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Alcohol Use Disorders Negatively Influence Antiretroviral Medication Adherence Among Men Who Have Sex with Men in Peru

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Abstract

Objective—As international guidelines increase access to antiretroviral therapy (ART) globally, ART adherence becomes increasingly important to achieve HIV treatment as prevention (TasP) goals. In the concentrated HIV epidemic among men who have sex with men (MSM) and transgendered women (TGW) in Lima, Peru, the independent correlates of ART non-adherence were examined to inform treatment intervention priorities.

Design—Cross sectional survey of HIV-infected MSM and TGW who are engaged in clinical care in Lima, Peru.

Methods—From June to August 2012, 302 HIV-infected Peruvian MSM/TGW from three clinical care sites were recruited using convenience sampling to participate in a cross-sectional computer-assisted adherence survey. Several standardized screening measures associated with ART non-adherence were examined in order to determine the independent correlates of optimal (≥90%) and perfect (100%) adherence, which were assessed using logistic regression.

Results—Of the 302 participants recruited, 263 (87.1%) were prescribed ART. Among those prescribed ART, 229 (87.1%) reported optimal and 146 (55.5%) reported perfect adherence. The prevalence of alcohol use disorders (AUD; 43.2%), alcohol dependence (5.3%), recent drug use (6.0%) and depression (44.5%) was high and most participants had some evidence of neurocognitive impairment. Meeting criteria for having an AUD and depression were collinear ($p<0.001$). On multivariate analysis, having an AUD was inversely related and the only

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independent correlate of optimal (AOR=0.427; 95% CI=0.187–0.976) and perfect (AOR=0.552; 95% CI=0.327–0.930) ART adherence.

Conclusions—AUDs are highly prevalent among Peruvian HIV-infected MSM and contribute significantly to ART non-adherence. These findings support the need for screening and treating underlying AUDs. In order to meet HIV TasP goals, evidence-based strategies targeting AUDs are likely to directly improve ART adherence and indirectly improve overall individual health, HIV treatment engagement and reduce transmission to sexual partners among this vulnerable and disproportionally affected population.

Introduction

Increasing antiretroviral therapy (ART) access using HIV treatment as prevention (TasP) strategies is central to global HIV prevention and treatment. If successful, TasP will increasingly play a significant role in decreasing HIV incidence and mortality [1]. The World Health Organization's (WHO) recommendation for earlier ART initiation at higher CD4 lymphocyte thresholds should increase the numbers of individuals eligible for and receiving ART [2,3]. Once prescribed, maintaining high ART adherence is crucial for achieving viral suppression (VS), thereby reducing sexual transmission to heterosexuals [4,5], people who inject drugs [6,7] and men who have sex with men (MSM) [8]. Optimal ART adherence associated with VS also reduces development of drug resistance [9].

Individual and structural factors undermine optimal ART adherence. Individual factors include the presence of alcohol use disorders (AUDs) and other substance use disorders (SUDs) [10,11], HIV-associated neurocognitive impairment (NCI) [12] and psychiatric illnesses [13] – all of which are also associated with risky sexual behaviors. Social issues like HIV-related stigma, low social support, health literacy [14], and food insecurity [15] may also contribute to ART non-adherence [13]. Structural factors associated with ART non-adherence include clinic and provider characteristics, costs and availability of ART and other health care delivery considerations [2,16,17].

Globally, over half of new HIV infections in North and South America, Western Europe and Australia is concentrated among MSM [18-22]. MSM represent a particularly vulnerable population in Peru, a middle-income country where the government provides free ART. Given the high levels of stigma against same-sex relations in Peru [23], the consumption of disinhibiting substances like alcohol is common among MSM [24,25], and is associated with high-risk sexual behaviors [26-28] and being unaware of being HIV-infected [29]. In light of these concerning findings, we hypothesized that mind-altering substances like alcohol and/or drugs or underlying NCI may also negatively impact HIV treatment outcomes, even in the presence of medication reminders. We therefore sought to comprehensively explore the facilitators and barriers to optimal ART adherence among Peruvian MSM who are engaged in clinical care.

Methods

Ethics Statement

Institutional Review Boards at *Impacta Peru* and Yale University approved this research.

Study participants and procedures

Between June and August 2012, 302 consecutive HIV-infected Peruvian MSM were recruited to participate in a self-administered survey to examine correlates of ART adherence and access to care; only adherence was examined in this study. Participants were defined as MSM if they were born male and self-reported having sex with a man in the past year. Using convenience sampling, we recruited consecutive patients receiving HIV care from three clinics located in Lima. Eligibility included age ≥18 years, born male and diagnosed with HIV for over one year to ensure that participants had had sufficient time and opportunities to initiate ART. Recruitment included clinic-based advertisements and flyers, or clinical staff approaching patients at the end of their clinical visits; no patients refused study participation. Participants providing written informed consent then completed a 60-minute computer-assisted survey instrument (CASI) in a private setting and were paid 25 soles (∼$10 US) for their time.

Survey Content and Variable definitions

Literature review informed variable selections associated with ART non adherence [26-29]. We also collected demographic and social characteristics, education, occupation and monthly salary earned, living circumstances, year of HIV diagnosis, and self-reported sexual identity and orientation. Self-reported adherence, the dependent variable, was assessed using a validated visual analog scale (VAS) [30], and analyzed as optimal (≥90%) and perfect (100%) adherence [31].

AUD screening deployed the WHO's validated 10-item Alcohol Use Disorders Identification Test (AUDIT) [32], with standard cut-offs to define any AUD (score ≥8) and alcohol dependence (score ≥20) which are highly correlated, have high internal and external validity [33], as well as sensitivity and specificity [34]. A drug use battery over the past 6 months was assessed using a modified Addiction Severity Index (ASI) [35]for known drugs used in Peru, while addiction severity was measured using the 10-item Drug Abuse Screening Test (DAST-10) [36], with bivariate cutoffs of >2 for moderate to severe addiction severity. Depressive symptoms were measured using the 10-item Center for Epidemiologic Studies Depression Scale (CES-D 10) with scores >7 being correlated with moderate to severe depressive symptoms [37]. HIV-related stigma and social support were analyzed continuously as previously described using the Wright Stigma Scale [38] and the Modified Social Support Survey (MSSS-5) [39], respectively. Food insecurity was measured using 6 items from the National Center for Health Statistics (NCHS) [40]. Health literacy was assessed continuously using the Short Test of Functional Health Literacy in Adults (STOHFLA) [41] and barriers to medical care deployed a validated 10-item scale [42].

NCI was assessed using the 95-item standardized Neuropsychological Impairment Scale (NIS) [43]. Though the NIS features many subscales, we focused only on the influence of general cognitive impairment, which was analyzed using a validated NCI summary score called the Global Measure of Impairment (GMI). Consistent with prior analyses involving the NIS, raw scores were transformed to t-scores and then treated as a continuous variable [44]. Facilitators of ART adherence included a battery of cues and reminders often used to

assist medication-taking, like alarm clocks and calendars, association with meals and hour of sleep, reminders from friends, and putting ART in a highly visible place.

Standardized measures that have previously been translated and validated in Spanish were used. Other survey components were created in English, translated to Spanish and then back-translated into English to ensure understanding as previously described [45]. Pilot testing with HIV-infected persons in Lima was conducted to further ensure understanding.

Data Analysis

Statistical analyses were performed using SPSS (Version 20). The dependent variables were optimal (≥90%) and perfect (100%) adherence over the past 30 days. Bivariate associations of all clinically relevant variables first assessed their association with the dependent variables using chi-square and t-tests were used for categorical and continuous variables, respectively. Using a deterministic approach, bivariate associations significant at $p<0.20$ were then incorporated into the multivariate logistic regression model. Stepwise forward and backward elimination regression both showed the same results as our deterministic model, which was ultimately selected based on having the best goodness-of-fit using the Akaike Information Criterion (AIC). The Variance Inflation Factor (VIF) was used to test for collinearity between variables that were significant in the bivariate analysis but no longer significant in the final model.

Results

Description of the study sample

Table 1 describes the characteristics of the participants. Most were in their early thirties (mean=32.0 years), earned greater than minimal wage (58.6%) and completed high school (68.8%). Most (87.1%) participants were on ART and, of those, 87.1% reported optimal (≥90%) and 55.3% reported perfect (100%) adherence. Only 6.0% of participants reported recreational drug use and 43.2% met screening criteria for AUDs, with 5.3% meeting criteria for dependence (AUDIT≥20).

Correlates of ART adherence

Table 2 highlights factors significantly correlated with both optimal and perfect adherence among the 263 participants prescribed ART. On bivariate analysis, only three factors were inversely correlated ($p<0.05$) with optimal adherence, including having an AUD, higher levels of NCI, and being transgendered women (TGW). Having moderate to severe depressive symptoms ($p=0.066$) and lower monthly income ($p=0.084$) trended towards significance. Similarly, for perfect adherence, factors that were inversely and significantly ($p<0.05$) correlated included having an AUD ($p<0.001$), higher NCI ($p=0.001$), increasing age ($p=0.032$), having moderate to severe depressive symptoms ($p=0.002$).

Multivariate modeling, however, confirmed that having an AUD was the only independent factor associated with ART adherence, portending greater than a 55% reduction (AOR=0.427; 95% CI=0.187–0.976) in optimal adherence and 45% reduction in perfect adherence (AOR=0.552; 95% CI=0.327–0.930). Figure 1 depicts the proportion of study

participants with and without an AUD that reported optimal and perfect adherence. Compared to those without an AUD, those with an AUD were significantly less likely to report optimal (80.2% vs 91.9%; p=0.005) and perfect adherence (44.0% vs 64.2%; p<0.001). Including the use of any facilitating cuing reminder variable into the final model did not change the outcome for either of the dependent variables, suggesting that ART adherence facilitators do not overcome the influence of AUDs on non-adherence in our sample (data not shown).

Discussion

To our knowledge, this is the first study investigating correlates of ART adherence among HIV-infected MSM/TGW in Peru. Though alcohol and drug use have variably been associated with non-adherence in settings outside of South America and among non-MSM populations [46-49], a systematic review of the influence of alcohol and adherence showed conflicting findings, primarily because of a profound lack of using standardized measures of alcohol use, with almost none using validated screening criteria for “treatable” AUDs [50]. Findings here use standardized measures for both AUDs and ART adherence, overcoming problems identified with earlier studies. Moreover, this study was conducted among MSM, the primary drivers of HIV transmission in many regions globally [18], including South America [51].

In South America, only one longitudinal study in Brazil showed that *any* alcohol use negatively influenced ART adherence [52], but did not use standardized measures to screen for AUDs or depression [53]. Our study also included a larger sample size and included only MSM. Moreover, AUDs differ from alcohol use *per se* in that AUDs are medically defined conditions that are amenable to intervention [54]. AUDs have previously been associated with decreased ART adherence in other settings and populations [55,56] and to other poor HIV-treatment outcomes, including decreased health care utilization [57], decreased linkage to and retention in care [58,59], reduced ART medication access [60,61] and viral non-suppression [58]. In Peru's largest biobehavioral serosurveillance study of over 5000 Peruvian MSM, AUDs were previously found to be highly prevalent (62.3%) and independently associated with high-risk sexual behaviors [26-28] and being unaware of being HIV-infected [29]. This study builds on these concerning findings and is the first to demonstrate a concerning association between AUDs and suboptimal ART adherence among HIV-infected MSM enrolled in HIV clinical care in Peru.

Overall, 31.9% met criteria for hazardous (binge) drinking (AUDIT=8-16). According to WHO recommendations, hazardous drinkers should minimally undergo brief counseling interventions to reduce heavy drinking and to seek additional assistance [62]. In HIV-infected MSM, however, the risk is augmented because several days after heavy drinking episodes are associated with continued missed ART doses [63]. Moreover, in this relatively young group of MSM, without intervention, hazardous drinkers may progress to more serious AUDs, including alcohol dependence [64].

In addition, we used standardized measures to analyze other important correlates of ART adherence. First, we examined global indicators of NCI because to our knowledge, no

previous NCI assessment has been conducted among Peruvian MSM. Studies elsewhere have shown that various levels of NCI were present among HIV-infected persons [65-67], and that higher NCI levels were associated with decreased ART adherence and increased HIV risk behaviors [22,68]. The high GMI scores in our sample [50.8 (±10.8) of 80 maximum] suggest most participants had some degree of NCI. This is concerning because individuals with mild to moderate NCI may experience sub-optimal ART adherence [44] and increased HIV risk behaviors [70]. In turn, NCI symptoms will worsen in HIV-infected people not taking ART [71], because ART reverses some, but not all NCI-related symptoms [72]. Although the general measure of NCI did not remain significant in the multivariate model, it is possible that only the most severely neurocognitively impaired (e.g., worst decile) [43] or those with impairment of only one or a few of the cognitive domains (e.g., memory, learning ability, attention) [44] show suboptimal ART adherence [73]. Further exploration of NCI severity and NCI subscales on ART adherence is warranted.

For optimal, but not perfect adherence, TGW were significantly less likely to adhere to ART. This finding, however, did not remain significant in the multivariate analysis. While we speculated that TGW may have had higher levels of AUDs or HIV-related stigma [23,74], collinearity tests did not substantiate these assumptions, perhaps because TGW (N=20) comprised a small proportion (6.6%) of our sample.

Depressive symptoms were highly prevalent (44.5%) in this population. For both optimal and perfect adherence, being depressed was borderline and highly significant in the bivariate analysis, respectively, yet did not remain so in final models. Previous studies document correlations between depressive symptoms and ART non adherence [75,76], including in low- and middle-income countries [77]. Numerous studies also document a relationship between alcohol and depressive symptoms [78,79], and collinearity tests here confirm these two variables to be highly correlated ($p<0.001$; not shown). AUDs and depressive symptoms may both contribute to non-adherence, and from a purely clinical perspective, it is therefore essential to screen for and treat both disorders simultaneously in order to optimize treatment outcomes. This is particularly relevant since both disorders are under-diagnosed [80,81] and under-treated[82,83] in clinical settings, yet they are amenable to behavioral and/or pharmacotherapeutic interventions.

We also found that global stigma was not associated with non-adherence, yet the disclosure stigma subscale was negatively associated with perfect adherence. In our analyses, we did not explore in detail the impact of various types of stigma on ART adherence, but it is seductive to speculate that those who do not disclose their HIV status to others continually live in fear and miss doses based on concerns about someone finding out about their HIV status – as shown by previous studies conducted in Peru [84]. Further inquiry into various types of stigma is crucial for intervention development, especially with regard to HIV disclosure.

Unlike other studies examining alcohol and ART adherence, we assessed reminder interventions (e.g., alarm clocks, beepers, calendars) used clinically to improve ART adherence. Unlike a recent report conferring benefit among HIV-infected Peruvian men without assessment of alcohol or drug use [84], various reminders did not significantly

influence ART adherence in our sample. Though not shown, those with AUDs were no more likely to use medication reminders than those without them. Due to our survey not examining the consistency to which participants used these reminders, we are unable to contribute further to guidelines from the International Association of Physicians in AIDS Care, recommends them as an adherence strategy [85].

Despite our analysis examining numerous validated factors that may influence ART adherence, having an AUD was the only independent correlate that remained significant in the multivariate model. This study's cross-sectional assessment does not establish causality between AUDs and suboptimal ART adherence, yet it is reasonable to expect that AUDs negatively influence adherence for numerous reasons, including intoxication impairing one's capacity to plan for or remember dosing requirements [86], living in precarious conditions with lower ART access [87], alcohol consumption used to reduce ART-related side effects [88,89] and intentional “skipping” ART when drinking, due to misconceptions about drug interactions [90-92]. Additional research is needed to clarify the behavioral, environmental, and circumstantial conditions under which alcohol use is likely to influence adherence.

The high prevalence of AUDs among Peruvian MSM is alarming, and it can be partly explained by the cultural and sexual biases that are pervasive against same-sex relations in the wider Peruvian society [23]. As a result, MSM have found gay bars to be a sheltering environment, where the consumption of disinhibiting substances like alcohol became progressively popular, in the expectancy to overcome the taboo associated with stigmatizing behaviors [24,25]. This finding, along with the significant association between AUDs and suboptimal ART adherence, suggests the need to design and implement effective interventions targeting alcohol use among this vulnerable population. This is particularly important since Peruvian patients have been found to miss more ART doses due to alcohol use in comparison to their US and African counterparts [93]. WHO suggests that MSM with SUDs may be targeted using psychosocial interventions [62] such as cognitive-behavioral (CBT) and motivational interviewing (MI) approaches, which have been shown to be effective across a wide range of SUDs [58,85], including AUDs [94]. Counseling-based AUD strategies alone, however, have not documented HIV treatment benefits nor ART adherence. CBT and MI approaches targeting ART adherence and retention in care produce short-term, but not sustained benefits among MSM with AUDs [95]. Among the three approved pharmacological medications that treat AUDs (Naltrexone, Acamprosate and Disulfiram), only naltrexone, in its oral or extended-release formulation, is superior to either acamprosate alone [96,97] or to behavioral therapies in HIV uninfected persons [98,99]. Few studies, however, have investigated the influence of naltrexone on HIV treatment outcomes among patients prescribed ART [100], but data are beginning to emerge [101]. Since naltrexone appears to be safe in HIV-infected individuals [102-104] and in those with AUDs [105], naltrexone has the potential to improve ART adherence through reduction of alcohol use.

In addition to treating AUDs, mobile technologies that improve ART adherence are gaining traction among HIV-infected MSM in Peru who are interested in using the Internet and cellphones for HIV health promotion interventions [69,106], potentially to improve ART adherence [106-108]. Our finding of moderate levels of NCI among our sample, however,

may reduce their ability to effectively engage with such technologies [109]. Future ART adherence intervention development will require tailoring and testing along the spectrum of NCI for both content and delivery.

Even though our findings have important implications for HIV prevention and treatment among MSM with AUDs, study results should be interpreted in the context of inherent methodological limitations. The cross-sectional nature of this observational study does not allow us to establish causality. Other external variables could be responsible for both AUDs and poor adherence, specifically the relationship between depressive symptoms and AUDs. Also, we did not control for other factors associated with non-adherence in other studies, such as pill burden, dosing frequency and lifestyle changes required for ART adherence. Not presented, however, is the near uniformity in twice-daily and identical ART regimens prescribed. Second, sampling bias may have occurred, since patients were recruited from three clinics that provided dedicated MSM/TGW services. Since our convenience sampling method was not designed to be fully representative of HIV-infected MSM, caution is required when generalizing these results to the MSM elsewhere without more comprehensive and culturally competent services. Additionally, we used self-report instruments to gather data about alcohol use, ART adherence, and the other independent variables. Reporting of sensitive issues such as stigma or alcohol use might have also been influenced by social desirability bias, but CASI has been documented to reduce such biases [110] and the high self-reported levels suggest this not to be a concern. Despite this being the largest sample of HIV-infected MSM assessing adherence to date, a larger sample size might help balance these limitations.

Conclusions

Our study highlights the strong and significant association of AUDs with suboptimal ART adherence among HIV-infected MSM in Peru. Given that HIV remains a concentrated epidemic among Peruvian MSM and elsewhere, our findings underscore the importance of creating, testing and implementing interventions simultaneously targeting AUDs and ART adherence. Such interventions may simultaneously integrate pharmacological and multicomponent behavioral interventions. While the influence of other factors (e.g., NCI, depression and stigma) on poor adherence was not ultimately found to be significant among this sample, further research is needed to elucidate their possible influence on this vulnerable and disproportionally affected HIV-infected population.

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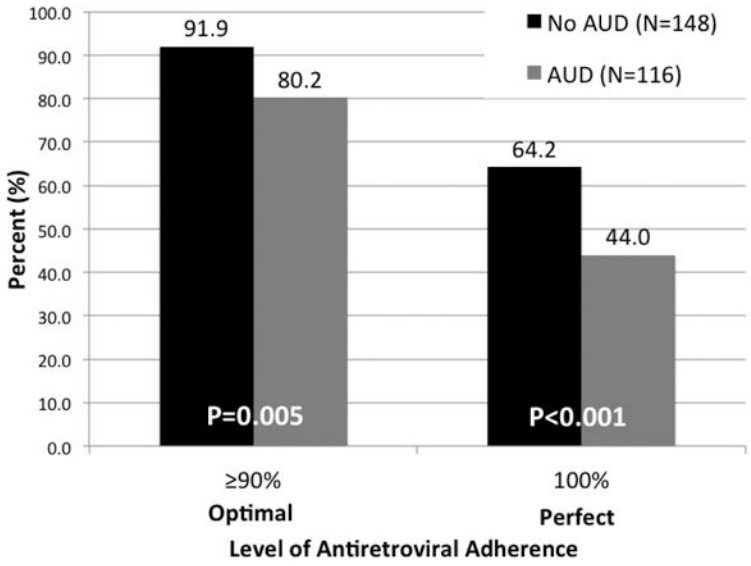

Figure 1. Comparison of Adherence Between Men Who Have Sex With Men With and Without Alcohol Use Disorders (AUD)

Table 1

Characteristics of the sample (N=302)

Characteristic	N = 302 (%)
Median Age, years (S.D.)	32.0 (± 8.1)
Monthly Income	
None	39 (12.9)
Less than minimum wage	84 (27.8)
Minimum wage or greater	177 (58.6)
Completed High School	
No	94 (31.2)
Yes	207 (68.8)
Sexual Orientation (self-identified)	
Homosexual (gay)	243 (80.7)
Bisexual	45 (15.0)
Heterosexual	13 (0.3)
Transgender	
No	282 (93.4)
Yes	20 (6.6)
Living Situation	
Alone	58 (19.3)
With sexual partner	49 (16.3)
With family or nonsexual partner	194 (64.4)
Occupation	
Full-time	146 (48.3)
Part-time	95 (31.5)
Unemployed	60 (19.9)
Alcohol Use Disorders	
No alcohol use disorder	171 (56.8)
Any alcohol use disorder	130 (43.2)
Hazardous drinking	96 (31.9)
Harmful drinking	18 (6.0)
Dependent drinking	16 (5.3)
Drug Use in the past 12 months	
No	281 (94.0)
Yes	18 (6.0)
Neurocognitive Impairment	
Mean t-score (S.D.)	50.8 (±10.8)
Depression	
No	168 (55.5)
Yes	134 (44.5)

Characteristic	**N = 302 (%)**
Participants on ART	**N = 263 (%)**
Adherence ≥ 90%	(229) 87.1
Adherence = 100%	(145) 55.3
Mean adherence	91.7%

Legend: S.D.=Standard Deviation

Table 2

Correlates Associated with Optimal (≥90%) and Perfect (=100%) Antiretroviral Therapy Adherence Among HIV-infected Peruvian Men Who Have Sex with Men and Transgendered Women (N=302)

	Optimal (≥90%) Antiretroviral Therapy Adherence				Perfect (=100%) Antiretroviral Therapy Adherence			
Covariates	**Bivariate Associations**		**Multivariate Associations**		**Bivariate Associations**		**Multivariate Associations**	
	OR (95% CI)	**p-value**	**AOR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**AOR (95% CI)**	**p-value**
Alcohol Use Disorder	0.357 (0.169 – 0.752)	0.005 *	0.427 (0.187 – 0.976)	0.044 *	0.438 (0.266 – 0.720)	0.001 *	0.552 (0.327 – 0.930)	0.026 *
Neurocognitive Impairment (global score)	0.965 (0.933 – 0.999)	0.041 *	0.975 (0.933 – 1.019)	0.266	0.959 (0.936 – 0.983)	0.001 *	0.978 (0.951 – 1.007)	0.132
Age	1.035 (0.989 – 1.083)	0.138	1.026 (0.978 – 1.075)	0.293	1.034 (1.003 –1.066)	0.032 *	1.029 (0.997 – 1.062)	0.078
Earned minimal wage or greater	1.868 (0.913 – 3.823)	0.084	1.295 (0.573 – 2.926)	0.534	0.922 (0.563 – 1.512)	0.749		
Living Alone	0.406 (0.119 – 1.386)	0.138	0.355 (0.077 – 1.627)	0.182	0.846 (0.444 –1.612)	0.611		
	0.317 (0.103 – 0.971)	0.035 *	0.369 (0.109 – 1.252)	0.110	1.1 (0.404 – 2.994)	0.852		
Full-time Employment (stable)	0.948 (0.461 – 1.950)	0.884			0.761 (0.465 – 1.245)	0.276		
Depression	0.513 (0.250 – 1.053)	0.066	1.101 (0.437 – 2.774)	0.838	0.455 (0.276 – 0.748)	0.002 *	0.632 (0.352 – 1.138)	0.126
Any Drug Use in Previous 12 Months	0.950 (0.310 – 2.194)	0.928			1.164 (0.532 – 2.545)	0.703		
Domestic Violence in Past 12 Months	2.752 (0.355 – 21.36)	0.313			0.794 (0.305 – 2.074)	0.637		
Wright HIV Stigma Scale	0.992 (0.938 – 1.050)	0.789			0.974 (0.937 – 1.013)	0.184	0.978 (0.939 – 1.019)	0.286
Food Insecurity								
Any	1.210 (0.590 – 2.482)	0.603			0.996 (0.611 – 1.622)	0.986		
Hunger	1.916 (0.643 – 5.706)	0.236			1.346 (0.713 – 2.538)	0.358		
Health Literacy	0.610 (0.066 – 5.620)	0.659			3.291 (0.363 – 29.849)	0.263		
Social Support	0.992 (0.979 – 1.005)	0.206			0.994 (0.986 – 1.003)	0.220		
Barriers to Medical Care	0.977 (0.819 – 1.165)	0.795			1.001 (0.887 – 1.130)	0.983		
			AIC = 233.3				AIC = 220.0	

Legend: OR=Odds Ratio; AOR=Adjusted Odds Ratio; AIC=Akaike Information Criterion