Factors Associated with Nonadherence to Antiretroviral Therapy in HIV-Positive Smokers

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Abstract

Adherence to antiretroviral therapy (ART) has markedly improved HIV disease management, and significantly reduced HIV/AIDS-associated morbidity and mortality. Although recent studies suggest a relationship between smoking and suboptimal adherence to ART, a more in-depth understanding of this relationship is needed. We conducted a secondary analysis using data from a randomized controlled smoking cessation trial to investigate the association of nonadherence to ART with potential demographic, psychosocial (perceived stress and depression), and substance use (nicotine dependence, illicit drug use, and alcohol use) variables among persons living with HIV/AIDS (PLWHA) who smoke. The mean (standard deviation [SD]) age of participants ($n=326$) was 45.9 years old ($SD=7.6$). Additionally, the majority were male (72.1%), self-identified as black (76.7%), and reported sexual contact as the mode of HIV acquisition (70%). Unadjusted logistic regression analysis indicated that depression (odds ratio [OR]=1.02; 95% confidence interval [CI]=1.00, 1.04), illicit drug use (OR=2.39; 95% CI=1.51, 3.79) and alcohol use (OR=2.86; 95% CI=1.79, 4.57) were associated with nonadherence. Adjusted logistic regression analysis indicated that nicotine dependence (OR=1.13; 95% CI=1.02, 1.25), illicit drug use (OR=2.10; 95% CI=1.27, 3.49), alcohol use (OR=2.50; 95% CI=1.52, 4.12), and age (OR=1.04; 95% CI=1.00, 1.07) were associated with nonadherence. Nicotine dependence, illicit drug use, and alcohol use are potentially formidable barriers to ART adherence among PLWHA who smoke. Future efforts should investigate the complex relationships among these variables to improve adherence particularly among populations confronted with multifaceted health challenges.

Introduction

THE ADVENT OF ANTIRETROVIRAL THERAPY (ART) has dramatically reduced HIV/AIDS-associated morbidity and mortality. However, maintaining adherence to ART remains critical for optimizing disease management and reducing HIV/AIDS-related complications.¹⁻³ Emerging research suggests a link between nonadherence to ART and cigarette smoking. For example, results from a longitudinal study demonstrated that adherence to ART was significantly lower among HIV-positive female smokers compared to nonsmokers.¹ Moreover, those who smoked exhibited poorer viral responses and poorer immune responses than nonsmokers.¹ Similar findings were noted in a study that found adherence rates among smokers in their study cohort to be on

average 21.3% lower than rates for nonsmokers.⁴ Researchers hypothesized that the relationship between current cigarette smoking and low ART adherence stemmed from a fatalistic view of HIV/AIDS disease progression held by those living with the disease.⁴ More recent findings examining ART adherence among persons living with HIV/AIDS (PLWHA) highlighted that those individuals who smoked demonstrated both higher levels of depression and lower ART adherence compared to PLWHA who did not smoke.⁵ Authors concluded that depression played a mediating role in the relationship between smoking and ART adherence, with greater levels of depression in smokers, thus predicting lower ART adherence.

Significantly elevated rates of smoking have been documented among PLWHA, generally two to three times higher

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than that of the general U.S. population.^{6–10} In addition to increased cancer risk, there is strong evidence suggesting that smoking is associated with a host of other adverse health outcomes for PLWHA, such as increased risk of numerous AIDS and non-AIDS-related diseases as well as reduced ART response.^{1,11–13} Thus, smoking represents an important health risk for PLWHA, and gaining a better understanding of the association between smoking and ART adherence is particularly salient. Although recent studies suggest a relationship between smoking status and low ART adherence, a more focused exploration of the variables underlying this relationship is needed. To address this need, we conducted a secondary analysis using baseline data from a randomized controlled clinical trial to identify factors associated with nonadherence to ART in a sample of low-income, HIV-positive smokers.

Methods

Data for this secondary analysis are derived from a larger randomized controlled trial assessing the efficacy of two smoking cessation strategies targeting PLWHA. The parent study was designed to compare a usual care approach (consisting of brief provider advice to quit smoking and self-help materials) to a cell phone counseling-based cessation intervention (consisting of the usual care components plus proactive smoking cessation counseling calls for 3 months). All data were collected utilizing an audio computer-assisted self-interview (ACASI) program.^{14,15} Further methodological detail about this trial has been previously published.¹⁶ The current study consists of data collected at the baseline assessment, prior to treatment group randomization. All participants in this study were recruited from a single HIV clinic in Houston, Texas. The clinic serves a predominantly low-income, ethnically diverse patient population, representative of the HIV population in the Houston area. Participants were recruited from February 2007 through December 2009. Upon completion of the baseline assessment, study participants received a \$20 gift card as compensation for participating. Only participants currently receiving ART at the baseline time point were considered in the current secondary data analysis ($n = 326$). The research protocol was approved by Institutional Review Boards of The University of Texas MD Anderson Cancer Center and The University of Texas Health Science Center at Houston.

Measures

Demographics. General demographic variables including race/ethnicity, age, sex, years of formal education, marital status, employment status, and mode of HIV acquisition were collected.

Psychosocial variables

Depression. To assess symptoms of depression, the 20-item Center for Epidemiological Studies Depression Scale (CES-D Scale) was utilized. In this scale, participants are asked to rate how often (on a four point scale ranging from “Almost Never” to “Almost Always”) they have had certain feelings such as, “I felt depressed” or “I was happy.” A score of 16 or greater suggests the presence of psychological distress.¹⁷ This scale has reliable psychometric properties and has been used with a variety of patient populations, including PLWHA.¹⁸

Self-efficacy. Participants’ self-efficacy for quitting smoking and staying quit was assessed with the 9-item self-efficacy scale developed by Velicer and colleagues.¹⁹ This is a widely used measure of smoking cessation self-efficacy and is an effective predictor of smoking outcomes. In this scale participants are asked to rate how confident they are that they will not smoke in a variety of situations such as “With friends at a party” or “When I am very angry about something or someone” with higher scores indicating higher self-efficacy for quitting smoking.

Stress. General stress was measured using the short form of the Perceived Stress Scale (PSS).²⁰ The PSS is a 4-item measure with well-established psychometric properties. The scale provides a single composite score for each participant’s level of stress, the lowest possible score, 0 indicating no stress up to a score of 16 indicating high levels of perceived stress. The PSS asks participants to comment on how often they felt overwhelmed or in control of various stressful situations over the course of the previous week.

Variables

Tobacco use. Data on participants’ tobacco use were gathered using items adapted from the National Health Interview Survey and from our previous studies.^{9,21–23} These items include questions related to the number of years of tobacco use, plans to quit smoking, previous quit attempts, and the use of Nicotine Replacement Therapy.

Nicotine dependence. The Fagerström Test for Nicotine Dependence (FTND) was used to assess level of nicotine dependence. The FTND is a commonly used dependence measure which has been previously administered with a variety of patient populations.²⁴ The FTND asks six questions and creates a score indicating how dependent an individual is to nicotine, such as: “How soon after you wake up do you smoke your first cigarette?” Scoring for the FTND is as follows: score 0–2 = Very Low Addiction, 3–4 = Low Addiction, 5 = Medium Addiction, 6–7 = High Addiction, 8–10 = Very High Addiction.²⁴

Alcohol use. The Alcohol Use Disorders Identification Test (AUDIT), a 10-item measure developed by a World Health Organization collaborative, was utilized to assess hazardous alcohol use.²⁵ In addition to the cumulative AUDIT score, the item, “During the past month, have you had at least one drink of any alcoholic beverage such as beer, wine, wine coolers, or liquor?” was used to define alcohol use in this analysis. A “drink” of alcohol is defined in the AUDIT as 1 can of beer (12 ounces), 1 glass of wine (4 ounces), or 1 shot of liquor (1 ounce).²⁵

Illicit drug use. Information on participants’ illicit drug use was ascertained with one dichotomous item (yes/ no), indicating any illicit drug use in the past 30 days.

Antiretroviral medication adherence. Last, ART adherence was measured with the Adult AIDS Clinical Trials Group (AACTG) adherence instrument. Our analysis included participant responses to one item, “During the past 4 days, on how many days have you missed taking all your doses?” Participants’ responses were dichotomized into adherent

TABLE 1. SOCIODEMOGRAPHIC CHARACTERISTICS OF STUDY SAMPLE (n=326)

Variable	Subgroup	Number (%)
Race/ethnicity	White	38 (11.7%)
	Black	252 (77.3%)
	Hispanic	30 (9.2%)
	Other	6 (1.8%)
Sex	Male	235 (72.1%)
	Female	91 (27.9%)
Education	Less than high school/GED	134 (41.1%)
	High school/GED	121 (37.1%)
	More than high school/GED	71 (21.7%)
Employment	Working full or part time	68 (21.0%)
	Not working because HIV or other health problems	212 (65.0%)
	Not working other ^a	46 (14.0%)
In a relationship	No	272 (83.4%)
	Yes	54 (16.6%)
HIV exposure	MSM	88 (27.0%)
	Heterosexual contact	141 (43.3%)
	IDU	57 (17.5%)
	Other	40 (12.3%)

^aNot working includes student, retired, housewife, and unable to find work.

MSM, men who have sex with men; IDU, injection drug use; Other, Women having sex w/women, blood transfusions, tattoos, and other routes of HIV infection.

(missed doses on zero days) and nonadherent (missed doses on one or more days). This item has been used with a variety of HIV populations and is accepted as a valid clinical measure of ART adherence.²⁶⁻³⁰

Analysis

Demographic characteristics were examined using descriptive statistics (e.g., means, frequencies and standard deviations). Unadjusted logistic regression was used to assess the relationships among the potential explanatory variables and nonadherence to ART. After the unadjusted analysis was completed, adjusted logistic regression was performed. Variables found to have a *p* value ≤ 0.15 in the unadjusted logistic regression analysis were included in the adjusted regression model. A backwards stepwise modeling approach was used to eliminate variables from the model with *p* values > 0.05 . Potential confounding variables for nonadherence to ART (age, race/ethnicity, and sex) were retained in the model regardless of statistical significance. All statistical analyses were performed using Stata, version 10.0 (College Station, TX).

Results

Of 474 participants who completed the baseline assessment, 326 (68.7%) reported current ART use and comprise the sample for this study. Summary data for this group are reported in Table 1. The mean (standard deviation [SD]) age of the participants was 45.9 (7.6) years. The majority of participants were male (72.1%), self-identified as black (77.3%), and reported sexual contact as their primary mode of HIV expo-

sure. Mean (SD) years of schooling was 10.7 (2.6), with most participants obtaining a high school diploma/General Equivalency Diploma (GED) or less. Although a large percentage of participants reported current unemployment (65.0%), the average (SD) number of hours worked per week by those who were employed was 31 (17.5) h.

Of the 326 participants currently prescribed ART, 60.4% reported not missing a dose within the past four days and were considered adherent. On average (SD), participants reported smoking approximately one pack of cigarettes (19.3 [11.6] cigarettes) daily, and further reported smoking for 21.7 (11.0) years. Half the sample lived with other smokers (52.2%) and had a moderately high level of nicotine addiction, with a mean FTND score of 5.71 (2.3). One third (38.7%) of participants reported illicit drug use within the past month and 54.6% reported alcohol use within the past month. Of those individuals reporting alcohol use, 55.6% had AUDIT Scores of 8 or higher, indicating a hazardous level of drinking. The mean (SD) stress score, as measured by the PSS, was 7.0 (2.8) while the mean (SD) depression score, measured with the CES-D, was 21.7 (10.6). The samples' mean (SD) self-efficacy score was 2.8 (0.95). A review of pairwise correlation coefficients revealed modest correlation ($r=0.62$) between CES-D and PSS scores. All other correlation coefficients were no higher than 0.2.

Unadjusted analysis

Results from the unadjusted logistic regression models are presented in Tables 2 and 3. None of the demographic variables were significantly associated ($p < 0.05$) with nonadherence to ART. Of the psychosocial smoking-related variables investigated, only depression as measured by the CES-D, was associated with nonadherence (OR=1.02; 95% CI=1.00, 1.04). Those who reported illicit drug use were two times more likely to not adhere to ART (OR=2.39; 95% CI=1.5, 3.79) while those who reported any alcohol use within the past 30 days were almost three times more likely to not adhere to ART (OR=2.86; 95% CI=1.79, 4.57). Although alcohol use within the past 30 days was significantly associated with nonadherence to ART, hazardous drinking as opposed to nonhazardous drinking, including not drinking at all, was not a significant correlate of nonadherence to ART (OR=0.95; 95% CI=0.57, 1.59; Table 3).

Adjusted analysis

Perceived stress, depression, nicotine dependence, illicit drug use, and alcohol use met the criteria ($p < 0.15$) for inclusion in the initial adjusted logistic regression model and were included along with the retained demographic variables (age, race/ethnicity, and sex). Using the backwards stepwise approach outlined in the methods section, depression ($p=0.568$) and then stress ($p=0.169$) were removed from the adjusted analysis because their *p* values were > 0.05 . The final adjusted regression model indicated that higher levels of nicotine dependence (OR_{adj}=1.13; 95% CI=1.02, 1.25), illicit drug use (OR_{adj}=2.10; 95% CI=1.27, 3.49) and alcohol use (OR_{adj}=2.50; 95% CI=1.52, 4.12) were statistically significant ($p < 0.05$) correlates of nonadherence. Age was additionally associated with nonadherence to ART (OR_{adj}=1.04; 95% CI=1.00, 1.07; Table 4).

TABLE 2. UNADJUSTED ANALYSIS: DEMOGRAPHIC VARIABLES CORRELATED TO NONADHERENCE TO ART

Variables	Subgroup	Odds ratio	95% Confidence interval	p Value
Race/ethnicity	White (referent)	—	—	—
	Black	1.21	(0.84–1.75)	0.297
	Hispanic	1.18	(0.85–1.65)	0.320
	Other	1.02	(0.65–1.61)	0.932
Sex	Male (referent)	—	—	—
	Female	0.68	(0.41–1.12)	0.130
Education	Less than high school/GED (referent)	—	—	—
	High school/GED	0.92	(0.71–1.19)	0.519
	More than high school/GED	1.05	(0.86–1.27)	0.642
Employment	Working full or part time (referent)	—	—	—
	Not working b/c HIV or other health problems	1.01	(0.78–1.29)	0.966
	Not working other ^a	1.06	(0.88–1.27)	0.538
Relationship	No (referent)	—	—	—
	Yes	1.06	(0.58–1.92)	0.847
HIV exposure	MSM (referent)	—	—	—
	Heterosexual contact	1.04	(0.79–1.36)	0.788
	IDU	1.00	(0.08–1.26)	0.996
	Other	1.01	(0.84–1.23)	0.883
Age (years)		1.02	(0.99–1.05)	0.232

^aNot working includes student, retired, housewife, and unable to find work.

ART, antiretroviral therapy; MSM, men who have sex with men; IDU, injection drug use; Other, Women having sex w/women, blood transfusions, tattoos, and other routes of HIV infection.

Discussion

This study investigated variables associated with nonadherence to ART among a population of low-income PLWHA who smoke. Results from logistic regression modeling indicated that the level of nicotine dependence, illicit drug use, alcohol use, and older age were each significantly associated with nonadherence to ART. Our analysis contributes to the existing literature on ART adherence among HIV-positive smokers specifically with the finding that participants with higher levels of nicotine dependence were more likely to be nonadherent to their ART regimen, compared to individuals with lower levels of nicotine dependence. Previous ART adherence studies have assessed individuals' smoking status as a dichotomous variable (yes/no).^{1,4,5} This study, however, expands on previous findings with a sample of all smokers, and provides evidence that nicotine dependence may play a significant role in nonadherence to ART that has been previously attributed to smoking status alone.

It is well documented that individuals who are more dependent on nicotine are less likely to achieve smoking cessation.^{31–33} Thus, nicotine dependence serves as a reliable predictor for failure to achieve a stable change of smoking behavior. Findings from the current study suggest that nicotine dependence may also be a predictor of success in relation to other health behaviors. While additional research is needed to identify the mechanisms, it would appear possible that nicotine dependence may be associated with a generalized discounting of the health effects of behavior change, including ART adherence. Regardless of the potential mechanisms, results from the current trial suggest that assessment of nicotine dependence may offer providers the opportunity to identify PLWHA who are at risk for poor ART adherence and would benefit from early interventions designed to maintain adherence.

Furthermore, this analysis indicates that nonadherence to ART was two times more likely among individuals engaging in illicit drug use and two and a half times more likely among those engaging in alcohol use both within the past month.

TABLE 3. UNADJUSTED ANALYSIS: PSYCHOSOCIAL VARIABLES (STRESS, DEPRESSION, SELF-EFFICACY FOR QUITTING SMOKING), NICOTINE DEPENDENCE, ILLICIT DRUG USE, ALCOHOL USE CORRELATED WITH NONADHERENCE TO ART

Variables	Odds ratio	95% Confidence interval	p Value
Perceived Stress scale	1.07	(0.99–1.16)	0.083
CES-D (depression)	1.02	(1.00–1.04)	0.037
Self-efficacy (for quitting smoking)	0.86	(0.68–1.09)	0.225
Fagerström Test for Nicotine Dependence	1.09	(0.99–1.21)	0.077
Illicit drug use (within last 30 days)	2.39	(1.51–3.79)	< 0.001
Alcohol use (within last 30 days)	2.86	(1.79–4.57)	< 0.001
Hazardous drinking vs. nonhazardous drinking (including nondrinkers) (alcohol)	0.95	(0.57–1.59)	0.845

ART, antiretroviral therapy; CES-D, Center for Epidemiological Studies Depression Scale.

TABLE 4. ADJUSTED ANALYSIS: AGE, SEX, RACE/ETHNICITY, NICOTINE DEPENDENCE, ILLICIT DRUG USE, ALCOHOL USE CORRELATED WITH NONADHERENCE TO ART

Variable	Subcategory	Odds ratio	95% Confidence interval	p Value
Age		1.04	(1.00–1.07)	0.034
Sex	Male (referent)	—	—	—
	Female	0.68	(0.40–1.17)	0.168
Race/ethnicity	White (referent)	—	—	—
	Black	1.09	(0.74–1.61)	0.673
	Hispanic	1.22	(0.85–1.75)	0.274
	Other	0.88	(0.54–1.44)	0.611
Nicotine dependence		1.13	(1.02–1.25)	0.023
Illicit drug use (within last 30 days)		2.10	(1.27–3.49)	0.004
Alcohol use (within the last 30 days)		2.50	(1.52–4.12)	< 0.001

ART, antiretroviral therapy.

Previous work in this realm has been somewhat inconclusive and has not specifically looked at PLWHA who smoke.^{4,34–38} In a review conducted by Ammassari and colleagues,³⁹ illicit drug use and alcohol consumption were found to be “inconsistently associated” with adherence. Conversely, Stone and colleagues noted that drug and alcohol use are “consistently linked to poorer adherence.” In our study, although alcohol use within the past month was associated with nonadherence to ART, hazardous drinking versus nonhazardous drinking was not associated with nonadherence to ART. This suggests that drinking within the past month explains more of the variance in nonadherence to ART than level of drinking (i.e., hazardous vs. not hazardous). Previous research studies among HIV-positive smokers demonstrate that illicit drug use and alcohol use are elevated in this population.^{1,40} Study findings provide additional contributions to the literature on substance use and ART adherence by suggesting that illicit drug use and alcohol use are potential obstacles to ART adherence among HIV-positive smokers.

Our current research findings contribute to the body of literature suggesting that demographic variables are not reliable correlates of nonadherence to ART.^{34,39} The one exception in this analysis was the variable of age. Among our study population, each additional year of age resulted in a modest increase in nonadherence to ART (4%). Previous findings have shown mixed results with regard to the association of age and ART adherence. Literature suggests that fatalistic views of HIV/AIDS disease progression and medication fatigue are contributing factors to a lack of ART adherence.^{4,41} Thus, higher levels of medication fatigue may have influenced the relationship between ART adherence and age in our study and led to higher rates of nonadherence among older participants.

Previous findings indicate that PLWHA who smoke have both higher levels of depression and higher rates of nonadherence to ART when compared to PLWHA who do not smoke.⁵ Webb and colleagues⁵ found that depression played a mediating role in the relationship between smoking and ART adherence, with greater levels of depression in smokers predicting greater levels of nonadherence to ART. Based on these findings, we examined stress and depression as potential correlates of nonadherence to ART. Interestingly, we did not observe a significant association between psychosocial variables, including depression and stress, and nonadherence to ART in the adjusted analysis. Our findings suggest that although de-

pression and other psychosocial variables do play a role in nonadherence to ART, the significance of this role diminishes when evaluated in combination with other relevant factors in this sample of smokers, i.e., level of nicotine dependence.

Past research has identified smokers as being a population at greater risk for nonadherence to ART.^{4,5} Our findings expand upon previous work focused on ART adherence and PLWHA who smoke by investigating correlates of nonadherence to ART among a sample of all smokers. In our study, level of nicotine dependence, illicit drug use, alcohol use, and older age help to further elucidate the relationship between smoking and nonadherence to ART established in previous studies.⁵ Our findings also suggest that for PLWHA who smoke, variables such as depression and stress may not tell the entire story of nonadherence. In fact, the relationship between nicotine dependence, illicit drug use, alcohol use, depression, and nonadherence to ART may well be complex. Research indicates that individuals who smoke typically engage in multiple risk behaviors. Furthermore, smoking combined with other behavioral risk factors is known to adversely affect health outcomes.⁴² In our study, we observed several risk behaviors (illicit drug use, alcohol use, and tobacco use) which appear to result in multiple poor outcomes, including nonadherence to ART. Understanding the complex relationship among these variables and the underlying mechanisms will be essential to improving health outcomes, specifically ART adherence, among PLWHA. Interventions that address multiple risk behavior patterns (i.e., drug use, alcohol use, tobacco use) could potentially improve ART adherence outcomes for individuals who smoke. Rather than focusing merely on individual-level behavior, addressing factors germane to an individual's social, economic, political, or physical environment that potentially shape and constrain health behaviors has become a salient priority in HIV/AIDS research. Hence, multilevel interventions that focus on managing behavioral risks and concomitant life stressors will be crucial to meeting the medical and social needs of this population and thereby improving their overall health and wellbeing.^{43,44} Findings further underscore the need to integrate evidence-based smoking cessation programs and practices into HIV care settings.⁶ Approaches that address the needs of HIV-positive patients by incorporating innovative strategies that can be sustained, particularly, in resource-limited HIV care settings are critical to optimizing smoking cessation efforts.⁴⁵

The current study is subject to several limitations including the analysis of cross-sectional data (limiting our ability to infer causality) and the reliance on self-report data (i.e., adherence rates, smoking history, and illicit drug use). For instance, the smoking history question that asks participants to recount how many years they smoked regularly may have introduced inaccuracies, resulting in a low mean duration of tobacco use. Additionally, the ART adherence measure, which is a clinically valid measure utilized in a variety of settings, lacks specificity, which can result in an overestimation of adherence rates.^{26–30} Furthermore, information on specific illicit drugs used by participants was not collected. Therefore, we were unable to assess differences between specific agents and ART adherence.

As this was a secondary data analysis, several key correlates of ART adherence (i.e., regimen complexity, pill count, and severity of side effects from the medications) were not available for analysis. Future studies should incorporate these variables of ART adherence, in addition to patient–provider interactions, which have been suggested by the literature to play a key function in ART adherence outcomes.^{34,46} Additionally, our ability to fully assess the role of depression may have been compromised. The mean CES-D score observed in our sample was 21.7. Because this score exceeds the typical depression score cut point of 16, we may have lacked the variability needed to appropriately evaluate the role of depression.¹⁷ Finally, although the study sample was diverse both in terms of HIV risk category and racial and ethnic make-up, all participants were recruited from a single study site. Thus, results might not be generalizable to other populations, particularly to those outside of a clinic-based setting.

In conclusion, level of nicotine dependence, illicit drug use, alcohol use, and age were associated with nonadherence to ART in this sample. This study adds to previous findings by identifying potential predictors of medication adherence in a sample of PLWHA who smoke. Future efforts should investigate the complex relationships among these variables to improve adherence, particularly among populations confronted with multifaceted health challenges. PLWHA often encounter numerous barriers affecting HIV-medical management, including access to healthcare, transportation services, crisis management, securing housing, and a general lack of support. In light of such barriers, additional research is needed to determine how to best address these desired behavior changes (nicotine dependence, illicit drug use, and alcohol use) in the context of an individual's daily life demands. Because this is an emerging area of research, future qualitative work may be critical to examining HIV-positive smokers' knowledge, attitudes, perceptions, and practices related to ART adherence to gain a contextual-based understanding of this complex problem. In addressing variables associated with smoking and those associated with low ART adherence, interventions can potentially reduce the severity of diseases related to both, and improve medical management and quality of life for individuals living with HIV/AIDS.

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Author Disclosure Statement

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