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## Short report

**Keywords:** HIV, depression, adherence, antiretroviral therapy, viral load suppression

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## **Association between Depression and HIV Treatment Outcomes in a US Military**

### **Population with HIV Infection**

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#### **Abstract:**

**Background:** Depression is common among HIV-infected individuals and may contribute to suboptimal adherence to antiretroviral therapy (ART) and subsequent inability to attain viral load

(VL) suppression. We evaluated longitudinal HIV treatment outcomes in US Military HIV Natural History Study (NHS) participants with depression.

**Methods:** Male NHS participants with available ICD-9 data for mental health diagnoses, Center for Epidemiological Studies Depression (CES-D) measures, and self-reported adherence (SRA) were included. ART use was defined as ART initiation between 2006-2010, with follow-up through 2015. SRA was defined as taking  $\geq 95\%$  of ART doses and continuous ART was defined as longitudinal ART use with gaps  $< 30$  days. Continuous VL suppression was defined as maintaining VLs  $< 200$  c/mL on ART. To analyze the association between depression and HIV treatment outcomes, latent class analysis was used to create classes of depression trajectories: low depression (LD), recent onset depression (ROD) and high Depression (HD).

**Results:** Participants had a mean age of 32 ( $\pm 8.3$ ) years at HIV diagnosis, and similar proportions were Caucasian (44.3%) or African American (40.8%). Overall, older participants at HIV diagnosis had greater odds of having 95% SRA (OR 1.06, 95% CI 1.02-1.12), and African Americans had lower odds (OR 0.41, 95% CI 0.22-0.76) compared to Caucasians (OR 1.49, 95% CI 0.52-4.28). However, there was no difference in SRA by depression trajectory. Participants with HD had a trend towards taking ART continuously (OR 1.75, 95% CI 0.99-3.09), and those with ROD had significantly higher odds of virologic failure (OR 0.58, 95% CI 0.38-0.91).

**Conclusions:** Although there was no observed association between depression and SRA, participants with ROD had lower odds of attaining the HIV treatment goal of VL suppression. Continued efforts to identify and aggressively manage mental health disorders is important to success along the HIV care continuum.

**Key Words:** HIV; depression; adherence; antiretroviral therapy; viral load suppression

## **Introduction:**

Adherence to antiretroviral therapy (ART) is essential for the achievement and long-term maintenance of viral suppression in people living with HIV (PLWH). Durable viral suppression has many benefits including immune reconstitution, reduced risk of AIDS and prevention of onward transmission to sex partners (Rodger et al, 2016; Del Ramero J et al 2010). However, concurrent mental health diagnoses such as depression may negatively influence adherence to ART, resulting in failed viral suppression. Major depressive disorder has been shown to be more prevalent in PLWH compared to those without HIV infection (van Coppenhagen, B & Duvenage, HS, 2019). A previous study reported that treatment-naïve patients with mental health disorders had slower rates of virologic suppression after ART initiation (Pence et al 2007).

The potential impact of depression on ART adherence has been evaluated in previous studies. For example, one study performed cross-sectional assessments of adherence and demonstrated greater odds of <80% ART adherence among HIV infected individuals diagnosed with depression compared to those without depression (Tiffany CC et al 2019).

Another cross-sectional analysis from 2011-2014 in Chicago looked into multiple psychosocial conditions to include depression and anxiety and their relation to adherence (described as “syndemic”). Controlling for demographics and treatment factors, symptoms of depression were present in 38% of participants; and the likelihood of ART adherence decreased with the number of syndemic conditions included for analysis as did the odds of VL suppression. While interventions to address these co-morbid psychosocial conditions have been recommended, there is limited understanding of the specific relationship between clinical depression and ART adherence. Furthermore, the cross-sectional design of these prior studies

limits the ability to substantiate links between treatment adherence/viral load suppression and depression among HIV infected persons.

We previously analyzed the relationship between longitudinal depression trajectories and sexual risk behaviors in US Military HIV Natural History Study (NHS), observing that participants with depression were less likely to use condoms and more likely to have sex with multiple partners (Carney et al 2019). The current analysis used the same longitudinal depression trajectories to further understand the potential impact of depression on HIV treatment outcomes.

## **Methods:**

The NHS is a prospective observational cohort of HIV-infected active duty military personnel and beneficiaries. All participants were at least 18 years of age and provided written informed consent for this IRB-approved study. Male NHS participants were included who met criteria for available mental health diagnosis data, self-reported adherence (SRA) and ART use (n=549). ART use was defined as ART initiation between 2006-2010, with follow-up through 2015. SRA was defined as taking  $\geq 95\%$  of ART doses and continuous ART was defined as longitudinal ART use with gaps  $< 30$  days. Continuous VL suppression was defined as maintaining VLs  $< 200$  c/mL on ART over the same time period.

Self-reported Center for Epidemiological Studies Depression (CES-D) measures and ICD-9 codes for depression collected from 2006-2010 were evaluated with self-reported depressive symptoms from 2014-2015 as previously described (Carney et al 2019). Using a cutoff score of 16 to identify respondents at risk for clinical depression, the 20-item CES-D

scores from 2006 (time period 1), 2007-08 (time period 2), and 2009 (time period 3), respectively, were coded such that 1 represented 16 or higher (at risk for clinical depression) and 0 indicating below 16 (less risk). The cutoff value of 16 was based on recommendations designated by the American Psychological Association (AERA). For the self-reported days of depression, participants were asked, “Thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?” Responses were coded into 1 being 1 or more days (at risk for clinical depression) and 0 indicating 0 days (no risk). These measures represent time periods 4 and 5 (2014-2015).

To utilize these self-reported depressive symptoms over the five time periods, Latent class analysis (LCA) was conducted to identify and categorize unmeasured, longitudinal depression trajectories rather than static group membership. LCA results revealed 3 trajectories: High Depression (HD; coded diagnosis for depression or CES-D score of 1 indicating higher risk of depression), recent onset depression (ROD; depressive symptoms present in periods 4 and 5 only), and low depression (LD; CES-D score of 0 indicated less depression risk). Socio-demographic characteristics were used as control measures. The 3 depression trajectories were further dummy-coded with LD serving as the reference for multivariate statistical modeling. The LCA was performed using MPlus and all other statistical analyses were conducted using Stata.

## **Results:**

The mean age at HIV diagnosis for the 549 participants included in this study was 32 years, and similar proportions were Caucasian (44%) and African American (41%; Table 1). Participants had a mean CD4 count at HIV diagnosis of 502 ( $\pm$  246) cells/ $\mu$ L and mean VL of

4.3 log<sub>10</sub> (±0.9) copies/mL. The mean time from HIV diagnosis to ART initiation was 5.3 (±4.8) years due to CD4-based thresholds for initiating ART at the time of this study. For depression outcomes, 90% had a high risk CES-D score (≥16) as opposed to having a coded diagnosis of depression. LCA for the CES-D and self-reported depressive symptoms categorized participants as LD (n=326, 59.4%), ROD (n=137, 25%), and HD (n=86, 15.7%).

Overall, participants with increased age at HIV diagnosis (per one year) had higher odds of having 95% SRA (OR 1.06, 95% CI 1.02-1.12) while African Americans had significantly lower odds in our study (OR 0.41, 95% CI 0.22-0.76) (Table 2). Individuals with ROD or HD did not demonstrate significant differences in SRA.

Participants with a CD4 count ≥500 cells/uL at HIV diagnosis had higher odds of increased delay from HIV diagnosis to starting ART (OR 5.22, 95% CI 3.45-7.89). This finding is likely due to the CD4 count thresholds from which to start therapy based on existing guidelines at that point in time. No significant association was found with age at HIV diagnosis or race for delay in starting ART.

Those with HD demonstrated a trend towards taking ART continuously (OR 1.75, 95% CI 0.99-3.09), but not those with ROD (OR 1.28, 95% CI 0.82-2.0). Other variables did not show statistical significance for continuous ART. Participants with ROD (0.58, 95% CI 0.38-0.91) had significantly lower odds of continuous VL suppression whereas no difference was observed for HD participants (OR 1.15, 95% CI 0.65-2.06).

## **Discussion:**

Analysis of different variables to include ART adherence and VL suppression among HIV-infected persons with a coded diagnosis of depression or self-reported data from the NHS cohort demonstrated that mental health comorbidities may influence these important elements of

longitudinal HIV disease management. Historically, for ART to be most effective in preventing HIV virologic failure, ART adherence of 95% or greater is strongly recommended (Davies et al 2006) as was investigated for our current study. While the necessary adherence rate for sustained VL suppression likely varies among different classes and combinations of agents included in ART regimens, a high adherence goal is necessary given the intricacies of some ART regimens and the increased morbidity/mortality seen with suboptimal adherence (Gordan et al 2015). In our study, increased age at HIV diagnosis per one year was associated with better adherence to ART. This reporting of age as a determinant for adherence has been published elsewhere, citing better medication adherence in older individuals (>35 years) compared with younger patients (Alemu et al 2011). Lower age as an independent risk factor for virologic failure has also been appreciated within our NHS cohort in prior literature looking at persistent low-level viremia and virologic failure (Joya et al 2019). Lower adherence in younger individuals may be related to more significant socioeconomic conditions as compared to older individuals or having less experience in interacting with the health care system (Watt et al 2010).

Lower adherence was observed in African Americans in our study. Young African American males may be less likely than Caucasian individuals to receive adequate mental health care secondary to economic, social or demographic barriers (Whitely et al 2014). Such perceived barriers may result in higher levels of healthcare mistrust than other racial groups, especially in the setting of concurrent psychosocial stressors as previously studied in this specific population (Heestermans et al 2016). Both measured and unmeasured factors may contribute to differences in adherence and warrants further study in our cohort.

Another variable assessed was documented adherence to ART over time. Participants in our study having HD showed a trend towards taking ART continuously, defined as gaps in ART

compliance. While this result wasn't statistically significant for our cohort and may seem contrary to other study findings, such an association has been discussed in previous literature. In a cross-sectional prospective survey among 300 HIV-infected adults on ART in Botswana, an 87 question survey to include graded questions about depression was explored in relation to adherence (European Quality of Life instrument). Of these participants, 21% had "severe depression," and while depression was found to be a predictor of poor adherence rates ( $p < 0.02$ ), adherence rates were poorest among those just starting ART, most notably within 1-6 months of starting compared to those on ART for  $> 12$  months (Do et al 2010). This may be related to side effects or other factors not related to depression. More notably, a meta-analysis looking into depression and HIV treatment interventions found that greater improvements in adherence were found in individuals with more severe depression, using instruments to include CES-D scale measures that were used in our study. It is possible those with classification of more severe depression may perceive a greater opportunity for improvement in both HIV and depression management (Sin and DiMatteo, 2015).

Additionally, participants with ROD had significantly lower odds of achieving viral load suppression compared to those with HD. Many studies have evaluated the effect of depression on virologic response to ART with significant associations identified, even after controlling for adherence (Hartzell et al 2008). In a study of 198 ART-naïve patients initiating therapy for whom a previously validated model to predict psychiatric illness was employed, patients with such a projected diagnosis were slower to reach VL suppression (AHR 1.2, CI: 1.06-1.4), a result that may be attributable to adherence or loss of follow up (Pence et al 2007).

One limitation of this study is that all types of mental health data were not available throughout the study period. The particular diction within ICD-9 codes apropos distinguishing

recurrent depression versus single episode depression for diagnosis is not always established. Another limitation is self-reported adherence as this is subject to social desirability bias. Additionally, our findings may not be generalizable to women as only males were included in this analysis. Furthermore, it would be reasonable to incorporate the number of participants undergoing active treatment for depression into future studies as this variable was not included in our analysis.

The relationship between depression and medication adherence among HIV-infected people to attain viral load suppression is complex. The marked improvements in ART have afforded PLWH an opportunity to live significantly longer and healthier lives than ever before. However, such benefits of ART depend on an individual's ability to adhere to daily medications, which can pose a challenge in those with comorbid mental health diagnoses such as depression. Improved identification and management of concurrent mood disorders are very important in optimizing ART adherence among HIV-infected persons.

## **Declarations**

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### **Disclaimer:**

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### **Competing interests**

The authors declare that they have no competing interests.

### **Consent for publication**

This study is IRB approved and full complete consent was obtained.

### **Ethics approval and consent to participate**

This study is IRB approved and full complete consent was obtained.

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<b>Table 1. Characteristics of NHS participants</b>	
Characteristic	Number (n) or Mean ( $\pm$ SD)
Number, n	549
Age	52.1 (10)
Mean age at HIV diagnosis (years)	32.7 (8.3)
Mean CD4 count at HIV diagnosis (cells/ $\mu$ L)	502.8 (246.1)
Mean viral load at HIV diagnosis (log <sub>10</sub> copies/mL)	4.3 (0.9)
Mean viral load at ART (log <sub>10</sub> copies/mL)	4.3 (0.9)
Time from HIV diagnosis to ART start (years)	5.3 (4.8)
Mean time from HIV negative to seroconversion (years)	2.0 (1.9)
Independent Variables	
Depression Classes	
Low Depression Throughout (reference)	326
Recent Onset Depression	137
High Depression Throughout	86
Race	
Caucasian	243
African-American	224
Other	82

<sup>1</sup>Some patients did not have information in their medical records on CD4 cell count at HIV diagnosis (9%) or VL at ART start (8%).

<b>Table 2. Association between depression and HIV treatment outcomes</b>			
Self-Reported Adherence ( $\geq 95\%$ of ART doses)			
Variables	OR	95% CI	P-value
Age at HIV diagnosis (per 1 year increase)	1.06	1.02-1.12	0.004
Race			0.003
African American	0.41	0.22-0.76	0.005
Caucasian (reference)	1.49	0.52-4.28	0.459
Recent Onset Depression	0.59	0.32-1.11	0.101
High Depression	0.61	0.29-1.27	0.187
CD4 count at HIV Diagnosis $\geq 500$ cells/uL	0.81	0.46-1.41	0.451
Delay from HIV Diagnosis to ART Start			
Variables	OR	95% CI	P-value
Age at HIV diagnosis	0.91	0.87-0.96	0.001
Race			0.273
African American	1.28	0.82-2.00	0.273
Caucasian (reference)	0.69	0.36-1.33	0.385
Recent Onset Depression	0.92	0.56-1.49	0.818
High Depression	1.17	0.66-2.01	0.603
CD4 count at HIV Diagnosis $\geq 500$ cells/uL	5.22	3.45-7.89	0.001
Continuous ART (Break $<30$ days)			
Variables	OR	95% CI	P-value
Age at HIV diagnosis	0.1	0.96-1.01	0.218
Race			0.671
African American	1	0.67-1.51	0.988
Caucasian (reference)	1.29	0.72-2.31	0.401
Recent Onset Depression	1.28	0.82-2	0.272
High Depression	1.75	0.99-3.09	0.057
CD4 count at HIV Diagnosis $\geq 500$	1.07	0.73-1.57	0.726
Continuous Viral Load Suppression ( $<200$ c/mL)			
Variables	OR	95% CI	P-value
Age at HIV diagnosis	1.01	0.99-1.03	0.451
Race			0.43
African American	0.92	0.6-1.4	0.693
Caucasian (reference)	1.37	0.74-2.53	0.312
Recent Onset Depression	0.58	0.38-0.91	0.017
High Depression	1.15	0.65-2.06	0.63
CD4 count at HIV Diagnosis $\geq 500$	1.15	0.77-1.71	0.495