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Neurocognitive Impairment Impacts Hiv Medication Adherence

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ABSTRACT

***Objective**:* To examine neurocognitive impairment (NCI) and its association with antiretroviral therapy (ART) medication adherence among HIV-infected men who have sex with men (MSM) and transgender women (TGW) in Lima, Peru.

Methods: A cross-sectional survey assessed 313 HIV-infected Peruvian MSM and TGW prescribed ART using a computer-assisted survey instrument to examine NCI and its association with optimal ART adherence, defined as taking ≥90% of prescribed medications. The survey included demographic characteristics and standardized measures for drug and alcohol use disorders, depression, and other factors associated with non-adherence.

***Results**:* An exploratory factor analysis was conducted to optimize an NCI self-report scale for use with HIV-infected MSM and TGW in Peru. Participant scores indicated moderate NCI and 131 (41.7%) and 134 (42.5%) participants met criteria for an alcohol use disorder (AUD) or depression, respectively, 33 (10.5%) reported recent recreational drug use, and 81 (26.3%) had low health literacy. Overall, 268 (85.9%) met criteria for self-reported optimal ART adherence. Psychomotor NCI subscale score (AOR=0.534; 95% CI=0.317-0.931), having an AUD (AOR=0.203; 95% CI=0.063-0.655), identifying as transgender (AOR=0.175 95% CI=0.032-0.954), and low health literacy (AOR=0.253 95% CI=0.077-0.831) were independently and negatively correlated with optimal ART adherence. Income of minimum wage or higher was independently and positively correlated with optimal ART adherence. Depression was significant only in the bivariate analysis, but did not remain significant after controlling for other covariates.

Conclusions: NCI is prevalent among Peruvian HIV-infected MSM and TGW and psychomotor impairment is independently correlated with suboptimal ART adherence. Our findings support the need to screen and treat or accommodate NCI in order to improve ART adherence among HIV-infected MSM/TGW.

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Table 1: Characteristics of HIV-infected men who have sex with men and transgender women on antiretroviral therapy in Lima, Peru (N=313)

Characteristic	**N = 313 (%)**
Median Age, years (S.D.)	34.3 (± 8.2)
Completed Secondary school	
No	97 (30.9)
Yes	217 (69.1)
Monthly Income	
None	38 (12.1)
Less than minimum wage	94 (30.0)
Minimum wage or greater	181 (57.8)
Sexual Orientation (self-identified)	
Homosexual (gay)	246 (78.3)
Bisexual	55 (17.5)
Heterosexual	13 (4.2)
Transgender	
No	282 (93.4)
Yes	20 (6.6)
Living Situation	
Alone	57 (18.2)
With sexual partner	50 (15.9)
With family or nonsexual partner	207 (65.9)
Occupation	
Full-time	163 (51.9)
Part-time	82 (26.1)
Unemployed	69 (22.0)
Adherence Facilitators	**N = 211 (%)**
Using an alarm clock	90 (42.8)
Taking ART with other medications	2 (0.9)
Placing ART in sight	32 (15.2)
Associating taking ART with sleeping or awakening	38 (18.0)
Placing ART in the same location	11 (5.2)
Using post-it notes or other paper reminders	6 (2.8)
Using a calendar	2 (0.9)
Associating taking ART with eating	29 (13.7)
Asking a family member or friend for a reminder	1 (0.5)
Multiple reminders	105 (38.3)

Neurocognitive Impairment	
Mean t-score (S.D.)	
Global Impairment	8.8 (±7.7)
Memory	5.2 (±4.0)
Frustration Tolerance	4.6 (±3.6)
Learning	3.5 (±2.6)
Attention	1.8 (±1.4)
Pain	1.6 (±1.9)
Language	0.9 (±1.4)
Psychomotor	0.5 (±1.2)
Alcohol Use Disorders	
No alcohol use disorder	183 (58.3)
Any alcohol use disorder	131 (41.7)
Hazardous drinking	102 (32.5)
Harmful drinking	18 (5.7)
Dependent drinking	11 (3.5)
Drug Use in the past 12 months	
No	282 (89.5)
Yes	33 (10.5)
Depression	
No	181 (57.5)
Yes	134 (42.5)
Health Literacy Issues	
No	227 (73.7)
Yes	81 (26.3)
HIV-related Stigma	
Mean t-score (S.D.)	22.4 (±6.2)
Personalized Stigma	8.5 (±3.2)
Disclosure Stigma	6.6 (±1.8)
Negative Self-Image Stigma	5.0 (±2.4)
Public Attitudes Stigma	5.2 (±1.9)
Participants on ART	**N = 313 (%)**
Adherence ≥ 90% (optimal)	268 (85.9)
Adherence = 100% (perfect)	170 (54.5)
Mean adherence	91.1%

Legend: SD=standard deviation; ART=antiretroviral therapy;

Table 2: Descriptive statistics (Revised NIS)

NIS Subscale	N	Minimum	Maximum	Mean	SD
GLOB	313	0	49	8.84	7.73
MEMR	313	0	20	5.17	3.96
FRUS	313	0	19	4.64	3.59
PSYP	313	0	12	0.49	1.23
LERN	313	0	12	3.51	2.60
LANG	313	0	7	0.91	1.42
PAIN	313	0	12	1.57	1.87
ATTN	313	0	8	1.79	1.38

Legend: GLOB = global impairment; MEMR = memory; FRUS = frustration tolerance; PSYP = psychomotor; LERN = learning; LANG = language; PAIN = pain; ATTN = attention

Table 3: Correlates Associated with Optimal (≥90%) Antiretroviral Therapy Adherence Among HIV-infected Peruvian Men Who Have Sex with Men and Transgender Women (N=313)

	Optimal (≥90%) Antiretroviral Therapy Adherence			
Covariates	**Bivariate Associations**		**Multivariate Associations**	
	OR (95% CI)	**p-value**	**AOR (95% CI)**	**p-value**
Neurocognitive Impairment				
Global Impairment	0.966 (0.931 – 1.003)	0.068	–	–
Memory	0.956 (0.927 – 0.985)	0.114	–	–
Frustration Tolerance	0.913 (0.844 – 0.989)	0.026	0.884 (0.769 – 1.017)	0.085
Learning	0.945 (0.841 – 1.063)	0.349	–	–
Attention	0.940 (0.751 – 1.176)	0.587	–	–
Pain	0.936 (0.800 – 1.094)	0.405	–	–
Language	0.854 (0.700 – 1.042)	0.119	–	–
Psychomotor	0.795 (0.647 – 0.978)	0.030	0.534 (0.317 – 0.931)	0.026
Alcohol Use Disorders	0.399 (0.207 – 0.768)	0.006	0.203 (0.063 – 0.655)	0.008
Transgender Women	0.386 (0.130 – 1.144)	0.086	0.175 (0.032 – 0.954)	0.044
Health Literacy	0.859 (0.685 – 1.078)	0.191	0.253 (0.077 – 0.831)	0.024
HIV-related Stigma	1.041 (0.984 – 1.101)	0.162	–	–
Initiation/Completion of Higher Education	1.885 (0.982 – 3.620)	0.057	–	–
CD4 Nadir	1.000 (0.998 – 1.001)	0.809	–	–
Time since HIV Diagnosis	0.989 (0.916 – 1.069)	0.788	–	–

Age	1.020 (9.80 – 1.062)	0.324	–	–
Earned minimal wage or greater	2.758 (1.375 – 5.535)	0.004	3.037 (1.016 – 9.081)	0.047
Living Alone	0.688 (0.276 – 1.717)	0.423	–	–
Full-time Employment (stable)	1.460 (0.748 – 2.849)	0.267	–	–
Depression	0.918 (0.864 – 0.975)	0.005	–	–
Drug Use in Previous 12 Months	0.939 (0.750 – 1.175)	0.581	–	–
Domestic Violence in Past 12 Months	0.939 (8.29 – 1.062)	0.316	–	–
Adherence Facilitators*	1.134 (0.630 – 2.041)	0.676	–	–
Food Insecurity			–	–
Any	1.401 (0.720 – 2.728)	0.321	3.789 (1.085 – 13.237)	0.037
Hunger	1.186 (4.98 – 2.825)	0.700		
			Log Likelihood = 90.931	

Legend: OR = Odds Ratio; AOR=Adjusted Odds Ratio; *An adherence facilitator is any cue or reminder that a participant regularly used to aid him or her with medication-taking.

Supplementary Table: Factor loadings from exploratory factor analysis of the original NIS

Items	Factor/Label							
	1 GLOB	2 MEMR	3 FRUS	4 PSYP	5 LERN	6 LANG	7 PAIN	8 ATTN
My reactions are slow.	.692	.241	.117	.075	.197	.111	.156	.199
I have trouble remembering.	.613	.185	.178	.337	.104	.120	.007	.152
My judgment is poor.	.581	.207	.238	.161	.132	.172	.026	.096
My mind is dull	.556	.113	.261	.213	.024	.196	.008	.103
Something is wrong with my mind.	.538	.108	.190	.085	.168	.162	.201	-.002
I do things slowly.	.535	.088	.062	.032	.145	.067	.153	.048
My mind works slowly	.534	.344	.096	.112	.105	.073	.084	-.075
My brain becomes tired easily.	.529	.293	.233	.317	.024	.034	.098	.144
I have trouble remembering important things.	.500	.399	.168	.116	.089	.175	.104	.136
I have trouble concentrating.	.494	.441	.165	.266	.216	.079	.065	.307
I get confused easily.	.489	.476	.160	.049	.197	.236	.128	.159
I forget what I read.	.488	.319	.154	.088	.110	.162	.186	.222
I have trouble writing sentences.	.476	.294	.140	.244	-.075	.188	-.047	-.038
My mind won't stay on any one thing.	.423	.190	.220	.027	.077	.084	.168	.289
My mind tends to wander.	.411	.127	.172	.053	.159	.292	.259	.142
I forget where I put things.	.126	.708	.150	.005	.155	.092	.059	.124
I am forgetful	.190	.680	.086	.048	.069	.054	.081	-.021

I have serious memory problems.	.331	.585	.015	.051	-.005	.154	.215	.030
I often lose things.	.320	.571	.109	.089	.093	.174	.129	.181
I have a hard time remembering people's names.	.123	.491	.063	.023	.148	.191	.072	.141
I have difficulty paying attention.	.318	.466	.174	.260	.083	.068	.040	.353
My words get mixed up.	.272	.403	.285	.187	.016	.340	.108	.017
I feel easily annoyed and irritable.	.247	-.015	.752	.093	.104	.062	.061	.113
I have a bad temper.	.155	.063	.687	.139	.089	.036	-.037	.029
I get into arguments frequently.	.130	.112	.651	.103	.198	.154	.086	.132
I have urges to break and smash things.	.154	.180	.597	.030	.032	.113	.142	.031
I fall apart under pressure.	.185	.262	.554	.137	.182	.087	.181	.108
Part of my body is paralyzed.	.057	.055	.128	.679	.050	.118	-.008	.121
I fall down sometimes.	.159	.090	.139	.594	-.067	.110	.159	-.010
I have been knocked unconscious.	.126	-.017	.008	.540	.118	.050	.139	.087
I have trouble with the right side of my body.	.358	.113	.141	.488	.053	.115	.100	-.196
Doing simple math problems in my head is difficult.	.256	.190	.200	.082	.797	.044	.055	.091
My arithmetic is poor.	.158	.102	.141	-.009	.728	.054	.085	.075
I count with my fingers.	.133	.223	.222	.252	.377	.019	.028	-.014
My speech has become worse.	.264	.311	.140	.124	.027	.689	.071	.019
I have trouble spelling.	.218	.160	.086	.263	.105	.585	.009	.171
I have trouble talking.	.346	.228	.207	.130	-.001	.492	.088	-.011

I have severe headaches.	.201	.238	.297	.071	.021	.029	.654	.057
I suffer from severe pain.	.270	.257	.301	.137	.040	.007	.550	-.038
I have had a head injury.	.061	.037	-.042	.130	.067	.058	.450	.079
I am easily distracted.	.303	.336	.288	.096	.121	.112	.106	.602
I am absent - minded.	.278	.337	.206	.112	.121	.117	.167	.471

Notes:

EFA excluded: 'validity scale' items, items with loadings below 0.40, and items with shared loadings of equal strength across multiple factors

Total percent of variance = 51.78%

Shaded areas represent the criteria that correspond to each factor

GLOB: Global impairment; MEMR: Memory-related impairment; FRUS: Frustration Tolerance-related impairment; PSYP: Psychomotor-related impairment; LERN: Learning-related impairment; LANG: Language-related impairment; PAIN: Pain-related impairment; ATTN: Attention-related impairment

INTRODUCTION

The global HIV pandemic affects nearly 35 million people [1] and the various manifestations of HIV negatively impact the lives of people living with HIV/AIDS (PLWHA). Even though a cure for HIV remains elusive, HIV has become a chronic disease requiring long-term management to reduce HIV-related morbidity and mortality, which allows PLWHA to have near-normal lifespans [2-6]. Despite recent increasing antiretroviral treatment (ART) coverage globally and resultant decreased HIV-related morbidity and mortality [5, 7], the central nervous system (CNS) is vulnerable to HIV [8]. The presence of HIV in the brain, spinal chord, and peripheral nerves and its impact on neurological function has been extensively studied [9, 10]. The neurological impact of HIV is now commonly referred to as neurocognitive impairment (NCI). NCI research among PLWHA has increased recently [11, 12], but many gaps remain in translating findings into clinical improvement [8].

Using various measurements, NCI is associated with numerous adverse clinical consequences, including ART non-adherence [6], increased HIV risk-taking behaviors [6, 13], difficulty in performing daily tasks [14, 15], shorter survival [8, 16], and reduced health-related quality-of-life [17, 18]. The negative consequences of NCI exacerbate HIV-related symptoms among PLWHA and increase transmission risk to uninfected partners [19]. ART adherence, while important for many reasons, is crucial to mitigate the effects of NCI. In the absence of ART, NCI-related symptoms worsen with HIV disease progression [20] and ART can significantly decrease NCI-related symptoms [21]. NCI not only impedes PLWHA from accessing ART, but may also reduce its efficacy through suboptimal ART adherence, thereby necessitating effective interventions to intervene in PLWHA with NCI.

While the severity of NCI among PLWHA has decreased in recent years, mild NCI is still prevalent, reaching levels of 50% in some settings [22, 23]. The ability of HIV to penetrate the

CNS negatively impacts several neurocognitive domains, including memory, executive functioning, attention, and psychomotor skills [24, 25], which in turn may impede ART adherence [26]. The direct association between general NCI and ART nonadherence was described in the early stages of HIV/AIDS [27]. Several subsequent studies have further elucidated this relationship, noting deficits in executive function, working memory, and attention [6, 28, 29]. This is particularly concerning, given the ambitious 90-90-90 target set by UNAIDS. The goals by 2020 are that 90% of all PLWHA know their HIV status, 90% of all people with diagnosed HIV infection will receive sustained ART, and 90% of all people receiving ART will have viral suppression [30]. In order to satisfy the third goal, viral suppression requires optimal adherence to ART, which is threatened by the presence of NCI.

To date, NCI in PLWHA has yet to be examined in the Latin American context, especially with regard to ART adherence [31]. In Peru and throughout much of Latin America, the HIV epidemic remains concentrated among men who have sex with men (MSM) and transgender women (TGW) [5, 32]. While the overall prevalence of HIV/AIDS in Peru is reported to be only 0.4% [33] HIV prevalence among MSM is between 18-22% [34] and approaches 33% in TGW [34, 35]. MSM represent a particularly vulnerable population in Peru, with HIV prevalence over 100-fold higher in the general population and 20-fold higher than in other vulnerable populations like in female sex workers [36]. Although Peru is a middle-income country that provides free ART with coverage exceeding 40% [5], there are currently no interventions tailored to the MSM community that promote ART adherence.

Given the potential for NCI to be a confounding variable in assessing HIV treatment outcomes, I sought to investigate the prevalence of NCI among HIV-infected MSM and TGW in Lima, Peru and characterize other demographic, cultural, and personal barriers to ART adherence among these two groups. In addition, I sought to determine the association of NCI and

these other variables with our outcome variable, ART adherence. I hypothesized that NCI would be prevalent among HIV-infected MSM and TGW in Lima, Peru. Likewise, NCI, especially among the most affected individuals, would be associated with decreased ART adherence, which has remained unexplored among Peruvian MSM and TGW.

LITERATURE REVIEW OF RELEVANT STUDIES

HIV/AIDS in Peru

In the 1980s and early 1990s, Peru was in a state of significant political turmoil. Since then, the country's economic conditions have improved in some ways, but remains bleak in others. For example, over 50% of Peru's population is estimated to be poor with about 25% living in extreme poverty. The health, education, legal, and other government sectors remain weak with suboptimal investment compared to sectors in other Latin American countries. These political and economic factors have played a large role in shaping the nation's HIV/AIDS epidemic [37]. UNAIDS reported the following country estimates in 2014: [A] 0.4% prevalence rate among 15-49 year olds; [B] 72,000 individuals living with HIV; [C] 21,000 women aged 15 and up living with HIV; [D] 2,200 children aged 0 to 14 years living with HIV; and [E] 2,500 deaths due to AIDS in 2014 [38]. While this information is useful for understanding the HIV/AIDS epidemic in the total population, these numbers mask the true nature of the epidemic. Since the first case was reported in 1983, the Peruvian HIV epidemic has been concentrated in vulnerable communities, specifically among MSM. HIV prevalence among MSM has consistently been above 10% in Lima, Peru in comparison to 1% among pregnant women and female sex workers – other traditionally vulnerable communities. Since 75% of Peruvians live in urban centers, the HIV epidemic is considered to be an urban issue and most cases are on the coastline or in rain forest regions of Peru. While it initially affected the wealthier segments of society, it quickly spread through the poorer communities [39].

Lima, the capital of Peru, has been the epicenter of innovative research and program implementation. From 1996 to 2002, HIV prevalence among MSM increased from 18.5% to 22.3% in Lima [40], suggesting that MSM in Lima constitute an important target population for intensified and innovative biomedical intervention, such as HSV-2 suppression, pre-exposure

chemoprophylaxis, HIV vaccines, and male circumcision [34]. HIV infection in this group has been associated with gay sexual orientation, high-risk sexual behaviors, drug and alcohol use, and other sexually transmitted infections (STIs) [41]. In a recent study, over 5,000 sexually active MSM were recruited to participate in a cross-sectional bio-behavioral study to better understand if these risk behaviors are mediated by the disinhibiting use of alcohol and other drugs. The authors found that the majority of participants (62.8%) met screening criteria for alcohol use disorders (AUDs) which were also independently associated with several high-risk sexual risk behaviors previously found to be associated with HIV transmission [42]. Because the HIV continuum of care includes several steps – including HIV diagnosis, linkage to and retention in HIV care, initiation and adherence with ART, and viral suppression – another study sought to address factors associated with suboptimal HIV treatment engagement and ART adherence. Of the 302 participants recruited, the prevalence of AUDs was 43.2% while 87.1% reported optimal adherence (defined as taking 90% or more of prescribed medications) and 55% reported perfect adherence (defined as taking all prescribed medications). AUDs were highly prevalent among the Peruvian HIV-infected MSM participants in the study and AUDs contributed significantly to suboptimal ART adherence. These findings further support the necessity of screening for and treating underlying AUDs [43].

HIV Medication Adherence

Since 1996, there has been an overwhelming amount of evidence supporting the use of antiretroviral therapy (ART) for the treatment of HIV/AIDS. Optimal ART adherence is associated with viral load suppression [44-46], improved quality of life [47, 48], longer survival [49], and decreased risk of transmitting HIV to others [50, 51], and reduced risk of developing resistance to HIV medications [52, 53].

One of the earliest and largest breakthroughs in the field of HIV/AIDS was the efficacy of triple-combination therapy in suppressing HIV viral load in PLWHA to non-detectable levels. One landmark study featured 97 HIV-infected patients who were assigned to one of three treatment groups: 800 mg of indinavir every eight hours; 200 mg of zidovudine every eight hours combined with 150 mg of lamivudine twice daily; or all three drugs. The decrease in HIV RNA over the first 24 weeks was significantly greater in the three-drug group compared to the other two groups and these results persisted up to the completion of the study (52 weeks). Therefore, the triple combination of indinavir, zidovudine, and lamivudine was a more effective treatment regime compared to these drugs separately or in dual combination [45].

The importance of adherence to ART is far more than the reduction of viral load and increase in immunological function in HIV-infected individuals. It also contributes to better overall health. In one study, 98 HIV-infected individuals in Central China were asked to self-report their ART adherence and had their quality of life (QoL) assessed using SF-36, a validated scale for measuring QoL. Of the total participants, 58% reported taking all their prescribed medications and were classified as consistent adherers. These individuals had better physical function, general health, vitality, social functioning, mental health, presented a higher CD4 cell count, and had overall lower healthcare costs [47]. Another study examined 1050 HIV-infected participants in two large, randomized, clinical trials. Adherence to ART was self-reported and QoL was assessed using the SF-12, as shorter version of the aforementioned SF-36. Individuals that reported 100% ART adherence achieved significantly higher QOL life scores as compared to those with poorer adherence. Those with at least 80% ART adherence had smaller but still significant increases in QoL, while those with less than 80% adherence reported worse QoL [48].

Optimal ART adherence has also been associated with higher survival rates and lower mortality. One team enrolled 6288 individuals, 52% of whom had adherence greater than or

equal to 80% and 30% of whom had perfect adherence. These authors showed that adherence of less than 80% was associated with lower survival. Medication adherence was also divided into 5 strata, each with a width of 20%; each stratum had lower survival rates than the next, higher-adherence stratum [49]. Finally, access and adherence to ART is associated with a decreased risk of HIV transmission. The landmark HPTN 052 study evaluated the effect of early vs. delayed ART on the prevention of HIV-1 transmission from an HIV-infected individual to their uninfected partners. Using pill counts, optimal adherence (defined as taking greater than or equal to 95% of medications) to the study regimen was observed in 79% of participants in the early-therapy group and 74% of those in the delayed-therapy group. Among the 1763 serodiscordant couples enrolled, there was a relative reduction of 96% in the number of linked HIV-1 transmissions in the early ART group as compared to the delayed ART group [50]. In another landmark prospective cohort study, researchers followed 16,667 individual who were HIV-uninfected and observed individual HIV seroconversions from 2004 to 2011. The authors found that the risk of individual HIV acquisition declined significantly with increasing ART coverage in the surrounding community when holding other key HIV risk factors constant. For example, an uninfected individual living in an area with 30-40% ART coverage was 38% less likely to acquire HIV as compared to someone living in a community with less than 10% ART coverage [51].

While optimal ART adherence provides a multitude of benefits, it is imperative to note the negative consequences of suboptimal adherence to ART, such as drug resistance. For HIV-infected individuals, drug resistance is a major concern. The relationship has been described to look “bell shaped” where the two extremes – total non-adherence and complete adherence – are associated with low probabilities of drug resistance, whereas intermediate levels of adherence increase the risk of drug resistance [52]. Another study quantified the risk factors associated with

drug resistance. The authors found that a cumulative adherence of 70%-89%, a CD4+ cell nadir of <200 cells/ul, and the missing of a scheduled clinic visit in the past month were all independently associated with increased hazard of viral rebound [53]. Therefore, clinicians and patients should set high adherence goals to avoid the development of drug resistance.

Barriers to HIV Medication Adherence

The aforementioned studies present invaluable examples of the benefits of optimal ART adherence. While these are goals that individuals and health systems should strive to meet, there are also a multitude of barriers that prohibit optimal adherence to ART. Depression is one serious barrier that has garnered attention and has been linked to poor health outcomes. One meta-analysis examined the relationship between depression and HIV medication non-adherence. Depression was associated with non-adherence across 95 independent samples, which was consistent over time and was not inflated by self-report bias [54]. Conversely, another study sought to determine whether antidepressant medication treatment increases the probability of HIV viral suppression. Among 158 homeless and marginally housed individuals living with HIV, there were 2.03 greater odds of achieving viral suppression when taking antidepressant medication treatment. Self-reported adherence to ART increased by 25% and the odds of reporting complete adherence nearly doubled [55]. Both of these studies suggest that interventions aimed at reducing depressive symptom severity should be explored to increase ART adherence among HIV-infected individuals.

Substance abuse is another barrier worth considering when dealing with HIV medication adherence. An early study examined the impact of ongoing drug use on ART adherence and viral suppression. The authors studied 85 HIV-infected current and former drug users and found that several variables were associated with poor adherence, including active cocaine use and the tendency to use alcohol or drugs to cope with stress. The strongest predictor of poor adherence

and the failure to maintain viral suppression was active cocaine use. Overall, adherence among active cocaine users was much lower (27%) as compared to subjects who reported no cocaine use during the 6-month study period (68%). Furthermore, only 13% of the former group maintained viral suppression as compared to 46% of the latter group [56]. Another longitudinal study examined the impact of drug use on medication adherence among 150 HIV-infected individuals, 102 of who reported recent illicit drug use. Not only did drug-positive individuals have worse medication adherence than drug-negative participants (63% vs. 79%, respectively), a logistic regression model showed that drug use was associated with over a four-fold greater risk of adherence failure. The authors concluded that stimulant users were at greatest risk for poor adherence [57]. While historically a great deal of attention on substance abuse has been directed at drug use, alcohol has emerged as a new focus of research. Alcohol use has been cited as a factor in non-adherence to ART. One meta-analysis aggregated findings across numerous studies to provide a quantitative evaluation of the alcohol-adherence association. In the combined analysis, alcohol drinkers were about 50% less likely to be adherent to ART as compared to those who abstained from drinking [58]. Another meta-analysis found similar results. Forty-one studies were included in the aggregate analyses to examine AUDs and ART adherence. These findings consistently support an association between AUDs and decreased adherence to ART and poor HIV treatment outcomes among HIV-infected individuals [59].

While HIV is a devastating biological agent that has revolutionized pharmaceutical research and medicine, the virus has also had a tremendous effect on social issues around the world. HIV largely affects the most marginalized communities, which have suffered from the virus itself and conservative social norms. Insight into the effects of social support has helped explain how social interactions could mediate adherence to ART. One early study examined 205 HIV-infected prisoners and details social desirability and trust in members of the medical field

and society at large. While adherence to ART was relatively high (84%) among this group of prisoners, the researchers found that social isolation was associated with decreased adherence to medications. Trust and the therapeutic relationship between the patient and physician remain central in the ART initiation process [60]. Another cross-sectional survey in Thailand analyzed patients on ART to examine barriers to adherence. Based on logistic regression analysis, HIV disclosure and family communication were among the significant predictors of adherence. While both of these variables were reported to play important positive roles [61], is it also worth examining the deleterious effects of stigma and discrimination on ART adherence among HIV-infected individuals. In one study, 202 HIV-infected participants in Los Angeles County were asked to self-report HIV stigma, access to medical care, and adherence to ART. About one-third of participants reported high levels of stigma and only 57.5% reported optimal ART adherence. In unadjusted analyses, those who reported high level of stigma were more likely to report poor access to care and lower ART adherence. Mental health was reported to mediate the relationship between stigma and ART adherence [62]. In another study, 204 HIV-infected patients in two Chicago hospital sites were recruited to determine the threat of social stigma. The authors found that people with high HIV stigma concerns were 2.5 times less likely to interpret the meaning of CD4 count correctly and 3.3 times more likely to be nonadherent to their medication regime as compared to those with low stigma concerns. In the multivariate analyses, concern over revealing HIV status was the only statistically significant, independent predictor of adherence [63]. The aforementioned research suggests that reducing stigma and discrimination among HIV-infected individuals would help improve treatment outcomes.

Neurocognitive Impairment

Over thirty years have passed since HIV emerged as a major challenge to health and united the scientific community worldwide to combat its devastating impact. While HIV has

largely been recognized for its deleterious effects on the cellular immune system, it has also had broad impact on the human nervous system. Over the years, research has elucidated HIV's pathology in the brain, spinal chord, and peripheral nerves, which has deeply impacted neurological function in a variety of ways. This neurological involvement of HIV is now commonly referred to as neurocognitive impairment (NCI). Until the introduction of combination ART in the mid-1990s, HIV-1 associated dementia (HAD) and other cognitive disorders affected 20-30% of patients with advanced immunosuppression or AIDS. Although combination ART dramatically reduced these severe manifestations of NCI, mild to moderate NCI exists in a significant portion of patients some of who are virally suppressed [9, 10, 64].

As with some other lentiviruses, HIV enters into the central nervous system (CNS) due to infection of the human immune cells. One of these host cells, monocytes, have been described as "Trojan horses" because they readily enter the CNS, bringing along HIV that replicates effectively in these cells [65]. In addition, HIV is brought into the CNS by lymphocytes, which can harbor viruses that replicated in macrophages or as free virions where the means of entry would be through endothelial cells [9]. Research has demonstrated that the virus is present in the cerebral spinal fluid (CSF) at early stages of HIV infection, including in patients diagnosed with primary infection [66]. While it is not certain how this manifestation affects HIV found in the brain, studies have shown that long-term HIV infection leads to genetically isolated populations of virus in the CNS [67, 68].

While research is ongoing to better characterize the impact of HIV on neurocognitive functioning, there is clear evidence suggesting the importance of ART adherence in minimizing NCI among HIV-infected individuals. It is worth noting that several other phrases have been used to describe HIV-related neurocognitive impairment, including HIV-associated neurocognitive disorders (HAND) [69] and HIV-associated dementia (HAD) [26]. A recent

study assessed the cognitive outcomes of 111 HIV-infected patients with varying levels of cognitive outcomes before beginning ART and compared these results after being on ART for one year. There was clear evidence that participants on ART had similar or improved cognitive function results after one year compared to those who were not on ART [70]. Another study sought to describe the prevalence of NCI among HIV-infected individuals who were diagnosed and clinically managed early and compare their neurological functioning to HIV-uninfected controls. The study concluded that HIV-infected patients who were diagnosed and managed early during the course of their HIV infection had a low prevalence of NCI, which was comparable to matched HIV-uninfected individuals. Early recognition and management of HIV infection may be important in limiting neurocognitive impairment [21]. Lastly, an early study of NCI found that patients with poor neuropsychological scores reduced from 81% to 50% and then to 22% following 6 and 15 months of ART, respectively. Prevalence of impaired memory was also reduced from 50% to 9% after 15 months of taking HIV medications [71]. In the absence of ART, NCI-related symptoms have been shown to worse with HIV disease progression. One study examining the neurocognitive functioning and brain magnetic resonance imaging in 389 HIV-infected individuals and 111 uninfected controls found increased rates of impairment at each successive stage of HIV infection. Impairment in HIV-infected subjects was related to central brain atrophy on MRI results as well as to evidence of cellular immune activation and neurological abnormalities linked to the central nervous system [20].

Using various measurements, NCI has been associated with numerous adverse clinical consequences. One study explored the nature of NCI caused by HIV and suggests that it plays a role in increased risk-taking behavior. Impaired executive function prevents rational decision-making by inhibiting the consideration of future outcomes, which may result in making unsafe sexual choices. In addition, reduced speed of information processing or reaction time may also

play a role in increasing risk. Impulse control may also be impaired in individuals suffering from HIV-associated NCI due to effects of HIV, substance abuse, or underlying mental illness, which could increase HIV risk behaviors [6]. NCI has also been associated with difficulty in performing daily tasks and higher risk of work disability. A prospective cohort study of gay and bisexual men examined the incidence of work disability related to the onset of NCI. Compared to HIV-uninfected individuals, asymptomatic HIV-infected participants were found to have almost three times the risk of reporting work disability and difficulty performing general tasks [15]. Negative effects of NCI on QoL and decreased neurological functioning has lead to examination of the effect of NCI on survival. In one study, 1,651 HIV-infected patients were assessed for neurologic disorders, 24.5% of which had one or more neurologic disorders. Those individuals with one or more neurologic disorders had higher mortality rates and AIDS-related deaths as compared to those without neurologic disorders [72].

Research has highlighted that NCI is associated with several adverse outcomes among HIV-infected individuals with underlying substance use disorders. For example, one study concluded that 50% to 80% of individuals with AUDs experience mild to severe neurocognitive impairment. Alcohol use has been linked to physiological and behavioral changes in the CNS, such as physical damage to the brain and personality disorders, respectively [73]. Individuals with opioid dependence and abuse demonstrate deficits in attention, working memory, episodic memory, and executive function during active use. These deficits have been shown to continue into periods of early abstinence and executive function did not show signs of improvements during abstinence [74]. Similarly, chronic cocaine users are at greater risk of NCI. Cocaine use exacerbates HIV replication by increasing the permeability of the blood-brain barrier and promoting cellular apoptosis [75]. Chronic cocaine users also have impaired executive function, learning, information-processing speed, memory, attention, and other issues [6, 76].

Given the goals of this thesis, it is worth understanding some literature findings on the inverse relationship between neurocognitive impairment and ART adherence. That is, increasing severity of NCI has been associated with poorer medication adherence. One article reviewed studies that have investigated the neuropsychological effects of ART for HIV-1 infection and found that, while ART reduces the prevalence of severe NCI manifestations, mild NCI is still prevalent. Mild NCI has been associated with poor CNS penetration of some antiretroviral drugs, drug resistance, and poor adherence [26]. Another study of adherence examined the extent to which neuropsychological compromise and medication regimen complexity are predictive of poor adherence in a convenience sample of 137 HIV-infected adults. Both NCI and complex regimens were associated with lower adherence rates, with cognitively impaired individuals on complex regimens having the lowest adherence rates. NCI associated manifestations – such as deficits in executive function, memory, and attention – were associated with 2.3 times greater risk of adherence failure [27]. Research done in older HIV-infected individuals, normally an age group with higher medication adherence, also found that NCI was associated with lower medication adherence. It is possible that there is a vicious cycle of bidirectional influence, where poor adherence results in NCI and NCI may contribute to lower medication adherence [14].

Assessing Medication Adherence and NCI

While there is no gold standard for assessing adherence among PLWHA [77], several tools have been implemented over the years. One popular method is self-report of ART adherence using the visual analog scale. The VAS is simple and quick to administer which makes it an attractive tool for research and routine patient care [78]. Despite these benefits, self-report measurements should be properly and carefully assessed as patients may overestimate adherence. Because various factors may influence patients' responses, including phrasing of the question or the doctor-patient relationship, it is imperative that self-report adherence

measurements are simple, nonjudgmental, routine, and structured [79]. One solution for minimizing reporting bias in self-report measures is to use Audio Computer-Assisted Self Interview (ACASI). Participants enter their responses privately into a computer, which makes it more likely that these individuals will provide honest responses [80]. Other methods for measuring ART adherence include medication event monitoring system (MEMS) [81], pharmacy records [82], and pill counts [83].

There are several instruments used to measure NCI, including the HIV Dementia Scale [84], Grooved Pegboard [85], Montreal Cognitive Assessment [69], and Neuropsychological Impairment Scale [86]. Due to the multifaceted impact of HIV on neurocognitive functioning, simple and effective instruments to measure NCI are preferred. The 95-item Neuropsychological Impairment Scale, for example, has been used to monitor NCI in a variety of patients including PLWHA [19, 43, 86].

RESEARCH DESIGN

Study participants and procedures

From June to October 2012, a convenience sample of 361 HIV-infected MSM and TGW in Lima, Peru were recruited to participate in a cross-sectional survey to examine HIV treatment outcomes. Eligible participants were ≥18 years, born male and diagnosed with HIV≥1 year. Data analyses were restricted to 313 eligible participants who were prescribed ART for ≥1 month. Recruitment occurred at three HIV clinical sites in Lima: 1) Asociación Civil Impacta Salud y Educación (IMPACTA) 2) Via Libre and 3) Hospital 2 de Mayo. The first two sites are NGOs that provide HIV/AIDS-related medical care and promote HIV/AIDS awareness throughout the city, while the third is a public hospital with outpatient clinics. After clinical care visits, participants meeting eligibility requirements were approached by clinical staff; no participants refused study participation. Supplemental recruitment occurred via internet-based advertisements and flyers posted in clinics. After providing written informed consent, participants completed a 60-minute computer-assisted self-administered interview (CASI) and were paid 25 Peruvian Nuevos Soles (~$10 US) for their time and travel expenses.

Ethics Statement

Ethical oversight was provided by the Institutional Review Boards of IMPACTA, Via Libre, Hospital 2 de Mayo, and Yale University.

Survey Content and Variable Definitions

NCI was assessed using the standardized 95-item Neuropsychological Impairment Scale (NIS; Western Psychological Services, Torrance, CA), which is a self-report measure developed as a quick and convenient way to help elicit diagnostically relevant information about both general NCI and specific symptom areas (i.e. attention, memory, linguistic functioning, etc.). Because this scale had not been previously validated in Spanish and in the Peruvian context, we

first translated and back-translated the scale and tested the wording for meaning [87]. We then conducted an exploratory factor analysis (EFA) to optimize the scale for use with HIV-infected MSM and TGW in Peru. The revised 42-item, 8-factor NIS includes a diverse set of factors with excellent overall reliability (α=0.94; Table 2). Factors include Global Impairment (e.g., "My reactions are slow" and "I have trouble remembering"), Memory-related (e.g., "I forget where I put things" and "I am forgetful"), Frustration tolerance-related (e.g., "I feel easily annoyed and irritable"), Psychomotor/perception-related (e.g., "Part of my body is paralyzed"), Learning-related (e.g., "Doing simple math problems in my head is difficult"), Language-related (e.g., "My speech has become worse"), Pain-associated (e.g., "I have severe headaches"), and Attention-related (e.g., "I am easily distracted"). The reliability of the 8 factors ranged from excellent to good (by factor: F1 α=0.92; F2 α=0.84; F3 α=0.83; F4 α=0.69; F5 α=0.75; F6 α=0.77; and F7 α=0.67). All the subscales were analyzed as continuous variables, with higher score as an indication of higher degree of NCI. The findings from the EFA are found in the supplementary table.

The primary outcome, adherence, was assessed by self-report using a validated visual analog scale (VAS) [78]. Other independent facilitators and barriers associated with adherence were derived from the literature and included demographics, clinical and social characteristics, education, income, and self-reported sexual identity and orientation. Screening for AUDs was done using the World Health Organization's validated 10-item Alcohol Use Disorders Identification Test (AUDIT) [88], with standard cut-offs associated with any AUD (score≥8) and alcohol dependence (score≥20). Health Literacy was measured continuously using the Short Test of Functional Health Literacy in Adults (STOHFLA), a 4-item, self-report scale with scores ≥2 indicating health literacy problems [89]. Past 12-month drug use was self-reported and addiction severity was measured using the 10-item Drug Abuse Screening Test (DAST-10), with bivariate

cutoffs of >2 for moderate to severe addiction [90]. Depressive symptoms were measured using the 10-item Center for Epidemiologic Studies Depression Scale (CES-D 10) with scores >7 indicating moderate to severe depressive symptoms [91].

The study also included ART adherence facilitators. Participants were asked to identify any cue or reminder, from a list of 9, that they regularly used to aid them with medication-taking – including reminders from friends, association with routine activities, alarm clocks and calendars, and locating medications in highly visible places. A summary variable that included none, a single type of reminder or the use of multiple reminders was created to examine the extent to which reminders facilitated adherence.

All standardized measures used have previously been translated and validated in Spanish with the exception of the NIS, which was translated to Spanish and then back-translated into English to ensure accuracy using previously described methods [92]. Pilot testing with PLWHA in Lima was conducted prior to the main study to further ensure survey comprehension.

Analyses

Statistical analyses were performed using SPSS (Version 20). The dependent variable, *optimal adherence*, was defined by self-report as having taken ≥90% of prescribed ART in the previous month. Based on prior studies, this cut-off is associated with high-level ART adherence and plasma viral suppression [93], although more recent studies of more contemporary ART regimens suggest that ART adherence levels of 85% or higher are associated with viral suppression [94, 95]. Bivariate associations between all clinically relevant covariates and the dependent variable were analyzed using chi-square and t-tests for categorical and continuous variables, respectively. Three analytic approaches were deployed. Covariates with $p<0.20$ in the bivariate analysis were incorporated into a multivariate logistic regression model. Additionally, stepwise forward and backward elimination regression models were conducted; all generated

similar findings. The final backward elimination model was selected by goodness-of-fit, using log likelihood criteria. For variables significant in the bivariate analysis but no longer remaining significant in the final model, we tested for collinearity using the Variance Inflation Factor (VIF) test.

RESULTS

Description of the study sample

Table 1 displays the characteristics of the participants, who were mostly in their mid-thirties (mean=34.3 years), had completed secondary school (69.1%), earned more than minimal wage (57.8%) and were employed full-time (51.9%). TGW constituted 6.6% of our sample and 78.3% of our sample self-identified as "gay". Optimal (≥90%) and perfect (100%) ART adherence was self-reported by 85.9% and 54.5%, respectively. Substance use disorders were prevalent with 41.7% meeting screening criteria for an AUD (AUDIT ≥8) and 10.5% reporting recreational drug use; 42.5% met criteria for moderate to major depressive symptoms. The average score for the Global Impairment was 8.8 ±7.7. Table 2 describes the descriptive statistics for the revised NIS and the supplementary table summarizes our new factor analysis of the NIS.

Correlates of ART adherence

Table 3 highlights factors significantly associated with *optimal* ART adherence. In the bivariate analysis, several factors were significantly ($p<0.05$) and negatively associated with adherence, including having an AUD, identifying as TGW, having health literacy issues, depressive symptoms and greater impairment within the following NIS subtest domains: 1) Frustration Tolerance; and 2) Psychomotor. Higher income was positively associated with optimal adherence.

We also examined the study participants' use of different types of medication-taking reminders, which were correlated with both NCI and adherence in bivariate analyses. Significant collinearity associations were not found between areas of NCI and the presence of various medication-taking reminders (data not shown). Individuals with greater impairment within the NIS subtest for Memory showed stronger associations with using an alarm clock and putting their medications within their sight.

After controlling for variables significant in the bivariate analysis, multivariate modeling confirmed that several factors were independently associated with optimal ART adherence. Participants with higher levels of Psychomotor impairment (AOR=0.534; 95% CI=0.317-0.931) and those that met criteria for an AUD (AOR=0.203; 95% CI=0.063–0.655) were nearly 2 times and 5 times less likely to be optimally adherent to ART, respectively. Individuals that self-identified as TGW (AOR=0.175 95% CI=0.032-0.954) and those with health literacy issues (AOR=0.253 95% CI=0.077-0.831) were nearly 6 times and 4 times less likely to be optimally adherent to ART, respectively. In contrast, participants earning higher incomes, specifically minimal wage or greater, were 3 times more likely to be optimally adherent (AOR=3.037; 95% CI=1.016-9.081). ART adherence reminders however, did not influence the final model outcomes.

DISCUSSION

To our knowledge, aside from one study using global NCI measures in PLWHA in Peru (29), this is the first study investigating the extent and subscale assessment of NCI in Peru and their associations with ART adherence among HIV-infected MSM and TGW. Here we find that the Psychomotor NCI subdomain was significantly associated with suboptimal ART adherence [96]. A recent meta-analysis of 207 studies from low-to-middle income countries identified factors associated with non-adherence after controlling for study design and country income level and, like our study, both substance use disorders and financial constraints were associated with non-adherence. This meta-analysis, however, did not include NCI [97].

Despite the identification of HIV-associated NCI more than 25 years ago, the pathophysiology of HIV-mediated neuronal cell death has yet to be fully characterized [98] [10, 99]. CNS inflammation and immune activation are one of the earliest signs of CNS injury in HIV (37). Neurological images have shown evidence of brain atrophy [100], disruptions in brain connectivity networks [101], and reduced cerebral blood flow [102] within the first year of infection. Today, acute neurocognitive decline is less prevalent as severe forms of NCI have been greatly reduced since ART introduction, especially at higher CD4 counts [103, 104]. NCI symptoms, as suggested in our study, continue to persist with mild to moderate symptoms, which are often under-recognized [105], yet contribute to poor outcomes. For example, one study found that among PLWHA with undetectable viral loads, 27% self-reported cognitive complaints but upon further examination, 74% of the study participants met NCI criteria, including 64% of participants without complaints [106].

Though other studies have documented NCI during early stage HIV infection [107], HIV-associated NCI is particularly concerning because it typically worsens with advancing HIV progression [108]. Given that NCI disrupts several cognitive domains such as memory, learning

ability, attention and executive functioning [19], we speculated that many of these factors could pose significant barriers to a patient's ability to take prescribed ART medications. Previous studies among individuals with substance use disorders (SUDs) have found that NCI, in addition to the complexity of a medication regimen, was predictive of lower adherence [6]. One study in PLWHA found that deficits in executive function, memory, and attention domains are most closely associated with poor adherence [27]. Older, HIV-infected adults are particularly vulnerable, since increasing age is an additional risk factor that independently causes cognitive decline and dementia [109-111]. In terms of medication adherence, older adults have traditionally had higher levels of adherence, but nonetheless, the negative impact of NCI on medication adherence has also been confirmed in older patients [14]. It is worth considering the existence of a self-destructive, bidirectional, vicious cycle between NCI and suboptimal medication adherence: impaired cognitive function may hamper adherence just as sub-optimal adherence may contribute to NCI. Therefore, optimal adherence is predicated on the argument that there is sound functioning across the aforementioned cognitive domains [19]. Patients must be cognizant of their condition, remember to take their medications, and do so according to instructions. In the context of neurocognitively-impaired patients, having optimal ART adherence is not only essential for ideal HIV treatment, but also a mean to significantly reduce NCI symptoms. For example, one study found that, after 6 and 15 months of ART, the proportion of subjects with poor neuropsychological scores decreased over time from 81% at baseline to 50% and 22%, respectively. This finding suggests that NCI symptoms, if present, would in turn contribute to better ART adherence [71].

The revised NIS measures several NCI subscales designed to quantify various cognitive domains commonly affected by HIV. In a previous study, mean levels of general cognitive impairment, known as the Global Impairment, were associated with suboptimal ART adherence

on the bivariate level, but not in the final model [96]. In the latest analyses presented here, we conducted a factor analysis to optimize the scale for HIV-infected MSM and TGW in Peru. The revised 42-item, 8-factor NIS includes a diverse set of factors with excellent overall reliability (α=0.94; Supplementary Table). Factors include: Global Impairment, Memory, Frustration Tolerance, Psychomotor, Learning, Language, Pain, and Attention. Each of these subscales is straightforward in its ability to identify key cognitive issues. To our knowledge, this is the first revision to the NIS for our study population in Peru. Although some of the NIS subscales were significant in the bivariate model, the Psychomotor subscale was the only subscale that remained significant in the multivariate model, reflecting difficulties in taking medications due to physical disabilities. Nurses and physicians should be more aware of their patients' physical and mental states when prescribing ART, and offer solutions that will maximize adherence. It is also worth noting that Frustration Tolerance approached significance in the multivariate model, which may suggest that individuals with NCI suffer from decreased patience and increased irritability.

Moderate to severe levels of depressive symptoms were highly prevalent (42.5%) and did not remain independently correlated with suboptimal adherence in the final model, despite depression not being collinear with NCI or AUDs as has been shown elsewhere [112, 113]. Previous studies have documented that depressive symptoms are highly correlated with ART non-adherence [114, 115], including in low- and middle-income countries [116], but these studies did not address NCI. Until prospective studies disentangle the relationship between depressive symptoms, AUDs and NCI, it would be worthwhile for treatment providers to screen for and treat each disorder to optimize HIV treatment outcomes. This is particularly relevant as each disorder is under-diagnosed in clinical care settings [117-120], remains inadequately treated [64, 121, 122] yet amenable to effective treatment interventions [123].

Though AUDs have been previously associated with ART non-adherence among HIV-infected MSM and TGW in Peru [96], findings here from a larger sample size of patients who were continuously on ART for at least one month re-confirm this association as has been described elsewhere [58, 124, 125] and extends to findings to include more specific aspects of NCI. Many other factors contribute to NCI, including drug and AUDs [103, 104]. The high prevalence of AUDs in this sample, similar to reported elsewhere in Latin America, exist partly due to cultural and sexual biases in vulnerable and marginalized MSM communities [126]. Outside of the context of HIV, AUDs cause harm through alcohol-related liver toxicity [127, 128] and poor decision-making [129].

Earning higher income was independently associated with optimal ART adherence. Though ART is provided free in Peru, the 94 (30%) participants earning less than minimal wage may be a surrogate for some other non-measured variable like food insecurity and limited transportation to renew ART, which has been associated with non-adherence in other settings where ART was provided for free [130, 131]. Although only 20 individuals self-identified as TGW (6.6%), our multivariate model shows that these individuals were almost 6 times as likely to have suboptimal adherence to ART. These further confirm other reports indicating that, within the HIV epidemic, TGW represent a highly vulnerable community that does not meet HIV standard-of-care and suffers from issues with risk perception and HIV care accessibility [132-134]. Low health literacy was independently associated with suboptimal ART adherence. Neurocognitive impairment hinders basic knowledge, such as numeracy, and critical-thinking skills, such as comprehension and application of healthcare information [135]. These findings support the need to explore new methods of informing patients of their conditions and details regarding their treatment, such as technology and interventions [136, 137].

While our findings examined adherence barriers, we also sought to explore adherence facilitators like medication reminders that might be used to overcome problematic adherence in other settings [138]. Though guidelines from the International Association of Physicians in AIDS Care do, in general, recommend the use or reminders to improve adherence, there is insufficient data to support their use in patients with underlying SUDs [139], with recommendations to further examine their use in this special population, especially since over 40% of our sample had an AUD. It is noteworthy that low-cost mobile technologies are gaining traction to improve adherence in a number of emerging settings and patient populations. Recent studies show that Peruvian PLWHA, including MSM and TGW, not only have access to mobile health technologies, but are interested in using them to improve health [140, 141]. These are pertinent findings since mobile technology offers a cost-effective method for accessing a larger proportion [142] with reminder options, and potentially to improve ART adherence [141, 143, 144]. Despite these promising results, it is unclear whether technology use will be hindered by various levels of NCI and the negative association between high levels of impairment in the Psychomotor domain and ART adherence among our sample [145]. Future intervention development will require carefully tailoring and testing among a spectrum of NCI for both content and delivery for HIV-infected Peruvian MSM and TGW.

Study Limitations

Our work included some inherent methodological limitations. First, causality cannot be determined because of the cross-sectional nature of this study. Second, while other factors associated with non-adherence (like pill burden, dosing frequency, and lifestyle changes) were not included, few first-line ART regimens are available in Peru and they do not allow sufficient variability in the regimen. Third, sampling bias may have occurred, since study participants were recruited from only three clinics in Lima, but these are among the largest clinics providing HIV

services to MSM and TGW. Social desirability bias may also have played a role in reporting of sensitive issues like stigma or alcohol use, although the use of CASI usually reduces this bias [146-148]. Fourth, the revised NIS has not been validated in Peru, although another other revised NIS study has recently been published [149]. Although the NIS features specific categorizations of severity, it only has validated normative scores for the US population [86]. Since our Peruvian MSM and TGW cohort has never been analyzed with respect to NCI, we conducted a new factor analysis to refine the instrument. Prospective studies with a larger sample size may help reduce these limitations. Fifth, there are inherent limitations to using VAS to measure self-reported ART adherence. This method has been cited to cause over-reporting bias [150] and may not be as effective as other methods, such as pharmacy refill or MEMS [81, 151]. Lastly, the 90% cutoff used in this study may not have been precise and future studies could explore more robust measurements.

CONCLUSION

This study is the first to describe the magnitude and impact of NCI on ART adherence among HIV-infected MSM and TGW in Lima, Peru. Though drug use, AUDs, depression and NCI were prevalent in the population prescribed ART, only the presence of AUDs, increasing levels of psychomotor NCI, self-identifying as a TGW, and health literacy issues were associated with suboptimal ART adherence. Future studies that incorporate standardized measures of NCI are crucial to assess their contribution to adherence, but more importantly, to understand how to intervene when NCI is present, especially through the creation and testing of evidence-based adherence interventions. The next generation of adherence interventions will need to be more cost-effective and tailored to the unique need of patients, especially those with NCI. Earlier initiation of ART at higher CD4 counts, before NCI manifests itself clinically, is also central to better ART treatment outcomes, since NCI contributes to ART non-adherence.

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