0.001
Undetectable HIV	-0.64	-1.21, -0.071	0.03
Detectable HIV	-0.48	-0.67, -0.29	<0.001
Unstratified	-1.88	-2.12, -1.64	<0.001
Undetectable HIV	-1.83	-2.09, -1.58	<0.001
Detectable HIV	-1.77	-2.38, -1.16	<0.001

Abbreviations: ART: antiretroviral therapy; ASSIST: Alcohol, Smoking and Substance Involvement Screening Test; AUDIT-C: Alcohol Use Disorders Identification Test-Consumption; CI: confidence interval; CNICS: Centers for AIDS Research Network of Integrated Clinical Systems; GEE: generalized estimating equations
*P=0.01 for interaction term
[a]All substances jointly modeled in same model using GEE adjusted for age, sex, race/ethnicity, CNICS site, duration in study, and baseline depressive symptoms (continuous). Separate models were completed for each stratum of baseline HIV detectability (HIV RNA <200 copies/mL, ≥200 copies/mL). Additionally, separate models were completed for each substance using unstratified GEE models including interaction terms for the specific substance and baseline HIV detectability.
[b]Severity score defined by AUDIT-C: range 0-12. Estimates are based on per 1-point higher AUDIT-C score.
[c]Severity score defined by modified ASSIST: range 0-39. Estimates are based on per 5-point higher ASSIST score.

Table 3. Associations between time-varying number of substances used and illicit drugs used with antiretroviral therapy adherence among people with HIV in clinical care at CNICS sites in 2010-2021.

	ART Adherence[a]		
Covariate	**Estimate**	**95% CI**	**P**
Time-varying number of substances used (Continuous)	**-0.60**	**-0.88, -0.31**	**<0.001**
Time-varying number of substances used (Categorical)			
1	**-0.34**	**-0.75, 0.066**	**0.10**
2	**-0.82**	**-1.43, -0.22**	**0.008**
3	**-2.09**	**-3.12, -1.05**	**0.005**
4	**-3.01**	**-5.11, -0.91**	**0.005**
5	**-6.97**	**-12.38, -1.57**	**<0.001**
Time-varying number of illicit drugs used (Continuous)	**-2.45**	**-3.11, -1.80**	**<0.001**
Time-varying number of illicit drugs used (Categorical)			
1	**-2.87**	**-3.63, -2.11**	**<0.001**
2	**-3.94**	**-5.57, -2.31**	**<0.001**
3	**-6.94**	**-11.52, -2.36**	**0.003**

Abbreviations: ART: antiretroviral therapy; CI: confidence interval; CNICS: Centers for AIDS Research Network of Integrated Clinical Systems

[a]Linear mixed models were adjusted for age, sex, race/ethnicity, CNICS site, duration in study, baseline depressive symptoms, and time-varying substance use severity for all substances in study. Illicit drugs include cocaine/crack, illicit opioids, and methamphetamine. Referent group in categorical parameterizations is 0 substances or illicit drugs, corresponding to the specific analysis.

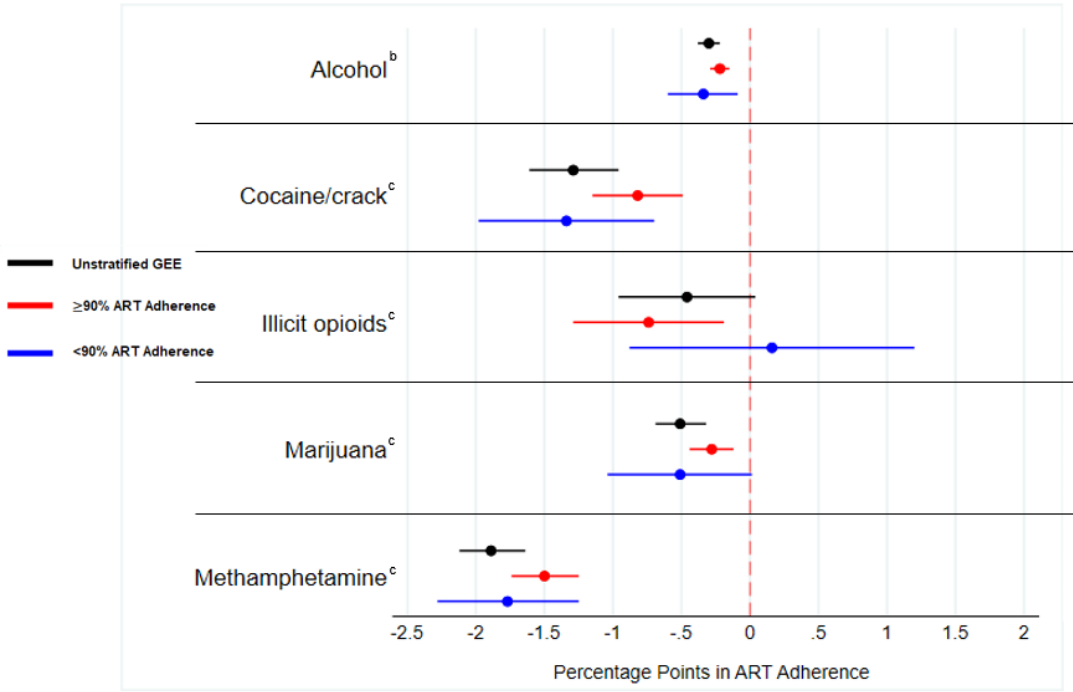
Appendix and Supplemental Materials

Supplemental Table 1. Sensitivity analysis with adjustment of time-varying frequency of heavy episodic drinking in previous 30 days for substance use severity and antiretroviral adherence among people with HIV in clinical care at CNICS sites in 2010-2021.

	Antiretroviral Therapy Adherence[a]		
Covariate	**Estimate**	**95% CI**	**P**
Alcohol[b]	**-0.26**	**-0.35, -0.17**	**<0.001**
Cocaine/crack[c]	**-1.49**	**-1.83, -1.15**	**<0.001**
Illicit opioids[c]	-0.40	-0.89, 0.097	0.12
Marijuana[c]	**-0.59**	**-0.78, -0.39**	**<0.001**
Methamphetamine[c]	**-1.86**	**-2.10, -1.62**	**<0.001**

Abbreviations: ASSIST: Alcohol, Smoking and Substance Involvement Screening Test; AUDIT-C: Alcohol Use Disorders Identification Test-Consumption; CI: confidence interval; CNICS: Centers for AIDS Research Network of Integrated Clinical Systems
[a]All substances were jointly modeled in linear mixed models adjusted for age, sex, race/ethnicity, CNICS site, duration in study, baseline depressive symptoms, and time-varying frequency of heavy episodic drinking in previous 30 days.
[b]Severity score defined by AUDIT-C: range 0-12. Estimates are based on per 1-point higher AUDIT-C score.
[c]Severity score defined by modified ASSIST: range 0-39. Estimates are based on per 5-point higher ASSIST score.

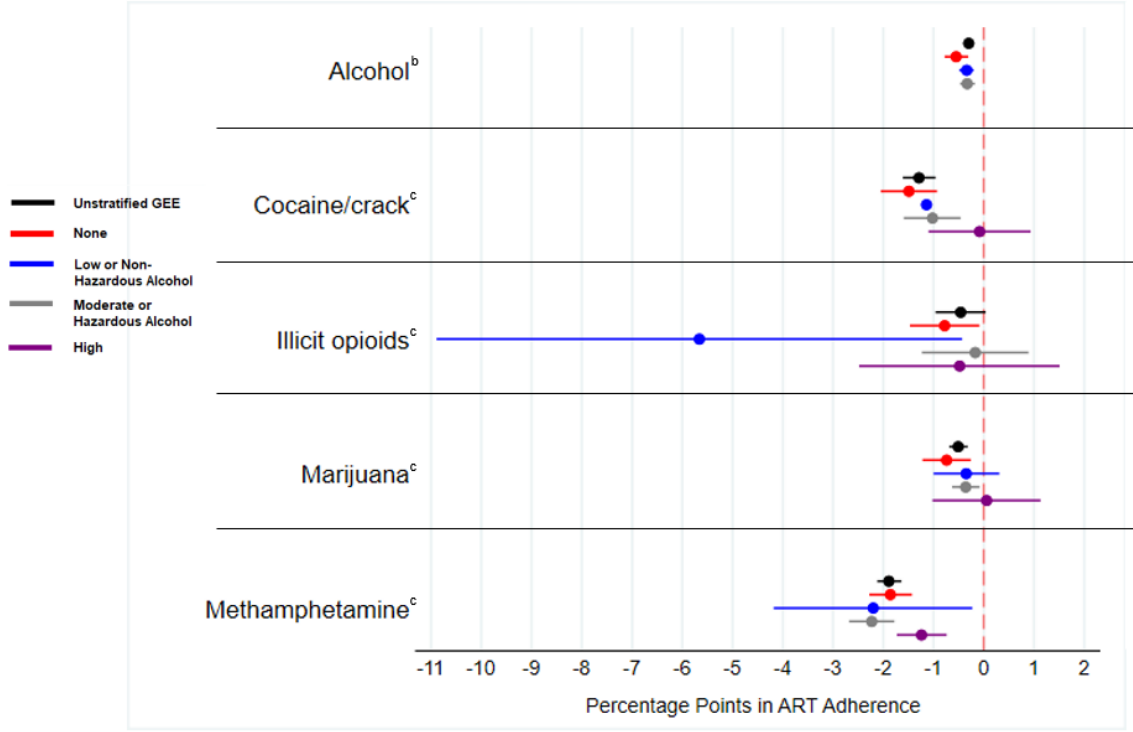
Supplemental Figure 1. Sensitivity analysis of substance use severity (continuous) and ART adherence stratified by baseline ART adherence among people with HIV in clinical care at CNICS sites in 2010-2021 (N=10336, ≥90% adherence n=8870, <90% adherence n=1391).



Baseline ART Adherence	Estimate[a]	95% CI	P
Unstratified	-0.30	-0.38, -0.22	<0.001
≥90% Adherence	-0.22*	-0.29, -0.15	<0.001
<90% Adherence	-0.34*	-0.60, -0.09	0.008
Unstratified	-1.29	-1.61, -0.96	<0.001
≥90% Adherence	-0.82**	-1.15, -0.49	<0.001
<90% Adherence	-1.34**	-1.98, -0.70	<0.001
Unstratified	-0.46	-0.96, 0.039	0.07
≥90% Adherence	-0.74	-1.29, -0.19	<0.001
<90% Adherence	0.16	-0.88, 1.20	0.76
Unstratified	-0.51	-0.69, -0.32	<0.001
≥90% Adherence	-0.28*	-0.44, -0.12	0.001
<90% Adherence	-0.51*	-1.04, 0.013	0.06
Unstratified	-1.88	-2.12, -1.64	<0.001
≥90% Adherence	-1.50	-1.74, -1.25	<0.001
<90% Adherence	-1.77	-2.28, -1.25	<0.001

Abbreviations: ART: antiretroviral therapy; ASSIST: Alcohol, Smoking and Substance Involvement Screening Test; AUDIT-C: Alcohol Use Disorders Identification Test-Consumption; CI: confidence interval; CNICS: Centers for AIDS Research Network of Integrated Clinical Systems; GEE: generalized estimating equations.
*P≤0.001 for interaction term
**P=0.003 for interaction term
[a]All substances jointly modeled in same model using GEE adjusted for age, sex, race/ethnicity, CNICS site, duration in study, and baseline depressive symptoms (continuous, PHQ-9). Separate models were completed for each stratum of baseline ART adherence (≥90% vs <90%). Additionally, separate models were completed for each substance using unstratified GEE models including interaction terms for the specific substance and baseline ART adherence.
[b]Severity score defined by AUDIT-C: range 0-12. Estimates are based on per 1-point higher AUDIT-C score.
[c]Severity score defined by modified ASSIST: range 0-39. Estimates are based on per 5-point higher ASSIST score.

Supplemental Figure 2. Sensitivity analysis of substance use severity (continuous) and ART adherence stratified by baseline substance use severity among people with HIV in clinical care at CNICS sites in 2010-2021.



Baseline Severity	N	Estimate[a]	95% CI	P
Alcohol[b]				
Unstratified	10336	-0.30	-0.38, -0.22	<0.001
None	3559	-0.55	-0.78, -0.31	<0.001
Non-Hazardous	5339	-0.34	-0.49, -0.20	<0.001
Hazardous	1848	-0.33	-0.47, -0.18	<0.001
Cocaine/crack[c]				
Unstratified	10336	-1.29	-1.61, -0.96	<0.001
None	9636	-1.49	-2.05, -0.93	<0.001
Low	1975	-1.14	-2.94, 0.65	0.21
Moderate	528	-1.02	-1.59, -0.46	<0.001
High	60	-0.085	-1.10, 0.93	0.87
Illicit opioids[c]				
Unstratified	10336	-0.46	-0.96, 0.04	0.07
None	10253	-0.78*	-1.47, -0.09	<0.001
Low	101	-5.66*	-10.89, -0.43	0.03
Moderate	161	-0.17*	-1.23, 0.89	0.76
High	31	-0.48*	-2.48, 1.51	0.64
Marijuana[c]				
Unstratified	10336	-0.51	-0.69, -0.32	<0.001
None	6996	-0.74	-1.22, -0.26	0.003
Low	936	-0.35	-1.00, 0.31	0.30
Moderate	2534	-0.36	-0.63, -0.09	0.010
High	80	0.057	-1.02, 1.13	0.92
Methamphetamine[c]				
Unstratified	10336	-1.88	-2.12, -1.64	<0.001
None	9407	-1.86**	-2.28, -1.43	<0.001
Low	203	-2.20**	-4.18, -0.23	0.03
Moderate	760	-2.23**	-2.68, -1.78	<0.001
High	176	-1.24**	-1.73, -0.74	<0.001

Abbreviations: ASSIST: Alcohol, Smoking and Substance Involvement Screening Test; AUDIT-C: Alcohol Use Disorders Identification Test-Consumption; CI: confidence interval; CNICS: Centers for AIDS Research Network of Integrated Clinical Systems; GEE: generalized estimating equations.

*P=0.01 for interaction term

**P<0.001 for interaction term

[a]All substances jointly modeled in same model using GEE adjusted for age, sex, race/ethnicity, CNICS site, duration in study, and baseline depressive symptoms (continuous). Separate models were completed for each stratum of baseline severity.[b,c] Additionally, separate models were completed for each substance using unstratified GEE models including interaction terms for the specific substance and baseline severity.

[b]Severity score defined by modified AUDIT-C: range 0-12, non-risky use defined as 1-4 for men and 1-3 for women, unhealthy use defined as >4 for men and >3 for women. Estimates are based on per 1-point higher AUDIT-C score.

[c]Severity score defined by modified ASSIST: range 0-39, low severity use defined as 1-3, moderate severity use defined as 4-26, and high severity use defined as >26. Estimates are based on per 5-point higher ASSIST score.

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