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Alcohol Use and Ethnicity Independently Predict Antiretroviral Therapy Non-adherence among Patients Living with HIV/HCV Co-infection

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Abstract

Background: Adherence to antiretroviral therapy (ART) is important to counter synergistic effects of HIV and hepatitis C (HCV) in patients living with co-infection. Predictors of ART non-adherence among patients living with HIV/HCV co-infection are not well established. This knowledge would be advantageous for clinicians and behavioral health specialists who provide care to patients living with HIV/HCV co-infection.

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CONFLICTS OF INTEREST

Authors Chiu, Melton, Wang, Richey, and Odum declare that they have no conflicts of interest.

STATEMENT OF HUMAN RIGHTS

Ethical Approval—Retrospective Studies

Analysis of this study—a retrospective analysis of secondary data—was approved by the institutional review board at University of Alabama at Birmingham.

STATE ON THE WELFARE OF ANIMALS

This article does not contain any studies with animals performed by any of the authors.

Objectives: The purpose of this study was to assess prevalence and predictors of ART non-adherence in a sample of patients living with HIV/HCV co-infection who were actively in HIV clinical care.

Method: A sample of patients living with HIV/HCV co-infection who received care at a university-affiliated HIV clinic (n=137) between January 2013 and July 2017 were included in the study. Computerized patient reported data or outcomes (PROs) and electronic medical records data of these respective patients were collected and analyzed. Binomial logistic regression was used to examine predictors of ART non-adherence.

Results: The prevalence of ART non-adherence was 31%. In multivariate analysis, African American ethnicity (OR=3.28, CI: 1.241–8.653, p=0.017) and a higher number of alcoholic drinks per drinking day (OR=1.31, CI: 1.054–1.639, p=0.015) were positively associated with ART non-adherence.

Conclusions: Behavioral health providers are encouraged to incorporate alcohol use reduce interventions in HIV clinical settings to reduce ART non-adherence among patients living with HIV/HCV co-infection. Additionally, public health professionals and researchers, and clinicians are encouraged to use inductive methods to discover why ART non-adherence disproportionately impacts African American patients living with HIV/HCV co-infection and to develop approaches that are sensitive to those respective barriers.

Keywords

HIV; hepatitis C; co-infection, alcohol use; ethnicity; patient reported outcomes

INTRODUCTION

In the United States, more than 1 million people are living with human immunodeficiency virus (HIV) and more than 5 million people are living with hepatitis C virus (HCV) [1,2]. It is estimated nearly a third of those living with HIV are living with HCV co-infection (HIV/HCV), and HCV is the leading non-AIDS cause of death of people living with HIV [3–5]. In tandem, HIV accelerates viral replication of HCV and HCV further ignites HIV-related immunodeficiency [6]. Consequently, patients living with HIV/HCV co-infection have greater risks of liver-associated and HIV-associated morbidity and mortality than those living with HIV mono-infection [7–10].

Adherent use of antiretroviral therapy (ART) can reduce the risk of morbidity and mortality for patients living with HIV mono-infection and HIV/HCV co-infection. Patients who are adherent to prescribed ART regimens are most likely to achieve and sustain HIV viral suppression and immunological recovery. The benefits of ART adherence are well documented and include sustained viral suppression, decreased likelihood of HIV drug resistance, fewer hospitalizations, improved quality of life, and lower incidences of mortality [11–13]. In contrast, ART non-adherence typically facilitates the inverse of optimal health outcomes for patients' living with HIV. ART adherence is especially important for patients living with HIV/HCV co-infection to circumvent the synergistic effects of HIV/HCV co-infection [14].

Braitstein et al. 2006 published the first study that provided empirical evidence that HCV positivity was negatively associated with ART non-adherence among patients living with HIV [15]. Despite this finding, to date only two published studies have examined predictors of ART non-adherence among patients living with HIV/HCV co-infection [16,17]. The majority of ART studies have examined predictors of non-adherence among patients living with HIV; whereas, predictors of ART non-adherence among patients living with HIV/HCV co-infection are not well established. This knowledge would be advantageous for clinicians, behavioral health specialists, and public health professionals who provide care to patients living with HIV/HCV co-infection. Hence, the purpose of this study was to assess prevalence and predictors of ART non-adherence in a sample of patients living with HIV/HCV co-infection who were actively in HIV clinical care.

METHODS

Sample

This study collected and analyzed computerized patient reported data or outcomes (PROs) and electronic medical records data of patients living with HIV/HCV co-infection who were in clinical care at the University of Alabama at Birmingham's HIV Clinic between January 2013 and July 2017. The clinic provides primary and sub-specialty HIV care and behavioral health services and treatment to patients living with HIV. At each clinic visit, patients complete PROs using a touch-screen tablet. Standardized usage of touch-screen PROs in clinical practice and research with patients living with HIV is a mode of capture promoted by the National Institute of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) initiative. The PROs are comprised of a set of self-report questionnaires with validated psychometric properties.[18] The PROs used in this study measured and captured data on depression, anxiety, quality of life, ART adherence, tobacco use and alcohol and substance use.

The initial sampling frame was **composed** of 529 patients with confirmed HCV RNA by polymerase chain reaction (PCR). The CONSORT flow diagram [19] was used to outline the sampling procedure (Figure 1). From the initial sampling frame, 311 patients were excluded due to not having a HIV diagnosis, and thereafter 81 patients were excluded due to incomplete ART, quality of life, and alcohol and substance use PRO data. In turn, the sample for this study was **composed** of patients with complete PRO data who were living with HIV/HCV co-infection and receiving ART (n=137). The study was approved by the institutional review board at University of Alabama at Birmingham.

Outcomes

Antiretroviral Therapy (ART) Non-adherence.—Primary outcomes of interest were prevalence and predictors of ART non-adherence. The following question from the AIDS Clinical Trials Unit (ACTU-4) [20], an ART adherence questionnaire, was used to determine which patients were and were not ART adherent: "How many doses of your medications did you miss in the last 7 days?" Patients who self-reported missing 2 or more ART doses on 2 or more clinic visits during the study period were defined as ART non-adherent, and those

who reported 0 or no missed ART doses during the study period were defined as ART adherent.

Predictors

Demographics.—Data on age, sex, **ethnicity**, insurance status, HCV genotype, and psychiatric and medical diagnoses were extracted from patient medical records.

Alcohol and Substance Use Disorder.—Alcohol and substance use disorder diagnoses were extracted from patient medical records.

Alcohol Use.—Two questions from the Alcohol Use Disorders Identification Test (AUDIT-C) [21,22] were used to identify patients with current alcohol use. The following question was used to categorize non-users and current users of alcohol: “How often do you have a drink containing alcohol (during the past 12 months)?” Patients who consistently endorsed “never” during the study period were defined as non-users of alcohol and those who at any point during the study period who endorsed usage (e.g. monthly or less, 2–4 times a month, 2–3 times a week, 4–5 times a week, or 6–7 times a week) were defined as current users of alcohol. The following question from the AUDIT-C was used to assess the number of alcoholic drinks per drinking day for those who endorsed alcohol use: “How many drinks containing alcohol do you have on a typical day you are drinking (during the past 12 months)?”

Substance Use.—The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[23] was used to identify patients with lifetime and current substance use and a history of receiving substance use treatment. Specifically, the ASSIST assesses lifetime and current usage of cocaine, amphetamines, street opiates, hallucinogens, inhalants, and non-medical use of cannabis, sedatives or sleeping pills, or prescription stimulants.

Tobacco Use.—A single question that asked “Do you currently smoke cigarettes?” was used to group patients with and without current tobacco use.

Health-Related Quality of Life.—The three-level European Quality of Life Five Dimensions (EQ-5D-3L) [24] instrument was used to measure patients’ health-related quality of life. The EQ-5D-3L is comprised of two sections, a set of five questions and a visual analogue scale, and this study only analyzed the five health-related quality of life questions. The scale assesses health-related quality of life in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each question uses a 3-point scale: no problems, some or moderate problems, extreme problems. The US population-based EQ-5D index scoring algorithm[25] was used to calculate the EQ index score (i.e. quality of life score) for each patients’ total score during the study period. For EQ index scores ranging from 0 to 1, 0 represents worst imaginable health and 1 represents representing best imaginable health.

Statistical Analysis

Measures of central tendency and frequency distributions were used to characterize the sample. Dichotomous variables were compared between patients with and without ART non-adherence using chi-square, substituting Fisher's exact tests when expected cell sizes were <5. Numerical variables were compared between the two patient groups using the Student's *t*-test, using Satterthwaite comparisons in cases of unequal variances. Binomial logistic regression was used to examine predictors of ART non-adherence. All statistical analyses were performed using IBM Corp. Released 2016. SPSS Statistics for Windows, Version 24.0 Armonk, NY: IBM Corp.

RESULTS

The majority of patients were male (75%), African American (61%), insured (80%), and with a mean (SD) age of 56 (10.1) years. Nearly 50% of patients had medical conditions in addition to HIV/HCV co-infection. Most were genotype 1 and 23% had cirrhosis of the liver. Sixty-three percent of patients, 75%, and 32% had a psychiatric disorder, substance use disorder, and alcohol use disorder, respectively. Thirty-two percent had a prior history of receiving substance use treatment.

The prevalence of ART non-adherence was 31%. Compared to patients living with HIV/HCV co-infection with ART adherence, a higher proportion of those with ART non-adherence were African American (55% vs. 74%, $p=0.035$), self-reported alcohol use during ART (58% vs. 82%, $p=0.010$), and reported a higher number of alcoholic drinks per drinking day (1.54 ± 1.88 vs. 2.38 ± 2.03 , $p=0.028$). Compared to patients living with HIV/HCV co-infection with ART non-adherence, those who with ART adherence were older (53 ± 9.02 vs. 56.71 ± 9.85 , $p=0.039$).

In multivariate analysis, self-reported alcohol use was not used to avoid multicollinearity with quantity of daily alcoholic drinks. African American ethnicity (OR=3.28, CI: 1.241–8.653, $p=0.017$) and a higher number of alcoholic drinks per drinking day (OR=1.31, CI: 1.054–1.639, $p=0.015$) were positively associated with ART non-adherence; whereas, older age (OR=0.95, CI: 0.909–0.994, $p=0.026$) was negatively associated with ART non-adherence.

DISCUSSION

Using a sample of patients living with HIV/HCV co-infection who were actively in clinical care at a university-affiliated HIV clinic that provides primary and sub-specialty HIV care and behavioral health services and treatment, this study assessed prevalence and predictors of ART non-adherence. Several main findings emerged from this study. First, the prevalence of self-reported ART non-adherence among patients living with HIV/HCV co-infection was 31%. In a meta-analysis conducted by Ortega and colleagues, the worldwide prevalence of ART non-adherence among patients living with HIV was 38% [26]. Compared to the most recent study published by Shuper et al. 2016 that estimated ART non-adherence specifically among patients living with HIV/HCV co-infection, 16% were ART non-adherent [16]. The study was conducted in Toronto, Canada and the sample was largely comprised of men who

have sex with men (MSM) and men who have sex with men and women (MSM/W). The sample size of patients in Shuper et al. 2016 and the present study were similar: 110 vs. 137, respectively. The present study was conducted in the United States, in particular the south, and sexual orientation was not available for inclusion in the analysis. However, it remains unclear why this study's ART non-adherence estimate was higher than the study published by Shuper and colleagues, but consistent with Ortega and colleagues' worldwide estimate of ART non-adherence for those receiving ART. Nonetheless, an elucidation of small differences between the estimates is likely trivial because a high frequency of ART non-adherence alone compromises HIV viral suppression among this patient population. Evidence-based research is needed to develop and implement behavioral approaches to reduce the frequency of ART non-adherence in patients living with HIV/HCV co-infection, and HIV clinics that provide both HIV care and behavioral health services and treatment to these respective patients—similar to the clinic included in this study—are ideal settings for behavioral intervention development and implementation.

Second, the majority of those with ART non-adherence were African American (74%) and those who were African American were 3.28 times more likely to self-report ART non-adherence. African American ethnicity has been found to be an independent predictor of ART non-adherence among patients living with HIV [27–29], and in the present study African American ethnicity was an independent predictor of ART non-adherence among patients living with HIV/HCV co-infection. The disproportionate frequency of ART non-adherence by **ethnicity** warrants further investigation along with other well-known racial disparities in the context of HCV. For example, African Americans only account for approximately 12% of the US population, but they account for 42% of those living with HIV/HCV co-infection [10]. African Americans living with HCV are less likely than any other racial group to be deemed eligible for and offered HCV treatment by providers [30]. Altogether, HIV/HCV co-infection prevalence, ART non-adherence, and HCV treatment ineligibility disparities experienced by African Americans living with HIV/HCV co-infection increases their risks for virologic suppression failure and HIV-related and HCV-related death.

Bogart et al. 2010 found that medical mistrust, in particular genocidal beliefs (e.g., HIV is manmade) and treatment-related beliefs (e.g., people who take antiretroviral treatments are human guinea pigs for the government), was associated with ART non-adherence among African American men living with HIV [31]. Other studies have found that perceived racism and discrimination within health care settings and appointment non-adherence were associated with ART non-adherence among African Americans [32–35]. Perhaps it is time to move beyond studies that characterize non-adherence disparities and that deductively identify potential etiologies of the racial disparity. Studies aiming to rectify medical mistrust and racism and discrimination experienced by African American patients living with HIV are lacking; and there are no published studies that have attempted to qualitatively elucidate potential reasons for ART non-adherence among African Americans living with HIV/HCV co-infection. There is a need for future research to use inductive approaches and findings to design, implement, and test novel evidence-based interventions to decrease the frequency of

ART non-adherence among African American patients living with HIV and HIV/HCV co-infection.

Third, patients living with HIV/HCV co-infection who had a higher number of alcoholic drinks per drinking day were 1.31 times more likely to self-report ART non-adherence. Surprisingly, the majority of those with alcohol use were non-dependent users (56%). The findings **suggest** there is a need for integration of alcohol use reduction interventions in HIV clinics providing care to patients living HIV/HCV co-infection. There is no safe threshold of alcohol use for patients living with HIV/HCV co-infection—even for those with moderate levels of alcohol use [36]. Alcohol use and HCV both independently increase risk for liver cancer (5-fold and 20-fold respectively)—with the initiation of cancer formation being amplified to 100-fold with alcohol use in patients living with HIV/HCV co-infection [37,38]. Alcohol use in patients living with HIV/HCV co-infection accelerates viral replication of both HIV and HCV, progression to severe liver fibrosis and cirrhosis [39], and it impairs immunologic response **to ART** [9,40]. As a result, clinical guidelines and HIV clinicians advise patients living HIV/HCV co-infection to abstain from alcohol use [41]. Despite receiving this advisement from their service providers, 66% of patients living with HIV/HCV co-infection reported alcohol use during the study period.

Personalized cognitive counseling (PCC), motivational interviewing (MI), cognitive behavioral therapy (CBT), and a repeated-dose brief behavioral intervention (REBOOT) have shown promise for alcohol use reduction in patients living with HIV [42–47]; however, the studies did not include or examine intervention outcomes in patients living with HIV/HCV co-infection. Prior to adapting and testing an existing intervention from published HIV studies, it is important to qualitatively elucidate reasons why patients living with HIV/HCV co-infection and without alcohol dependency continue to use alcohol despite knowledge of adverse risks associated with use. This type of formative work may be more ideal, because patients living with HIV/HCV co-infection have been shown to consume more alcohol than patients living with HIV mono-infection [48,49], and they are less likely to be successful in their efforts to restrict use[50]. A qualitative approach has the potential to facilitate a non-judgmental inquiry of patients' reasons for continued alcohol use behaviors, which are often stigmatized in medical settings.

Fourth, current substance use was not associated with ART non-adherence. It is probable that patients under-reported their current substance use and under-reporting may have compromised the study's ability to statistically detect associations between substance use and ART non-adherence. Though this study did not have access to or include laboratory substance screenings, the use of confirmatory lab findings for recent substance use in iterative studies should eliminate bias associated with analysis of self-report data. Nonetheless, the majority of published studies have consistently demonstrated that substance use is positively associated with ART non-adherence [51–53]. Smartphone applications, two-way short-text messaging service (SMS) reminders, treatment education, personalized-personal counseling, peer-led approaches, and other behavioral interventions have been used to improve ART adherence among patients living with HIV with substance use [46,54–58]. It is probable that these interventions may achieve similar outcomes among patients living

with HIV/HCV co-infection with substance use as well, but future studies are needed to test these respective interventions in this patient population.

The present study had some noteworthy limitations and strengths. More than a third (37%) of patients were excluded from the study sample due to incomplete PRO data. Other racial groups were not represented in the study sample—three patients who were not African American or White were grouped with non-African American patients. The study was conducted at a single-site and relied on self-report patient data. The study did not include other patient-related variables (e.g. social support, housing, appointment adherence) that may negatively impact ART adherence. Notwithstanding, the study analyzed PRO data supported by NIH's PROMIS initiative, and many other HIV studies have successfully conducted and published research using the PRO questionnaires that were used in this study [35,59–65]. The AUDIT-C has been shown to be a reliable and valid measure of alcohol use, and self-reported alcohol use on the AUDIT-C has been shown to be correlated with confirmatory biomarkers of alcohol use [49,59,66]. African Americans constituted the majority (61%) rather than the minority of the sample, and the entire sample was comprised of patients who were actively and not transiently in HIV clinical care.

Based on findings from this study, behavioral health providers are encouraged to incorporate alcohol use reduce interventions in HIV clinical settings that provide behavioral health services and treatment to patients living with HIV/HCV co-infection. Additionally, public health professionals and researchers, and clinicians are encouraged to use inductive methods to discover why ART non-adherence disproportionately impacts African American patients living with HIV/HCV co-infection and to develop approaches that are sensitive to those respective barriers. Otherwise, patients living with HIV/HCV co-infection who are African American or who consume alcohol will continue to have higher rates of HIV and HCV-related morbidity and mortality compared to patients living with HIV/HCV co-infection who are not of African American ethnicity or who do not consume alcohol.

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HCV+, positive for HCV
HIV-, negative for HIV
HCV+/HIV+, positive for both HCV and HIV
PRO, Patient Reported Outcomes

Figure 1.
Sampling Procedure

Table 1.

Bivariate Comparisons of Patients Living with HIV/HCV Co-infection with and without Antiretroviral (ART) Adherence

Variables	Sample	ART Adherence	ART Non-Adherence	Significance
N	137 (100%)	95 (69%)	42 (31%)	P-value
Demographics				
Sex				0.299
Male	103(75%)	69 (73%)	34 (81%)	
Female	34 (25%)	26 (27%)	8 (19%)	
Age	55.59 (10.09)	56.71 (9.85)	53.00 (9.02)	0.039 *
Ethnicity				0.035 *
Non-African American	54 (39%)	43 (45%)	11 (26%)	
African American	83 (61%)	52 (55%)	31 (74%)	
Insurance Status				0.582
Private	34 (25%)	26 (27%)	8 (19%)	
Public	76 (56%)	51 (54%)	25 (60%)	
Uninsured	27 (20%)	18 (19%)	9 (21%)	
Medical Conditions				
Medical Conditions in Addition HIV/HCV Co-infection	64 (47%)	46 (48%)	18 (43%)	0.547
HCV Characteristics				
Genotype 1	39 (91%)	30 (88%)	9 (100%)	0.564
Cirrhosis	31 (23%)	25 (26%)	6 (14%)	0.121
Psychiatric Disorders				
Psychiatric Disorder	66 (63%)	46 (66%)	20 (57%)	0.392
Alcohol Use				
Alcohol Use Disorder	34 (32%)	20 (29%)	14 (40%)	0.238
Current Alcohol Use	78 (66%)	46 (58%)	32 (82%)	0.010 *
Number of Alcoholic Drinks per Drinking Day	1.85 (1.98)	1.54 (1.88)	2.38 (2.03)	0.028 *
Tobacco Use				
Current Tobacco Use	80 (59%)	54 (57%)	26 (65%)	0.378
Substance Use				

Variables	Sample	ART Adherence	ART Non-Adherence	Significance
Substance Use Disorder	79 (75%)	50 (71%)	29 (83%)	0.201
Lifetime Illicit Substance Use	116 (87%)	78 (85%)	38 (91%)	0.370
Current Illicit Substance Use	40 (30%)	27 (29%)	13 (31%)	0.851
Substance Use Treatment				
Ever Received Treatment for Substance Use	42 (32%)	29 (32%)	13 (32%)	0.985
Health-Related Quality of Life				
EQ Index (Health-Related Quality of Life) Score	0.76 (0.18)	0.81 (0.17)	0.74 (0.18)	0.07

*
 $P < 0.05$

Table 2.

Binomial Logistic Regression Predicting Antiretroviral (ART) Non-adherence among Patients Living with HIV/HCV Co-infection

Variables	Categories	OR	95% CI	P-value
Age		0.951	0.909–0.994	0.026 [*]
Ethnicity	Non-African American	1		
	African American	3.277	1.241–8.653	0.017 [*]
Number of Alcoholic Drinks per Drinking Day		1.314	1.054–1.639	0.015 [*]
Current Illicit Substance Use	No	1		
	Yes	0.762	0.310–1.871	0.553

^{*} $P < 0.05$; OR, odds ratio; CI, confidence interval.