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# The Association Between Peripheral Oxytocin Levels and Depressive Symptoms in People With HIV

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## ABSTRACT

**Objective:** Depression is common in people with HIV (PWH), yet little is known about the mechanisms contributing to depressive symptoms in PWH. Previous research across a range of populations has suggested a relationship between the neuropeptide oxytocin and depressive symptoms, with variable directionality. This article investigated the association between peripheral oxytocin levels and depressive symptoms in PWH.

**Methods:** Unextracted oxytocin serum concentrations were assayed in 79 PWH (44% female, mean age = 34.35 [8.5], mean body mass index = 25.69 [5.46], mean CD4 = 516.60 [271.15]) who also completed the Center for Epidemiologic Studies Depression Scale (CES-D). CES-D items were evaluated in an exploratory factor analysis (EFA), and the relationships between oxytocin, total CES-D score, and the resulting EFA factors were analyzed with multivariate linear regressions conducted in R. Multiple regression models were used to adjust for age, sex, body mass index, CD4, and education.

**Results:** Contrary to hypothesized, higher peripheral oxytocin levels were associated with higher CES-D total scores with a small-to-moderate effect size ( $\beta = 0.26$ ,  $p = .009$ ). Following Bonferroni correction, oxytocin was not significantly associated with any of the five factors identified from the EFA: depressed affect, positive affect, appetite, cognitive symptoms, or perceived failure ( $p$  values > .042). Small effect sizes were found for the depressed affect ( $\beta = 0.22$ ) and perceived failure ( $\beta = 0.21$ ) factors ( $p$  values > .042).

**Conclusions:** In a sample of predominately Black or African American individuals with HIV, higher oxytocin was associated with higher total depressive symptoms. In addition, this relationship was slightly stronger than those of specific depressive symptoms. These findings warrant further study into the role of oxytocin in mood symptoms within PWH.

**Key words:** HIV, depression, oxytocin.

## INTRODUCTION

Mental health and substance use disorders are the leading cause of years lived with disability worldwide (1,2), representing a significant and growing economic burden with an estimated global expenditure of \$2.5 trillion dollars in 2010 (3,4). Depressive disorders, in particular, account for much of that burden. Globally, depressive disorders were listed as the “single largest contributor to non-fatal health loss,” in the World Health Organization’s 2017 report (5). In the United States, depressive disorders alone represent the fifth most common cause of disability-adjusted life years (6). Depression is associated with numerous negative health-related outcomes, including decreased quality of life (7,8) and increased risk of heart disease (9), hypertension (10), diabetes (11), stroke (12), progression to dementia (13,14), and mortality (15,16).

People with HIV (PWH) are particularly affected by the burden of depressive symptoms. Although estimates vary, research suggests that the prevalence of depressive disorders in PWH is two to four times

higher than in individuals without HIV, with an average of 40% to 42% of PWH experiencing depressive disorders in their lifetime (17,18). Moreover, a recent systematic review estimated the global prevalence rate of comorbid HIV and depression to be 31% from 2000 to 2018 (19), representing a striking contrast from the 2015 global prevalence rate of depression at 4.4% (5). Not only is depression common in PWH, it is also associated with poor medication adherence (20), reduced likelihood of sustained viral suppression (21), missed primary care appointments (22), cognitive impairment (23), and a doubled mortality rate (22) in PWH. Despite common health-related consequences of depression in PWH, depression is a heterogeneous syndrome, and PWH represent a diverse group of individuals. More research is needed on potentially modifiable

**BMI** = body mass index, **CES-D** = Center for Epidemiologic Studies Depression Scale, **EFA** = exploratory factor analysis, **PWH** = people with HIV

## SDC Supplemental Digital Content

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biological factors associated with depression symptoms, especially within diverse, at-risk populations.

One such biological factor is the peptide hormone, oxytocin. Oxytocin is thought to affect and be affected by depressive symptoms through various mechanisms including attenuation of cortisol release in response to stress, attenuation of proinflammatory cytokines, and modulation of brain regions involved in depression (24–28). Previous research has yielded variable results regarding the directionality of the relationship between oxytocin levels and depression. Although some research has demonstrated that low plasma and serum oxytocin levels are associated with depressive symptoms (29–33), other research has found higher oxytocin levels in individuals with higher depressive symptoms (34,35). This ambiguity has been captured in a recent qualitative review (28) and a meta-analysis comparing basal endogenous oxytocin concentrations in patients with depression versus healthy controls (36). Possible reasons for equivocal findings include sample differences in age, sex (27,37), and the clinical severity of depressive symptoms. In addition, heterogeneous findings may be the result of sampling only one or a few time points, which provides only a brief snapshot of the dynamic oxytocin system. Although differing methodologies may also contribute to variable results, they may also allow for sampling oxytocin in different conformational states (38).

Few articles have explored the relationship between oxytocin levels and depressive symptoms in the context of HIV. Fekete et al. (39) conducted bivariate correlations to identify covariates for their main analysis. They found a nonsignificant, less-than-small relationship ( $r = 0.14$ ) between depressive symptoms on the Center for Epidemiologic Studies Depression Scale (CES-D) and plasma oxytocin levels in low-income, racial/ethnic minority women with HIV. Similarly, another sample of 79 PWH found no association between oxytocin levels and depression (40). Seay et al. (41) found a nonsignificant, small, and negative linear relationship between change in depressive symptoms for 10 weeks on the Beck Depression Inventory-II and baseline oxytocin. The relationship was better explained by a significant quadratic term. After an initially negative association, the relationship inverted: as baseline oxytocin levels increased, depression scores during the 10 weeks increased as well. However, their sample included predominantly African American or Caribbean women with HIV. Considering the diversity within PWH, their results warrant additional investigation in other samples as well as further exploration into what role oxytocin may play in the experience of specific symptoms of depression.

In the present study, we aimed to examine the relationship between peripheral oxytocin levels and total self-reported depressive symptoms as well as specific depressive factors in a predominantly Black or African American sample including both men and women with HIV. We hypothesized that higher oxytocin levels would be associated with lower total depression symptoms. Moreover, we expected that oxytocin would be negatively related to nonsomatic mood symptoms (i.e., depressed mood) but not related to somatic symptoms (e.g., appetite changes) or positive affect.

## METHODS

### Participants

Seventy-nine PWH (35 women, 44 men) were included in a secondary analysis from a double-blind, randomized-controlled crossover study on the effect of single administration of 10 mg of low-dose hydrocortisone on cognition in PWH. Information on the parent study has been reported elsewhere

(42,43), and only data from the day of placebo administration were included in the analyses. Inclusion criteria included HIV-seropositive status confirmed by the individual's medical record, an age range of 18 to 45 years, English as a first language, and use of the same combination antiretroviral therapy for at least 3 months. Exclusion criteria were a Structured Clinical Interview for *DSM-IV* mood disorder diagnosis in the past year, a history of anxiety/psychotic disorders, a history of nonalcohol or nicotine-related substance use/dependence in the past 6 months, current use of psychiatric medications, reported neurological conditions impacting cognition (e.g., stroke), body mass index (BMI)  $>40$  kg/m<sup>2</sup>, and use of illicit substances 24 hours before urine toxicology screen. No individuals in the sample were pregnant or had recently given birth. Data were collected from March 2013 to March 2017 through Chicago-based HIV primary care clinics and the surrounding community.

## MATERIALS

### Oxytocin

Oxytocin assays occurred as reported previously (44,45). Briefly, blood samples were drawn once at the same time of day during both sessions to control for circadian rhythm effects (46). Samples were stored in plain tubes, centrifuged (2400g for 15 minutes at 4°C), placed into  $-80^{\circ}\text{C}$  freezers, and assayed in duplicate. Batched samples (placed in dry ice and shipped overnight) were sent to the University of Alabama at Birmingham's General Clinical Research Center for analysis. Oxytocin was quantified at the University of Illinois at Chicago with an enzyme immunoassay (EIA) kit (Assay Designs, Ann Arbor, Michigan; sensitivity of 16 pg/ml, intra-assay coefficient of variance  $<11\%$ ) that is highly specific for oxytocin versus other peptides, as determined by high-performance liquid chromatography (47). Samples were initially run undiluted. Any oxytocin values  $>2000$  pg/ml were rerun to verify their accuracy. Oxytocin levels were not associated with markers of HIV disease progression (Supplemental Digital Content, Table S1, <http://links.lww.com/PSYMED/A861>). Samples were not extracted before the EIA because studies using mass spectrometry demonstrate high levels of oxytocin in plasma and serum, suggesting that methods involving sample extraction remove much of this peptide (48,49). Although some have argued that this approach is reflective of oxytocin and oxytocin-like immunoreactivity (i.e., including other immunoreactive compounds in addition to oxytocin), we will discuss our measurement as oxytocin throughout the article.

### Center for Epidemiologic Studies Depression Scale

Depression symptoms were assessed via the CES-D. The CES-D is a 20-item self-report measure used to assess the frequency of symptoms associated with depression. Internal consistency has been demonstrated to be high in the general population (.85) and in inpatient psychiatric populations (.90) (50). Other studies in PWH have found good internal consistency on the CES-D across a wide range of ages and cultures, including Cronbach  $\alpha$  values of .71 (51), .81 (52), .84 (53), .91 (54), and .92 (55). The internal consistency of the CES-D in our sample also demonstrated acceptable reliability (Cronbach  $\alpha = .79$ ). Although not diagnostic, scores of 16 or greater are associated with increased risk for clinical diagnoses of depression, although a recent meta-analysis including 28 studies and 10,617 individuals found better sensitivity and specificity with a cutoff score of 20 (56). The average CES-D total score in this sample was under the clinical cutoff (mean = 13.32) with a range of 1 to 34. The CES-D has been used globally in PWH, including in Vietnam (52), Botswana (57), women in the United States (58),

and Italy (59), among others. Initial principle components analysis of CES-D items identified a four-factor structure with depressed affect, positive affect, somatic symptoms, and interpersonal factors (50). Subsequent confirmatory factor analyses in PWH have also validated a four-factor structure (52,58).

### Statistical Analyses

Before the analysis, data were evaluated for outliers by using the interquartile rule and examining leverage indices for each participant. Of the 80 total participants with available data for both oxytocin and CES-D, oxytocin was the only variable with an outlier value ( $n = 1$ ) that was removed from analyses. A multivariable linear regression model was conducted to examine the association between oxytocin and the CES-D total score. Covariates included in the analyses were based on the literature and included age, education (<high school, high school, some college/college), sex (60–62), BMI (in kilograms per meter squared) (63,64), and CD4 count (in cells per microliters) (65). For the full covariate inclusion rationale, please see Supplemental Digital Content, <http://links.lww.com/PSYMED/A861>.

To better understand the relationship between oxytocin and types of depressive symptoms, we first conducted an exploratory factor analysis (EFA) on the CES-D items, using a polychoric matrix for ordinal variables. The EFA followed a principal axis factor analysis with a maximum likelihood factor method and unrotated factor solution. See Supplemental Digital Content, Table S2, <http://links.lww.com/PSYMED/A861>, for factor loadings. The factor loadings were used in a series of subsequent multivariable linear regressions to determine associations between oxytocin and specific types of depressive symptoms (e.g., depressed affect, positive affect, etc.). Bonferroni corrections were applied for multiple comparisons between these secondary outcomes. All analyses were completed in R version 4.0.4 (2021-02-15, “Lost Library Book”) (66).

## RESULTS

### Sample Characteristics

The sample was predominately Black or African American ( $n = 74$ ) with one individual who identified as White and four who identified as more than one race. Average age was 34.35 years with a range of 18.49 to 45.93 years. Less than half of the sample had undetectable HIV RNA levels ( $n = 32$ ; 42%), with 36% of those with detectable HIV RNA having >200 copies/ml. The sample had a mean CD4 count of 538.0 cells/mm<sup>3</sup> with a range of 5 to 1208 cells/mm<sup>3</sup>, and the average number of years lived with HIV was 10 with a range of 0.38 to 24.18 years. Thirty-one individuals completed at least some college or a bachelor's degree, 24 had a high school diploma, and 24 completed some high school or less. See Table 1 for further descriptive statistics.

### Relationship Between Oxytocin and Depressive Symptoms

In the sample of 79 PWH, the overall regression equation was significant, explaining 28.3% of the variance in CES-D total scores (Table 2;  $R^2_{\text{adjusted}} = 0.28$ ,  $F(7,71) = 5.40$ ,  $p < .001$ ). In particular, higher peripheral oxytocin levels were associated with higher CES-D scores with a small-to-moderate effect size ( $t(71) = 2.70$ ,  $p = .009$ ,  $\beta = 0.26$ ). Of the covariates, being female ( $t(71) = 3.33$ ,  $p = .001$ ,  $\beta = 0.38$ ), higher CD4 count ( $t(71) = 2.31$ ,  $p = .024$ ,  $\beta = 0.24$ ), and lower BMI ( $t(71) = -4.31$ ,  $p < .001$ ,  $\beta = -0.51$ ) were associated with higher depressive symptoms. The unadjusted Pearson

**TABLE 1.** Study Characteristics of the Total Sample ( $N = 79$  PWH)

Variable	<i>n</i> (%) or Mean (SD)
Demographics	
Female	35 (44%)
Race	
Black or African American	74 (94%)
White	1 (1%)
More than one race	4 (5%)
Education	
Some high school or less	24 (30%)
High school graduate	24 (30%)
Some college or college graduate	31 (39%)
Age, y	34.35 (8.48)
Body mass index, kg/m <sup>2</sup>	25.69 (5.46)
HIV RNA ( $n = 76$ )	
>200 copies/ml	16 (36%)
<200 copies/ml	28 (64%)
Undetectable (<50 copies/ml)	32 (42%)
Years with HIV	10.01 (6.47)
CD4 count, cells/ $\mu$ l	516.50 (271.15)
CES-D total	13.32 (8)
Peripheral oxytocin level, pg/ml	1538.40 (365.51)

PWH = people with HIV; SD = standard deviation; CES-D = Center for Epidemiologic Studies Depression scale.

correlation coefficient between peripheral oxytocin levels and depressive symptoms on the CES-D was small and positive ( $r = 0.23$ ).

Next, we examined associations between oxytocin and the five factors generated from the EFA: a) factor 1—depressed affect (explained 34.6% of the variance in the CES-D), b) factor 2—positive affect (explained 9.4% of the variance), c) factor 3—appetite (explained 4.2% of the variance), d) factor 4—cognitive symptoms (explained 14.2% of the variance), and e) factor 5—perceived failure (explained 5.3% of the variance). In follow-up multivariate linear regressions (Table 3), oxytocin levels were not significantly associated with any factors following Bonferroni correction: factor 1—depressed affect ( $t(74) = 2.07$ ,  $p = .042$ ,  $\beta = 0.22$ ,  $R^2_{\text{multiple}} = 0.25$ ), factor 2—positive affect ( $t(67) = 0.19$ ,  $p = .85$ ,  $\beta = 0.02$ ,  $R^2_{\text{multiple}} = 0.13$ ), factor 3—appetite ( $t(67) = 0.14$ ,  $p = .80$ ,  $\beta = 0.015$ ,  $R^2_{\text{multiple}} = 0.17$ ), factor 4—cognitive symptoms ( $t(67) = -0.82$ ,  $p = .41$ ,  $\beta = 0.015$ ,  $R^2_{\text{multiple}} = 0.09$ ), and factor 5—perceived failure ( $t(67) = 1.78$ ,  $p = .08$ ,  $\beta = 0.21$ ,  $R^2_{\text{multiple}} = 0.10$ ).

## DISCUSSION

Counter to our hypothesis, higher peripheral oxytocin levels were associated with higher total depressive symptoms in PWH. Given the heterogeneity of findings on the association between oxytocin and depression in people without HIV, this result is not altogether surprising. As discussed previously, these findings are consistent with numerous studies demonstrating positive relationships between oxytocin and depressive symptoms. These results are also partially consistent with longitudinal conclusion reported by Seay et al. (41) indicating a U-shaped relationship between oxytocin levels and change in depression from baseline to 10 weeks in

**TABLE 2.** Multivariate Linear Regression Statistics for Oxytocin and Covariates Predicting Total Depression Symptoms on the CES-D in 79 PWH

Variable	<i>B</i>	SE	<i>t</i>	<i>p</i>	$\beta$	95% CI
Oxytocin	0.01	0.002	2.70	.009	0.26	0.257 to 0.265
Age	0.08	0.10	0.79	.43	0.08	-0.11 to 0.27
Sex	6.12	1.84	3.33	.001	0.38	-3.29 to 4.05
Some HS or less	1.17	2.01	0.58	.56	0.68	-3.94 to 4.08
Some college or college graduate	-3.52	1.88	-1.87	.66	-0.22	-3.97 to 3.54
CD4	0.01	0.003	2.31	.024	0.24	0.23 to 0.25
BMI	-0.75	0.17	-4.31	<.001	-0.51	-0.86 to -0.17

CES-D = Center for Epidemiologic Studies Depression scale; PWH = people with HIV; SE = standard error;  $\beta$  = standardized beta; CI = confidence interval; HS = high school; BMI = body mass index.

Education reference group is high school graduate.

African American or Caribbean women with HIV. Although, their results are difficult to compare with the current study because of differences in oxytocin measurement (i.e., extracted versus unextracted) and study design (i.e., longitudinal versus cross-sectional). The researchers proposed that at low-to-moderate levels, oxytocin may have a protective effect on depressive symptoms. However, very low and high levels of oxytocin were associated with either no change or worsening depressive symptoms, potentially representing dysregulated oxytocinergic pathways. Given the paucity of literature examining oxytocin levels and depression in PWH, our results are among the first to demonstrate a relationship between oxytocin and depressive symptoms and are the first to establish significant positive linear directionality. Nevertheless, the directionality of the relationship may change in a broader sample, particularly in individuals with higher depressive symptoms or those meeting the criteria for a depressive disorder, as the average CES-D score for this sample was below the clinical cutoff.

Follow-up EFA of the CES-D in this sample yielded a five-factor model comprising a) depressed affect, b) positive affect, c) appetite, d) cognitive symptoms, and e) perceived failure. Although not as widely used in comparison to the four-factor model, a five-factor model has been proposed previously. In this case, the fifth factor related to feelings of worthlessness, including perceived failure similar to the fifth factor generated in our analysis (67). After Bonferroni correction, oxytocin levels did not significantly relate to any of the factors; however, small effect sizes were noted for the depressed affect and perceived failure factors. These results are consistent with our understanding of depression as a heterogeneous syndrome with the potential for differing symptom profiles between individuals. Rather than associate with specific subcomponents of depressive symptoms, oxytocin significantly associated with the total depressive symptom profile, including the combination of affective, cognitive, and physical symptoms that together comprise depression. The effect size between oxytocin and total depressive symptoms was also slightly larger than those for both the depressed affect and perceived failure factors, although more research is needed to replicate this finding.

The mechanisms behind the relationship between oxytocin and depressive symptoms in PWH are likely complex because oxytocin could have a protective or facilitatory role in depressive symptoms and possibly be influenced by HIV. Although speculative, the relationship between increased oxytocin and increased depressive

symptoms found in our sample may reflect an anti-inflammatory role of oxytocin. As a result of the HIV virus, PWH experience chronic inflammation even when on antiretroviral therapy for HIV (68,69). High levels of psychological distress (e.g., depression) that are common in PWH can further exacerbate levels of inflammation, which in turn may further worsen mental health conditions (70). In response to these challenges, oxytocin may be released to lower inflammation and stress levels via reducing activity in the hypothalamic-pituitary-adrenal axis, reducing activity in the sympathetic nervous system, and increasing activity in the parasympathetic nervous system (71). Previous work in PWH indicates a positive relationship between perceived stress and CD4 T-lymphocyte count in individuals with high levels of plasma oxytocin. In contrast, in PWH with low oxytocin levels, as stress increased, CD4 cell count decreased (39). These results suggest that the association between perceived stress and CD4 immune cell count varied by oxytocin level.

Further illustrating a link between oxytocin and stress, acute oxytocin administration has been shown to increase individual sensitivity to a wide range of social information in the environment (72). In high-stress environments, this could make individuals vulnerable to negative affective consequences. Previous research has shown differences in levels of dispositional empathy, sympathetic nervous system activity, and subjective arousal by oxytocin receptor genotype in individuals viewing a 28-minute mixed martial arts fight. Individuals with an A allele were lower on all three measures than those homozygous for the G allele (73). Other research has found that individuals homozygous for the A allele reported elevated feelings of alienation, increased levels of suicidal ideation, and elevated depressive symptoms, suggesting that oxytocin might increase the salience of social stimuli, positive or negative, and increase the risk of negative mental health outcomes in some individuals as a result (74).

In addition, impaired function of the hypothalamic-pituitary-thyroid axis, previously reported in PWH (75–77), may contribute to the relationship between depression and oxytocin reported in the present study. Although little is known about changes to the oxytocin system as a result of HIV, previous research in 20 individuals with AIDS found 40% less oxytocin-expressing neurons in the hypothalamus compared with 10 controls upon autopsy (78). Almost two decades later, autopsy of four individuals with AIDS, encephalitis, and substance use found HIV in hypothalamic tissue and 81% fewer oxytocin immunoreactive neurons compared with two controls (76).

**TABLE 3.** Multivariate Linear Regression Statistics for Oxytocin and Covariates Predicting Individual EFA Factors in PWH

Variable	<i>b</i>	SE	<i>t</i>	Sig.	$\beta$	95% CI
<b>Depressed affect factor</b>						
Oxytocin	0.001	0.001	2.07	.042	0.22	0.22 to 0.22
Age	0.003	0.01	0.22	.83	0.025	0.002 to 0.048
Sex	0.54	0.22	2.44	.017	0.31	-0.14 to 0.75
Some HS or less	0.17	0.24	0.40	.49	0.089	-0.40 to 0.57
Some college or college graduate	-0.31	0.23	-1.35	.18	-0.17	-0.62 to 0.28
CD4	0.001	<0.001	1.83	.072	0.21	0.21 to 0.21
BMI	-0.07	0.02	-3.24	.002	-0.43	-0.47 to -0.38
<b>Positive affect factor</b>						
Oxytocin	<0.001	<0.001	0.19	.85	0.02	0.021 to 0.022
Age	0.027	0.013	2.11	.039	0.25	0.23 to 0.28
Sex	-0.21	0.25	-0.83	.41	-0.11	-0.60 to 0.38
Some HS or less	0.29	0.27	1.06	.30	0.14	-0.40 to 0.69
Some college or college graduate	-0.18	0.25	-0.71	.48	-0.096	-0.60 to 0.41
CD4	<0.001	<0.001	1.66	.10	0.21	0.20 to 0.21
BMI	-0.003	0.024	-1.44	.15	-0.20	-0.25 to -0.16
<b>Appetite factor</b>						
Oxytocin	<0.001	<0.001	0.14	.89	0.015	0.01 to 0.02
Age	0.004	0.013	-0.30	.77	-0.035	-0.06 to -0.01
Sex	-0.17	0.26	-0.65	.52	-0.086	-0.60 to 0.43
Some HS or less	0.86	0.28	3.04	.003	0.40	-0.15 to 0.97
Some college or college graduate	0.32	0.26	1.20	.23	0.16	-0.37 to 0.69
CD4	<0.001	<0.001	-0.39	.70	-0.05	-0.05 to -0.05
BMI	0.049	0.025	1.97	.053	0.27	0.22 to 0.32
<b>Cognitive symptoms factor</b>						
Oxytocin	<-0.001	<0.001	-0.82	.41	-0.10	-0.01 to -0.01
Age	0.014	0.014	1.00	.32	0.12	0.10 to 0.15
Sex	0.38	0.26	1.46	.15	0.20	-0.32 to 0.72
Some HS or less	-0.30	0.29	-1.04	.30	-0.14	-0.72 to 0.43
Some college or college graduate	0.19	0.27	0.72	.47	0.10	-0.44 to 0.64
CD4	<-0.001	<0.001	-0.11	.92	-0.01	-0.01 to -0.01
BMI	-0.028	0.025	-1.11	.27	-0.16	-0.21 to -0.11
<b>Perceived failure factor</b>						
Oxytocin	<0.001	<0.001	1.78	.079	0.21	0.21 to 0.21
Age	-0.013	0.014	-0.95	.34	-0.12	-0.15 to -0.09
Sex	-0.79	0.27	-0.30	.77	-0.04	-0.57 to 0.49
Some HS or less	-0.38	0.29	-1.32	.19	-0.18	-0.77 to 0.40
Some college or college graduate	-0.22	0.27	-0.80	.43	-0.11	-0.66 to 0.43
CD4	<-0.001	<0.001	-0.12	.91	-0.015	-0.02 to -0.01
BMI	0.027	0.025	1.06	.29	0.15	0.10 to 0.20

EFA = exploratory factor analysis; PWH = people with HIV; SE = standard error;  $\beta$  = standardized beta; CI = confidence interval; HS = high school; BMI = body mass index. Education reference group is high school graduate.

Although these studies represent small samples of people with severely progressed HIV and comorbidities, they provide important evidence that HIV may affect systems related to oxytocin as well as neurons expressing oxytocin. More research is needed on the oxytocin system in PWH, particularly how oxytocin may relate to their high burden of mental health conditions, such as depression. Mechanistic and administration studies will be critical for evaluating the role of oxytocin in depressive symptoms in PWH

compared with individuals without HIV. In addition, longitudinal studies will be necessary to determine how dynamic interactions between oxytocin and depressive symptoms covary over time.

### Limitations

Although the study had several strengths, including its measurement of oxytocin at the same time of day and its investigation into which aspects of depression oxytocin may relate to specifically,

the study had several limitations. The oxytocin system is a dynamic system, interacting with and influenced by various factors. As a cross-sectional analysis, our study was only able to analyze the association at one point in time. As a result, it cannot address causation or how oxytocin and depressive symptoms may covary over time. In addition, without a control group, the study was unable to compare PWH with individuals without HIV to determine if the relationship between oxytocin and depressive symptoms varied by HIV status. Furthermore, although our sample meets the criteria for an EFA, future analyses should incorporate larger samples. Finally, although the sample included a normal distribution of CES-D scores, the average total score was below the questionnaire's clinical cutoff. As a result, future analyses conducted in PWH meeting the criteria for current depressive disorders will be important to better understand the relationship between oxytocin and depressive symptoms in PWH.

Another limitation to our study is the lack of consensus regarding the best method to measure oxytocin, as the debate is ongoing. A review article by MacLean et al. (38) summarized some of the difficulties with oxytocin measurement. Mainly, common oxytocin measurement methods often are not correlated with each other, and concentrations of oxytocin can vary by an order of magnitude. However, they noted that these differences do not mean that some methods are valid and others are not, as we may all be sampling different parts of the system. The data analyzed in this article include unextracted methods, which have been shown to produce significantly higher oxytocin concentrations than extracted methods (79,80). As a result, multiple articles have highlighted the rationale behind the use of extraction in oxytocin assays (79–81), noting that unextracted assays may tag oxytocin and other molecules (81). In some cases, however, extraction may remove significant amounts of oxytocin bound to plasma proteins, thus only measuring free oxytocin rather than total oxytocin (38,49). The decision to measure oxytocin without extraction was based on the previously established validity of the method as well as its association with clinically relevant behavioral measures. Results from tests for parallelism, spike recovery, and cross-reactivity/specificity have validated the ability of the present study's EIA procedure to provide useful measurements of oxytocin in human blood plasma (38,47). Moreover, studies comparing unextracted and extracted methods have found statistically stronger relationships between behavior and unextracted blood samples rather than extracted samples (82–84). Future replication of the current study with extracted oxytocin measurements will be important to determine the influence of oxytocin measurement on depressive symptoms in PWH.

## CONCLUSIONS

In a sample of predominately Black or African American individuals with HIV, higher oxytocin levels were associated with higher total depressive symptoms. In addition, the relationship between oxytocin and total depressive symptoms in PWH was slightly stronger than those between oxytocin and specific factors identified via EFA. Although the mechanism of action is complex and remains unknown, these results are among the first to establish a relationship between peripheral oxytocin levels and depressive symptoms in PWH. These findings warrant further study into the role of oxytocin in mood symptoms within PWH.

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