

Effect of Depression and Substance Abuse on Antiretroviral Therapy (ART) Adherence in Men Who Have  
Sex With Men (MSM) of Mexican Descent on the US-Mexico Border

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A thesis submitted in partial fulfillment of the  
requirements for the degree of

Master of Public Health

University of Washington

2016

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Program Authorized to Offer Degree:

School of Public Health

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**Abstract**

Effect of Depression and Substance Abuse on Antiretroviral Therapy (ART) Adherence in Men Who Have Sex With Men (MSM) of Mexican Descent on the US-Mexico Border

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Latinos in the United States bear a disproportionate burden of HIV, suffering a three-fold incidence as compared to Non-Latino Whites (NLWs). People living with HIV (PLHIV) experience high levels of depression, which has been associated with antiretroviral therapy (ART) non-adherence in several meta-analyses; however, the relationship between depression and ART non-adherence has been studied very little among the Latino population. This study aimed to characterize the relationship between depression and ART adherence, and the role of substance use in mediating or modifying that effect, among Latinos. Using baseline survey data previously collected by Simoni et al. during an RCT [NCT01411839] in El Paso, Texas, 150 men who have sex with men (MSM) of Mexican descent were included in this cross-sectional analysis. Adherence, depression, and substance use were measured using the Simplified Medication Adherence Questionnaire (SMAQ), Beck Depression Inventory Version IA (BDI- IA), and the Addiction Severity Index (ASI-Lite), respectively. Using relative risk regression models we found that those with depression were 37% more likely to be non-adherent than those without depression [aPR: 1.37 (95%CI: 1.10-1.70),  $p = 0.006$ ]. There was some evidence that substance use modified the effect of depression on adherence, and there was some evidence for mediation by substance use, but our power was limited to detect these effects. Our results indicate a need for more longitudinal studies to determine causality between depression and ART non-adherence in this high-risk group.

## Introduction

People living with HIV (PLHIV) experience high levels of depression, with some prevalence estimates as high as 36%.<sup>1</sup> Adherence to antiretroviral therapy (ART) is essential for effective management of HIV, both to manage disease progression for individual patients and, from a public health standpoint, to decrease HIV transmission. The association between depression and antiretroviral therapy (ART) non-adherence has been well-established by numerous studies and several meta-analyses,<sup>1,2</sup> with subjects endorsing symptoms of depression more likely to have poorer clinical outcomes, including higher rates of mortality<sup>1,3</sup>. Importantly, depression is a modifiable risk factor for non-adherence and treating depression is associated with an 83% increased odds of ART adherence per a recent meta-analysis<sup>4</sup>.

Substance use represents a second modifiable factor. A recent meta-analysis found that current substance use was negatively associated with adherence, with a standardized mean difference (SMD) of -0.395 (95% CI -0.49 to -0.30,  $p=0.001$ )<sup>5</sup>. A recent literature review noted that the prevalence of substance use among United States Latinos is as high or higher than among non-Latino whites (NLWs), and that Latinos are less-likely to seek and receive treatment<sup>6</sup>. Understanding the nature of the relationship between substance use, depression, and ART adherence—effect modification or mediation—can inform interventions both to improve ART adherence and treat co-morbid conditions.

Depression is also associated with substance use, although it is challenging to determine the direction of the causal relationship. A meta-analysis from 2009 confirmed an association between alcohol use and depression; however, the authors also noted that individual studies have found both that alcohol abuse leads to depression, and that depression leads to alcohol abuse, suggesting a possible bi-directional relationship or a common causal factor for the two<sup>7</sup>. Understanding the relationship between depression and substance use in the context of ART adherence is critical to determine optimal areas for intervention.

While comparatively well-studied in the general population, the association between depression and ART non-adherence has been studied minimally in U.S. Latinos, with only one known study of 81 participants published. This study was primarily qualitative and noted that depression was the most commonly cited

barrier to adherence and that only 32% of participants were consistently adherent. However, the study sample size was small, heterogeneous in national origin of participants, and not statistically representative.<sup>8</sup> The same qualitative study reported that substance use was a barrier for ART adherence, but substance use was not analyzed quantitatively. We are aware of no studies that have considered the modifying or mediating role of substance abuse on adherence in this population.

Latinos bear a disproportionate burden of HIV in the U.S. as compared to the rest of the population, having an annual incidence of HIV infection nearly three-fold higher than non-Latino whites (NLWs).<sup>9</sup> While Latinos comprise approximately 17% of the U.S. population, Latinos accounted for 20.8% of new HIV diagnoses from 2008-2013<sup>10</sup>. Data suggest that the overall incidence of HIV infection has decreased for Latinos from 28.3 per 100,000 to 24.3 per 100,000 for the period 2008-2013; however, the number of HIV diagnoses attributable to male-male sex among Latinos has increased by 16% during this same time period from 6,141 to 7,098<sup>9,10</sup>. MSM accounted for 82.8% of new HIV diagnoses among Latinos in 2013<sup>10</sup>.

Of special concern is the U.S.-Mexico border region, which presents unique challenges for surveillance and treatment of HIV/AIDS—due to high rates of migration, complicating surveillance—and for Latinos living with HIV/AIDS in the region. Data from 45 U.S. counties along the Mexican border between 2003 and 2006 revealed a 7.8% (95% CI: 3.3%-13.3%) increase in HIV diagnoses each year, of which almost half were among Latinos<sup>11</sup>. The increases in incidence were especially high among MSM of all races in this area at 11.4% (95% CI: 5.4%-17.9%)<sup>11</sup>. As the authors note, in a period in which testing remained static nationally, it is unlikely that increased incidence in the border region merely represents an increase in testing. There are a number of factors that may be contributing to this trend—many people living in this area are migratory, many are of low socioeconomic status (the border region is among the poorest regions in the U.S.), and living in unincorporated settlements (*colonias*) with little in the way of basic services and healthcare infrastructure.<sup>12</sup>

In summary, depression is an important modifiable risk factor for ART non-adherence that has been minimally studied among Latinos, a group with disproportionately high HIV burden. Substance use may modify or mediate the relationship between depression and ART adherence, and may be an important target for interventions. The depression-adherence association has not been studied among Latinos in the U.S.-Mexico border region, a high-risk group. In this study, which is the first of its kind, we aimed to determine the relationship between depression and ART adherence --and characterize the effect of substance use on this relationship-- among HIV+ Latino MSM living in the U.S.-Mexico border region, an especially high-risk and vulnerable population.

## **Methods**

### Study Design

This study is an analysis of cross-sectional baseline survey data previously collected by Simoni et al. during an RCT [NCT01411839] entitled: "A preliminary RCT of CBT-AD [Cognitive Behavioral Therapy for Adherence and Depression] for adherence and depression among HIV-positive Latinos on the U.S.-Mexico border: the Nuevo Día study."<sup>13</sup>

### Data Collection

Data were collected between October 2009 and August 2011 at a community health clinic in El Paso, Texas. Participants were recruited using flyers to advertise and through encouragement of participation from clinic providers, patients and staff. Interested participants were either interviewed the same day that they expressed interest in participating or were given an appointment to return for the survey.

Participants were eligible to participate if they were at least 18 years of age and had been receiving antiretroviral medication for at least 30 days. Participants meeting these criteria completed a 1-hour survey by a trained interviewer, assessing treatment adherence and a number of psychosocial variables. 295 patients were referred for participation and 253 participants completed the survey.<sup>13</sup> The survey included demographic information and the following tools:

- Addiction Severity Index-Lite (ASI-Lite)
  - Participants asked to report the number of times each of thirteen different substances have been used in the past month and during lifetime, as well as route of administration<sup>14</sup>
- Simplified Medication Adherence Questionnaire (SMAQ)
  - ♦Six total items; five binary items and one Likert scale item
  - ♦Participants asked if they have ever forgotten to take medication, are careless about medication, stopped taking medication due to feeling worse, or missed any doses over the past weekend (Yes or No), how often they have missed a dose in the past week (1-Never, 5-more than ten times), and asked how often they have missed doses in the past three months (more than two times or less than two times)<sup>15</sup>
- Beck Depression Inventory 1A (BDI)
  - ♦21 multiple-choice items measuring self-reported depressive symptoms over the past week including day of interview, with responses options ranging from 0-3
  - ♦Items are summed with possible scores between 0 and 63 with thresholds for minimal ( $\leq 9$ ), mild (10-18), moderate (19-29), and severe ( $\geq 30$ ) depression<sup>16,17</sup>

### Inclusion Criteria

Of the 253 participants who completed the survey, those included in this analysis identified as male or male-to-female transgender, reported sex with men (MSM), and were of Mexican descent. MSM status was assessed through self-report and participants who reported ever having had sex with a man were included. Of the 253 participants who completed the survey, 183 (72.3%) met the criteria of being male and having had sex with a man in their lifetime. Of these, 154 (84.15%) identified as being of Mexican descent and were included. No participants were missing all responses to the Beck Depression Inventory (BDI), those with at least one but not all responses were included based on their available answers (n=6). Participants who did not answer any items of the Simplified Medication Adherence Questionnaire (SMAQ) (n=4) were excluded from the study, while those that answered at least one item were classified based on their available answers (n=5).

### Analysis

*Exposure:* Depression was assessed through the Beck Depression Inventory (BDI), version IA, a 21-item Likert scale measure of depressive symptomatology<sup>16,17</sup>. Depression was modeled dichotomously, using an *a priori* cutoff of 19, which categorized moderate and severe depressive symptomatology as depressed.

*Exposure:* Substance use was assessed through the Addiction Severity Index - Lite (ASI-Lite), a questionnaire quantifying the number of days of use in the past month and the number of years over a lifetime that a participant endorses using substances<sup>14</sup>. In keeping with previous studies of the effects of drug and alcohol use on ART adherence<sup>18,19</sup>, participants were considered to use “hard” drugs if they endorsed using cocaine, heroin, or amphetamines in the past 30 days, and were considered to use alcohol if they endorsed consuming alcohol to the point of intoxication in the past 30 days. Separate dummy variables were created for “hard” drug use and alcohol use.

### *Covariates and demographic characteristics:*

Demographic characteristics, found in Table 1, were collected by self-report. To control for confounding, *age*, *time since diagnosis*, and *income* were included in the model as continuous variables. *Age* and *time since diagnosis* were calculated in years using self-reported date of birth and date of diagnosis in conjunction with date of interview. *Income* was self-reported in USD.

*Outcome:* ART adherence was assessed through the Simplified Medication Adherence Questionnaire (SMAQ), which contains 6 items, 5 of which are on a binary scale and one item that contains a Likert scale<sup>15</sup>. Participants were considered non-adherent if they answered positively to any of the qualitative questions or if they reported missing more than 2 doses in the last week or reported more than 2 non-medication days in the past 3 months. This categorization was determined *a priori* and in keeping with the original SMAQ validation study.<sup>15</sup>

### Statistical Analysis

We used a generalized linear model (GLM) with a Poisson family and log link (relative risk regression) with robust standard errors (Huber/White/sandwich estimator) rather than using logistic regression. Logistic regression yields an odds ratio, which cannot be interpreted as a relative risk when the outcome is not rare, as in this case with ART adherence. The ratios obtained from the GLM are prevalence ratios (PR) rather than relative risks (RR), as this study uses cross sectional data and temporality cannot be determined. All analyses were conducted using Stata 12.0 (StataCorp.; College Station, TX).

Multivariate analyses were conducted using the generalized linear model to control for the potentially confounding factors of *age*, *time since diagnosis*, and *income*, which were modeled continuously. A Pearson correlation coefficient was calculated to assess the association between *age* and *time since diagnosis*, which was significant ( $r = .502, p < 0.001$ ); simple regressions were performed and determined that *time since diagnosis* explained more of the variance in *adherence* than *age*. Thus, *age* was dropped from the multivariate analysis to prevent violation of the assumption of non-collinearity.

Effect modification by *substance use* was tested through stratified analyses and analyses using an interaction term. Participants were stratified based upon endorsement of “hard” drug use in the past month, and GLM regression was performed to determine if the association between depression and ART-adherence was modified by “hard” drug use. Similarly, participants were stratified based upon endorsement of alcohol use to the point of intoxication, and GLM regression was performed to determine if the association between depression and ART-adherence was modified by alcohol intoxication within the past month. Finally, an interaction term for “hard” drugs and depression and an interaction term for alcohol and depression were created and incorporated into the GLM.

In order to test for mediation by drug and alcohol abuse, GLM regressions were serially performed. The first regression included only depression (adjusted for time since diagnosis and income), the second depression and “hard” drug abuse, the third depression and alcohol to intoxication, and finally all three predictors (i.e., depression and “hard” drug use and alcohol to intoxication). Coefficients were compared

between different GLM regressions to examine the effect of inclusion of drug and alcohol abuse on the association between depression and non-adherence.

## **Results**

Of the 253 subjects in the parent study who completed the enrollment survey, 150 were included in our sample of MSM of Mexican descent with available data on depression, adherence, and substance use. The median age of participants was 45 years (IQR: 37, 52), and they tended to have low income (median \$10,980 (IQR: \$7,140, \$19,548)), and low frequency of consistent employment, with only 19 participants (12.7%) reporting full-time employment. Most were diagnosed with HIV within the past 10 years (median time since diagnosis: 9.4 years (IQR: 4.6, 14.0)), and few (47, or 31.8%) had steady partners.

Overall, 33 (22%) had moderate to severe depressive symptoms (median BDI score 11.9 (IQR: 4, 18)). Non-adherence was common, with 98 (65.3%) endorsing problems with adherence or more than 2 missed doses over that past week or over 2 days of non-medication over the past 3 months<sup>15</sup>. Use of “hard” drugs -- cocaine, heroin, or amphetamines -- was not uncommon with 14 (9.3%) reporting use in the past month. Alcohol consumption to the point of intoxication was more common, with 30 (20.0%) reporting intoxication in the past month.

Among ART-adherent participants, prevalence of depression was 13.5%; among non-adherent participants, prevalence of depression was 26.5%. After controlling for income and time since diagnosis, depression was associated with a 1.37-fold higher prevalence of non-adherence (PR: 1.37 (95%CI: 1.10 – 1.70)).

When use of “hard” drugs (cocaine, heroin, amphetamines) was considered as an effect modifier in stratified analyses, depression was more strongly associated with ART non-adherence in those participants without “hard” drug use, though not significantly so. Among those with “hard” drug use,

depression was associated with a 1.09-fold prevalence of non-adherence (95% CI: 0.66 – 1.82); among those without “hard” drug use, depression was associated with a 1.38-fold prevalence of non-adherence (95% CI: 1.08 – 1.75). In analyses that considered an interaction term between “hard” drug use and depression, the interaction term was not significant, suggesting no interaction between the two predictors ( $p= 0.532$ ).

When use of alcohol to the point of intoxication in the past month was considered as an effect modifier in stratified analyses, depression was also more strongly associated with non-adherence in participants without alcohol intoxication, but again, not significantly so. Among those with alcohol intoxication, depression was associated with a 1.19-fold prevalence of non-adherence (95% CI: 0.81 – 1.75); among those without alcohol intoxication, depression was associated with a 1.37-fold prevalence of non-adherence (95% CI: 1.05-1.80). In analyses that considered an interaction term between alcohol intoxication and depression the interaction term was not significant, suggesting no interaction between the two predictors ( $p= 0.640$ ).

In the model without inclusion of drugs and alcohol, depression was associated with a 1.37-fold higher prevalence of non-adherence ( $p=0.006$ ). When drug and alcohol use were considered as mediators, inclusion of both drug use and alcohol use attenuated the relationship between depression and adherence to a small degree. With inclusion of drug use, depression was associated with a 1.33-fold higher prevalence of non-adherence ( $p= 0.012$ ). Including alcohol abuse without drug abuse in the model, depression was associated with a 1.31-fold higher prevalence of non-adherence ( $p= 0.017$ ). Finally, with inclusion of both drug abuse and alcohol abuse in the regression, depression was associated with a 1.30-fold higher prevalence ( $p=0.026$ ).

## **Discussion**

In this sample of HIV-positive MSM of Mexican descent in El Paso, TX, we found a high prevalence of depression and ART non-adherence, with prevalence of depression being higher among subjects who were non-adherent to ART compared to subjects who were adherent. Participants with a longer time

since diagnosis were less likely to have good adherence. We found moderately high rates of hard drug use and problematic alcohol use; drug and alcohol abuse appeared to play some role in modifying or mediating the association between depression and non-adherence, but our study was underpowered to detect this effect.

The prevalence of depression among our study population appeared to be high (22%) but was moderate in comparison with other estimates; while we cannot make direct comparisons due to different measures that were employed, a commonly cited estimate of prevalence of depression is 36% in PLHIV<sup>20</sup> (using the Composite International Diagnostic Interview (CIDI) tool versus our own study which employed the BDI-1A), reflecting a more than two-fold increased prevalence of depression among PLHIV versus the general population<sup>20,21</sup>. Prevalence of ART non-adherence was also high in our study (65%) but not inconsistent with previous studies. Again, direct comparisons cannot be made because a different measure was used (AIDS Clinical Trials Group Baseline Adherence Questionnaire versus our own study which used the SMAQ tool), but a small study of adherence in Latinos showed a non-adherence prevalence of 68%<sup>8</sup>. Similarly, a larger longitudinal study examining racial disparities in ART adherence found that the prevalence of *adherence* was 31.8% among Latinos (so for non-adherence, 68.2%)<sup>22</sup>, again using a different measure from our own, precluding direct comparison. Other studies have shown ART adherence among Latinos to be higher than what we found,<sup>23,24</sup> which may reflect over-reporting of non-adherence in our study, differences in measurement, or actual differences in study populations.

The effect of depression on non-adherence observed in our study (aPR=1.37) was not dissimilar to a recent multi-national meta-analysis which obtained a pooled *OR* of 0.58 for adherence (i.e. those with depression were 42% less likely to be adherent.)<sup>2</sup> A recent self-report study which included Latinos showed an aOR of 1.15 for each point increase on the PHQ-9 on risk of treatment interruption and showed that Latinos' treatment adherence was more affected by depressive symptoms than that of NLWs.<sup>24</sup>

It seems likely that drug and alcohol abuse modified the effect of depression on non-adherence in our

stratified analysis, although this effect was not borne out in the model using interaction terms. It also seems likely from our data that drug and alcohol abuse accounted for a small degree of mediation (aPR of 1.37 vs. 1.30); however, given our limited power and lack of temporality, it is challenging to make hard conclusions from these data. In comparing the interaction of depression and substance abuse to other studies we encountered, one study reported an interaction between depression and illicit drug use among women at risk for ART non-initiation, but the study did not examine adherence.<sup>25</sup> By contrast, another study found no significant interaction between mental illness and drug use in their associations with receipt of ART<sup>26</sup>.

Our study is limited by several factors. Cross-sectional data does not allow us to establish directionality of the association between depression and non-adherence, and causality cannot be established for our mediation analysis. We had a relatively small sample size (n=150), and we had small counts in some cells. Additionally, because we used self-report measures of adherence rather than pill counts or viral load, it is possible that depressive symptomatology merely leads people to rate their adherence more poorly than those who are not depressed. Our self-report measures may also be subject to recall bias and social desirability bias.

Our study has several strengths in its favor. The sample was restricted to obtain a relatively homogenous population of MSM of Mexican descent living in the U.S.-Mexico border region, a study population comprising a geographic region and ethnic group little studied. Standardized and culturally validated tools were used to measure exposures and outcome, which improves the precision of our measures. Lastly, we employed robust statistical methods to obtain adjusted prevalence ratios, which are more readily interpretable than odds ratios.

In conclusion, our study contributes to the limited body of knowledge concerning Latino MSM living with HIV. Studies have shown that treating depression in the general population of PLHIV improves treatment adherence<sup>4</sup>. Given the disproportionate burden of HIV among Latinos, the high prevalence of non-adherence, and the relative lack of studies examining adherence behavior in Latinos, this study bears

important implications for tailoring interventions to improve ART adherence in an impactful way in this high-risk group. In moving forward, more longitudinal studies are needed to determine causality between depression and non-adherence among Latinos, and more studies are needed of the interaction between depression and substance abuse in PLHIV. Studies of other Latino sub-groups are needed, due to heterogeneity of depressive symptoms and adherence behavior between sub-groups. Finally, further studies to identify effective interventions for improving adherence in this population are needed, both for interventions treating depression, such as the Nuevo Dia parent study [NCT01411839], and for interventions to treat substance abuse.

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## Figures and Tables

**Table 1: Sociodemographic characteristics**

	Frequency/Median	Percent/IQR
Age (in years)	45	(37, 52)
Time since diagnosis (in years)	9.36	(4.57, 14.00)
Married or steady partner (N=148)	47	31.76
Employment Status		
Full time	19	12.67
Part time	18	12.00
Odd jobs	23	15.33
Unemployed	90	60.00
Annual Income (N= 147)	10,980.00	(\$7,140, \$19,548)

**Table 2: Distribution of depression, adherence, substance use, and alcohol use**

	n	%
Beck Depression Inventory (BDI) I-A		
Minimal Depression (0-9)	77	51.33
Mild Depression (10-18)	40	26.67
Moderate Depression (19-29)	27	18.00
Severe Depression (30-63)	6	4.00
BDI<19	117	78.00
BDI≥19	33	22.00
Simplified Medication Adherence Questionnaire (SMAQ)		
SMAQ = 0	52	34.67
SMAQ = 1-9	98	65.33
Substance Use		
Hard Drugs in Past 30 Days (Cocaine, Heroin, Amphetamines)	14	9.33
Alcohol to point of intoxication	30	20.00

**Table 3: Association between depression and adherence, effect modification by substance use and alcohol use**

	Adherent	Non-Adherent	aPR (adjusted for time since diagnosis and income)	95% CI	p- value
<b>Baseline model</b>	n(%) or median (IQR)	n(%) or median (IQR)			
	N = 52	N = 98			
Depression	7 (13.5%)	26 (26.5%)	1.37	(1.10 - 1.70)	<b>0.006</b>
Time since diagnosis (years)	8.0 (3.5, 12.2)	9.7 (5.1, 14.7)	1.02	(1.00 - 1.04)	0.016
Income*	\$11,220 (\$7,140, \$18,000)*	\$10,722 (\$7,100, \$19,850)*	1.00	(1.00 - 1.00)	0.977
* n = 51 for adherent, n = 96 for non-adherent					
<b>Effect modification analysis of hard drug use using stratified analysis</b>					
Hard drug use	(N = 3)	(N = 11)			
Depression	1 (33.3%)	5 (45.5%)	1.09	(0.66 - 1.82)	0.732
No hard drug use	(N = 49)	(N = 87)			
Depression	6 (12.2%)	21 (24.1%)	1.38	(1.08 - 1.75)	0.010
<b>Effect modification analysis of heavy alcohol use using stratified analysis</b>					
Heavy alcohol use	(N = 7)	(N = 23)			
Depression	2 (28.6%)	10 (43.5%)	1.19	(0.81 - 1.75)	0.368
No heavy alcohol use	(N = 45)	(N = 75)			
Depression	5 (11.1%)	16 (21.3%)	1.37	(1.05 - 1.80)	0.022
<b>Effect modification analysis of hard drug use using interaction terms</b>					
Depression	--	--	1.37	(1.08 - 1.75)	0.010
Hard drug use	--	--	1.36	(0.88 - 2.12)	0.170
Depression * Hard drug use	--	--	0.83	(0.46 - 1.50)	<b>0.532</b>
<b>Effect modification analysis of heavy alcohol use using interaction terms</b>					
Depression	--	--	1.36	(1.04 - 1.79)	0.027
Heavy alcohol use	--	--	1.30	(0.93 - 1.81)	0.120
Depression * Heavy alcohol use	--	--	0.89	(0.56 - 1.43)	<b>0.640</b>
<b>Mediation using nested models</b>					
Model 1: Depression + confounders only					
Depression	--	--	1.37	(1.10 - 1.70)	0.006
Model 2: Depression + confounders + drug use					
Depression	--	--	1.33	(1.07 - 1.67)	0.012
Model 3: Depression + confounders + heavy alcohol use					
Depression	--	--	1.31	(1.05 - 1.64)	0.017
Model 4: Depression + confounders + hard drug use + heavy alcohol use					
Depression	--	--	1.30	(1.03 - 1.63)	0.026