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Intentional Medication Non-Adherence Due to Interactive Toxicity Beliefs among HIV Positive Active Drug Users

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Abstract

Drug use poses significant challenges to medical management of HIV infection. While most research has focused on the influence of intoxication on unintentional adherence to HIV treatment, drug use may also lead to intentional non-adherence, particularly when individuals believe that mixing medications with drugs is harmful. This study examined whether interactive toxicity beliefs predict non-adherence to antiretroviral therapy (ART) over a prospective period of adherence monitoring. Men and women living with HIV who screened positive for drug use and were being treated with ART (N=530) completed computerized self-interviews, three prospective unannounced pill counts to measure ART adherence, provided urine specimens for drug screening, and HIV viral load results from medical records. Results showed that 189 (35%) participants indicated that they intentionally miss their ART when they are using drugs. These participants also reported common beliefs regarding the perceived hazards of mixing HIV medications with alcohol and other drugs. Multivariable models that controlled for demographic and health characteristics, as well as frequency of alcohol use, showed that intentional non-adherence predicted poorer ART adherence over the prospective month and also predicted poorer treatment outcomes as indexed by unsuppressed HIV viral load. These findings extend previous research to show that interactive toxicity beliefs and intentional non-adherence play a significant role in medication non-adherence for a substantial number of people living with HIV and should be actively addressed in HIV clinical care.

Introduction

Advances in the medical management of HIV infection have improved the health and increased the life expectancies of people living with HIV. To achieve optimal health outcomes, antiretroviral therapies (ART) demand considerably high-levels of adherence, with even the most forgiving regimens requiring at least 85% adherence to sustain HIV viral suppression. (1, 2) Among the most robust predictors of non-adherence in people living with HIV are alcohol and drug use, which can result in gaps in treatment and uncontrolled HIV replication. (3, 4)

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The most studied effects of substance use on HIV treatment involve intoxication. (5, 6) However, beyond unintentional non-adherence caused by intoxication, individuals may intentionally forego taking their medications when using alcohol or illicit drugs because they believe that to do so would be harmful, known as interactive toxicity beliefs. Although the hazards of using alcohol and illicit drugs in combination with antiretroviral therapy are well established for individuals with co-morbid liver conditions, such as Hepatitis-C infection, interactive toxicity beliefs are prevalent among HIV patients not diagnosed with co-morbid liver conditions. (7) For example, one-in-four people living with HIV who drink alcohol stop taking their HIV medications when drinking to avoid mixing medications with alcohol. (8, 9) Intentional non-adherence when drinking is also associated with missing medications over and above other predictors of non-adherence, including HIV-related health status, ART side-effects and frequency of alcohol use itself. While interactive alcohol toxicity beliefs contribute to intentional non-adherence, there are few studies of intentional non-adherence in relation to illicit drug use. This study aims to fill this gap by focusing on intentional non-adherence and interactive toxicity beliefs in a sample of people living with HIV who are active illicit drug users.

Studies show that continued substance use is common among people living with HIV who have a history of illicit drug use.(10, 11) Like alcohol use, unintentional medication adherence in relation to drugs has primarily been considered a collateral effect of intoxication. (3) However, there is emerging evidence that interactive toxicity beliefs regarding addictive drugs are associated with intentional non-adherence to ART. One study of patients in U.S. prison ambulatory HIV clinics found that 77% of patients believed ART is harmful when taken while using heroin, and 61% believed ART was harmful when taken with methadone. (12) In all, 67% of patients stated that they would not take ART if they were planning to get high on 'street drugs'. Results of this study suggest that interactive toxicity beliefs extend beyond alcohol use. However, we are not aware of studies that have examined interactive toxicity beliefs as predictors of ART adherence among active illicit drug users living with HIV infection.

The current study was conducted to determine the degree to which active substance users living with HIV intentionally forego taking their ART when using or planning to use drugs. In a prospective study conducted in Atlanta, GA we tested the hypothesis that active substance users who state that they intentionally stop taking medications when using drugs (intentional non-adherence) would demonstrate greater non-adherence to ART, including missing medications because of the effects of substance use (unintentional non-adherence). We also predicted that intentional non-adherence to ART would be directly related to poorer HIV viral suppression.

Methods

Participants

Participants in the current study were men and women living with HIV in Atlanta, GA who were receiving ART and screened positive for active illicit drug use. Specifically, the study entry criteria were (a) 18 years of age or older, (b) HIV positive, (c) prescribed antiretroviral therapy, and (d) tested positive for at least one illicit drug in a urine screening test.

Procedures

Men and women living with HIV were recruited at clinical services using snowball-sampling techniques. Specifically, we placed study brochures in waiting rooms of infectious disease clinics throughout Atlanta. The brochure announced a study opportunity for people living with HIV that included completing computerized interviews and telephone assessments and would provide an incentive payment for participation. We also implemented an explicit systematic approach to word-of-mouth chain recruitment. Specifically, participants were given copies of the study brochures and were encouraged to refer their HIV positive friends to the study.

Following informed consent, participants provided four sources of data assessing demographic, health, and substance use characteristics. First, participants completed audio-computer assisted self-interviews (ACASI) to assess demographic, health and behavioral characteristics at the start of the study. (13, 14) We also asked participants to provide a first catch urine specimen during this initial office visit. Drug test results were provided to participants when requested. We collected blood specimens from finger stick to test for HCV antibodies. Participants who tested positive for HCV antibodies were informed of their test results and given a written explanation to take to their medical provider. We also obtained HIV RNA (viral load) and CD4 cell counts from participants' medical records. Finally, participants were trained in conducting biweekly-unannounced adherence phone assessments and received three such calls over the coming six weeks. Participants were reimbursed up to \$175 for providing biological specimens and completing all behavioral assessments. A total of 958 individuals enrolled in the study of which 530 (55%) screened positive for any one of the 12 drugs tested. Only those who screened positive for drugs are included in the current study. The University of Connecticut Institutional Review Board approved all procedures.

Measures

Computerized self-interviews—Participants were asked their gender, age, years of education, income, ethnicity, and employment status. We also administered the Centers for Epidemiological Studies Depression Scale (CESD) to assess symptoms of depression ($\alpha = 0.87$). (15) Participants also reported the year that they first tested HIV positive, completed a measure of 14 HIV-related symptoms of 2-weeks duration (16) and reported whether they had been diagnosed with a liver disorder.

Intentional non-adherence when using illicit drugs was assessed with the item "I stop taking my HIV medications if I will be using drugs to get high", responded to as either Yes or No. We asked the same question regarding stopping medications if drinking alcohol. We also assessed interactive toxicity beliefs, reflecting the potential adverse outcomes of mixing substances and HIV medications using three items adapted from previous studies examining substance use and medication adherence among people with HIV who drink alcohol. Beliefs were responded to as agree/disagree (exact items are shown in the results). To assess alcohol use we administered the Alcohol Use Disorders Identification Test (AUDIT), a 10-item scale designed to measure alcohol consumption and identify risks for alcohol abuse and dependence. Scores on the AUDIT range from 0 – 40 and the AUDIT has demonstrated

acceptable reliability and validity, with scores of 8 or greater indicating risk for problem drinking, specificities between .80 and .90. (17) The first two items on the AUDIT index frequency and quantity of alcohol use over the previous week.

Current drug use—We conducted a multi-panel urine dip-test to detect common drug use. The test strip uses a lateral flow chromatographic immunoassay for qualitative detection of 12 drugs and drug metabolites (Redwood Toxicology Labs - Reditest-12). These tests are FDA approved and are reliable and valid for initial screening of drug use in the previous 72 to 96 hours. The specific drugs tested are shown in the results.

Hepatitis-C virus antibody test—To screen for HCV co-infection we used the OraQuick rapid HCV antibody test, which has demonstrated high sensitivity and specificity with results comparable to laboratory assays. (19)

Chart abstracted HIV viral load and CD4 cell counts—We used a participant assisted method for collecting chart abstracted viral load and CD4 cell counts from medical records. Participants were given a form that requested their health care provider to obtain results and dates of their most recent, and not older than 3-months, viral load and CD4 cell counts. These data were therefore obtained directly by the participant from their provider. The form included a place for the provider's office stamp or signature to assure data authenticity. HIV RNA below detection was defined as less than 100 copies/mL for uniformity across providers.

Antiretroviral medication adherence—Participants consented to three unannounced telephone-based pill counts that occurred over a six-week period. Unannounced pill counts are reliable and valid in assessing medication adherence when conducted in homes (20) and on cell-phones. (21, 22) In this study we conducted unannounced cell-phone based pill counts using study-provided free cell phones. Following an office-based interview that included a full accounting of all prescription medications and training in the pill counting procedure, participants were called at three unscheduled times over 12 to 16 day intervals. The first of the three pill counts is used to establish the initial number of pills in possession with the subsequent two pill counts allowing for calculation of adherence, defined as the ratio of pills counted relative to pills prescribed, taking into account the number of pills dispensed. We used pill counts to calculate a continuous measure of adherence and to define three clinically relevant levels of adherence, 75%, 85%, and 95% of pills taken. (1) Participants were also asked at each assessment if they recalled a time when they missed medications in the previous 2-weeks, and were asked to report the reasons for missing medications, including (a) 'I had been drinking or using drugs so I did not take my medications' and (b) 'I missed my medications because I was drunk or high.'

Data analyses

Participants were 530 individuals enrolled in the prospective adherence study who screened positive for at least one drug on the 12-panel drug test. Based on whether participants reported stopping HIV medications when using drugs at the initial assessment, we formulated two groups: (a) 341 participants who intentionally miss ART when using drugs

and (b) 189 participants who do not intentionally miss ART when using drugs. We constructed bivariate logistic regression models to test the associations between participant intentional non-adherence and demographic and health characteristics, substance use behaviors, and interactive toxicity beliefs. We tested our main study hypothesis that participants who intentionally miss their medications when using drugs would have poorer adherence beyond unintentional non-adherence over the prospective six weeks and poorer viral suppression after controlling for potential confounding variables. We also examined whether prospective non-adherence would be attributed to intoxication among individuals who claimed that they miss medications when using drugs. Missing data was minimal with < 7% missing adherence values and (2%) missing viral loads. For all analyses, complete cases were included in the models and statistical significance was defined by $p < .05$.

Results

In this sample the most frequently detected drugs were THC ($N = 314$, 59%) and cocaine ($N = 272$, 51%). A total of 157 participants screened positive for two drugs and 43 screened positive for three or more drugs. The mean ART adherence for the sample was 83.2% ($SD = 18.4$, with 25% of participants taking less than 75% of their ART and 37% taking less than 85% of their ART. A total of 189 (35%) active substance users reported that they intentionally stop taking their HIV medications if they are using drugs. Table 1 shows the demographic and health characteristics of individuals who did not and those who did indicate that they intentionally miss their ART when using drugs. Analyses showed that women were significantly more likely to intentionally miss their medications than men. In addition, intentional non-adherence was associated with lower income, less years of education, and a greater number of years since testing HIV positive. Intentional non-adherence was not associated with testing positive for Hepatitis-C virus, reporting a liver disease or other health-related characteristics. With respect to substance use, participants who intentionally miss their medications when using drugs reported greater frequency of alcohol use and more alcohol-related problems than their counterparts who do not intentionally miss their medications. (see Table 2) There were no associations between specific drugs detected and intentional non-adherence.

Interactive toxicity beliefs

Results showed that individuals who stated that they intentionally miss taking their ART when using drugs endorsed all of the interactive toxicity beliefs to a greater degree than those who are not intentionally non-adherent. (see Table 3) While it was common for both groups to endorse beliefs that substances and ART should not be mixed, only intentionally non-adherent participants indicated that people should stop taking ART when using substances. Overall more than half of individuals who were intentionally non-adherent endorsed all three of the interactive toxicity beliefs. In addition, 56% of those who were intentionally non-adherent when using drugs reported that they would also stop taking ART when drinking alcohol, compared to only 8% of participants who do not intentionally miss medications.

HIV treatment adherence and HIV suppression

Table 4 shows the results for the multivariable models that tested the association between intentionally not taking ART when using drugs and prospective HIV treatment adherence and HIV viral suppression. These analyses controlled for gender, education, income, CESD-depression scores, years since testing HIV positive, and frequency of alcohol use. Results of adjusted models showed that participants who reported intentional non-adherence at the initial assessment were significantly more likely to have poorer adherence over the subsequent six weeks; average of 79% of medications taken compared to 85% for persons who did not report intentionally missing ART. In addition, 32% of intentionally non-adherent participants had detectable HIV viral loads compared to 22% of persons who were not intentionally non-adherent, a significant association. Results found that 25% of intentionally non-adherent participants had purposefully missed taking their medications when using substances over the prospective month of assessment, compared to 18% of individuals who did not state that they intentionally miss their ART. In contrast, there were no differences between the two intentional non-adherence groups on prospectively missing medications attributed to intoxication.

Discussion

Consistent with past research we found that active drug users demonstrated poor adherence to their HIV medications. The average monthly adherence was 83% of medications taken, with nearly one in five participants having less than 75% adherence over the six-week prospective observation period. Our results showed that it was common for active drug users with HIV to believe that ART and drugs should not be mixed, and the outcomes from treatment were worse for individuals who said that they do stop taking their medications when using drugs. Our prospective assessment of adherence found that one in four participants who claimed to be intentionally non-adherent indeed did miss their medications because they were either drinking or using drugs over the subsequent month. However, it should be noted that 18% of individuals who did not state they intentionally miss medications at baseline also did not take their medications over the next six weeks because they were drinking or using drugs. This is in addition to the 8% that indicated missing medications because they were intoxicated. These findings again demonstrate the high-degree of variability in adherence behavior, a factor that should be taken into consideration when screening for adherence interventions. In addition, these results reflect the broad effects of substance use on adherence, including intentionally and unintentionally missing medications. These findings therefore demonstrate an urgent need to address interactive toxicity beliefs among active drug users who are intentionally non-adherent to ART.

Our results are the first of which we are aware to examine interactive toxicity beliefs and intentional non-adherence among biologically confirmed active drug users. Importantly, we observed a pattern of adherence that is strikingly similar to studies that have focused on self-reported alcohol use and interactive toxicity beliefs. (9, 22) We found significant overlap between intentional non-adherence when using drugs and intentional non-adherence when drinking. Although taking ART with alcohol and other drugs is hazardous for patients with co-morbid liver conditions, our results were not accounted for by co-occurring liver disease.

Patients with healthy liver functions may do more harm by being non-adherent to ART than from taking ART with alcohol and drugs. The association between intentional non-adherence and treatment outcomes was significant in multivariable models that adjusted for alcohol use and other factors. These findings therefore build confidence in previous research to show that interactive toxicity beliefs are prevalent among people living with HIV and account for some degree of non-adherence and treatment failure among those who continue active substance use.

The current study should be interpreted in light of its methodological limitations. First, the sample was one of convenience and cannot be considered representative of people living with HIV infection. Participants were recruited from multiple clinical services as well as through chain referrals. We cannot therefore know the range of care and clinical services that participants were receiving. In addition, participants in this study were taking a variety of ART regimens and we did not have information on their duration of treatment. The study also relied on self-report instruments to assess interactive toxicity beliefs and alcohol use. While each of these measures was collected using state of the science procedures, they may still be subject to biases. Socially sensitive behaviors such as alcohol use assessed by self-report may be underreported, suggesting that rates of drinking in this study should be considered lower-bound estimates. A strength of this study was our use of a biological screening test to determine current drug use. However, because the screening test only detected drug use in the past 72 to 96 hours we may have omitted active drug users from the study. Another limitation of our study was our definition of non-adherence applied equally to all medication regimens, which differ in their demand for optimal adherence. (1, 23, 24) With these limitations in mind, we believe that the current study results have important implications for improving HIV treatment adherence among people who are receiving ART and actively use drugs.

Adherence interventions that specifically target people living with HIV who continue drug use have shown inconsistent evidence of effectiveness. (25) While there are multiple challenges to improving ART adherence posed by intoxication and other drug-related factors, our data show that intentional non-adherence presents additional barriers to treatment. Unlike unintentional non-adherence, intentionally missing medications stems from beliefs about medication efficacy, necessity, and concerns. (26) As noted in previous research, interactive toxicity beliefs may result in a sense of having to choose between continued drug use and HIV treatment. (12) Health care providers should assess patient understanding of ART and specifically assess beliefs regarding their medications in relation to substance use. Health care providers are uniquely positioned to counter interactive substance use toxicity beliefs and their associated concerns that impede adherence. Future research should test efficient and effective educational messages to correct interactive toxicity beliefs that contribute to intentional ART non-adherence and treatment failure.

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Table 1

Demographic and health characteristics of HIV positive substance users who do not and do intentionally miss taking medications when using drugs.

Characteristic	Does Not Intentionally Miss ART When Using Drugs (N = 341)		Intentionally Misses ART When Using Drugs (N=189)		OR	95% CI
	N	%	N	%		
Gender						
Male	267	78	131	70	1.57*	1.04-2.35
Female	74	22	57	30		
African American	297	87	182	96	1.09	0.74-1.61
Unemployed	84	25	79	26	1.02	0.82-1.11
Income < \$10,000	206	61	145	77	2.19**	1.46-3.28
Hepatitis-C Seropositive	45	20	33	25	1.22	0.84-1.79
Liver disease diagnosis	42	12	26	13	1.13	0.67-1.92
	M	SD	M	SD		
Age	46.4	10.0	47.7	9.8	1.01	0.99-1.03
Years education	12.8	1.8	11.8	1.9	0.76**	0.69-0.84
CESD –Depression score	16.5	11.6	16.8	10.0	1.00	0.98-1.02
Years since testing HIV+	14.1	8.2	15.8	8.3	1.03*	1.01-1.04
CD4 cell count	458.4	283.7	510.9	471.8	1.00	1.00-1.01
HIV Symptoms	3.8	3.5	4.0	3.8	1.01	0.96-1.06

Note: M = mean, SD = standard deviation;

* p < .05,

** p < .01

Table 2

Substance use among HIV positive substance users who do not and do intentionally miss taking medications when using drugs.

	Does Not Intentionally Miss ART When Using Drugs (N = 341)		Intentionally Misses ART When Using Drugs (N=189)			
Behavior	N	%	N	%	OR	95% CI
Alcohol frequency						
Never drinks	107	31	82	43	1.28**	1.10-1.50
Monthly	66	19	45	23		
2-4 times/month	103	30	36	19		
2-4+ times/week	63	18	26	13		
Alcohol quantity						
Never drinks	107	31	82	43	1.14	0.94-1.37
1-2 drinks	150	44	74	39		
3-4 drinks	63	19	22	12		
5-10+ drinks	19	6	11	7		
AUDIT score >7	154	45	111	59	1.28**	1.10-1.50
Urine Drug Screen						
Cocaine	159	47	90	48	1.04	0.72-1.48
Cannabis	189	56	99	52	0.88	0.61-1.26
Opiates	32	9	14	7	np	
Oxycodone	22	7	7	3	np	
Propoxyphene(PPx)	1	>1	1	>1	np	
Phencyclidine(PCP)	6	2	0		np	
Barbiturates	0		1	>1	np	
Benzodiazepines	55	16	23	12	np	
Amphetamine	14	4	4	2	np	
Methamphetamine	20	6	15	7	np	
Methadone	4	1	2	1	np	
MDMA	3	1	3	1	np	
Poly-substance use	126	37	60	31	0.79	0.54-1.15

Note: np = not processed because of cells with expected frequencies < 5;

**
p < .01

Table 3

Interactive toxicity beliefs among HIV positive substance users who do not and do intentionally miss taking medications when using drugs.

Interactive Toxicity Beliefs	Does Not Intentionally Miss ART When Using Drugs (N = 341)		Intentionally Misses ART When Using Drugs (N=189)		OR	95% CI
	N	%	N	%		
Substance use and ART should never be mixed.	257	76	159	84	1.69*	1.06-2.68
A person should stop taking ART when using substances.	59	17	111	59	6.77**	4.52-10.14
Substance use breaks down HIV medications so they will not work.	190	56	148	79	2.92**	1.93-4.40
Number of beliefs endorsed						
0	55	16	17	9		
1	108	32	23	12		
2	136	40	52	28		
3	42	12	97	51	2.34**	1.87-2.90
Intentional non-adherence when drinking						
I stop taking my HIV medications if I will be drinking alcohol.	26	8	106	56	15.56**	9.50-25.48

* Note: $p < .05$,

** $p < .01$

Table 4

Multiple variable models for HIV viral suppression and medication adherence among HIV positive substance users who do not and do intentionally miss taking medications when using drugs.

	Does Not Intentionally Miss ART When Using Drugs (N = 341)		Intentionally Misses ART When Using Drugs (N=189)		Adjusted	
	N	%	N	%	OR	95% CI
Averaged biweekly prospective unannounced pill count						
< 75%	72	23	55	32	1.65*	1.05-2.58
< 85%	114	36	82	47	1.78**	1.17-2.69
< 90%	195	61	126	73	1.70**	1.10-2.63
Mean (SD) pill count adherence	85.1	17.0	79.7	20.3	0.22**	0.07-0.63
Biweekly Assessments of missed medications¹						
Intentional non-adherence when either drinking or using drugs						
0 assessments	146	82	84	75		
1 assessment	22	12	6	14		
2 assessments	9	5	5	5		
All 3 assessments	2	1	7	6	1.56*	1.06-2.28
Missed medications because drunk or high at the time						
0 assessments	139	86	83	81		
1 assessment	14	9	12	12		
2 assessments	6	4	4	4		
All 3 assessments	2	1	3	3	1.35	0.86-2.07
HIV viral load						
> 100 copies - Detectable	73	22	59	32	1.99**	1.27-3.12

¹ Note: Reported reason for missing medication among those who stated they had missed at least one dose of ART during each 2-week assessment period; ORs adjusted for gender, education, CESD-Depression scores, income, years since testing HIV positive, and frequency of alcohol use; SD = standard deviation;

* p < .05,

** p < .01