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Post-traumatic Stress Disorder, Cocaine Use, and HIV Persistence

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Abstract

Background Post-traumatic stress disorder (PTSD) and stimulant use disorders are highly prevalent, commonly co-occur, and predict faster clinical HIV progression. However, scant research has examined if PTSD and cocaine use are associated with the HIV reservoir that persists in immune cells, lymphoid tissue, and organs of people living with HIV that are receiving effective treatment.

Method This cross-sectional study enrolled 48 HIV-positive persons with sustained undetectable viral load (< 20 copies/mL) in the past year to examine the associations of PTSD and recent cocaine use with two measures of HIV persistence in immune cells: (1) proviral HIV DNA and (2) cell-associated (CA)-HIV RNA.

Results Greater PTSD symptoms were significantly associated with lower proviral HIV DNA ($r = -0.30$, $p = 0.041$) but not with CA-HIV RNA. Greater severity of PTSD symptom clusters for intrusions (Standardized Beta = − 0.30, $p = 0.038$) and hyperarousal (Standardized Beta = − 0.30, $p = 0.047$) were independently associated with lower proviral HIV DNA. Although participants with recent cocaine use had a significantly shorter duration of sustained undetectable HIV viral load (19.9 versus 26.9 months; $p = 0.047$), cocaine use was not significantly associated with proviral HIV DNA or CA-HIV RNA.

Conclusion Further research is needed to examine the potentially bi-directional pathways linking PTSD symptom severity and HIV persistence.

Keywords Cocaine · HIV persistence · Proviral HIV DNA · PTSD · VACS Index

Introduction

Post-traumatic stress disorder (PTSD) as well as stimulant use disorders are prevalent and commonly comorbid among people living with HIV. Nearly two-thirds of people living with HIV will experience two or more traumatic events in their lifetime [1, 2], and at least one third of HIV-positive persons have PTSD [1, 3]. Similarly, up to 40% of HIV-positive persons report either current or past use of stimulants such as powder cocaine, crack-cocaine, or methamphetamine [4, 5]. Consistent with negative reinforcement models of addiction [6], problematic patterns of substance use become an overlearned responses to escape or avoid PTSD symptoms. In fact, PTSD has been associated with more a 4.5-fold greater risk for developing a substance use disorder [7]. Among those seeking treatment for a cocaine use disorder, 42% meet criteria for lifetime PTSD [8] and one-in-five screen positive for current PTSD [9]. Interestingly, individuals with co-occurring PTSD and substance use disorders report more lifetime traumatic events as well as greater severity of avoidance and hyperarousal symptoms [10].

In the modern anti-retroviral therapy (ART) era, the medical management of HIV has improved substantially. Many people living with HIV take one pill daily with far fewer side effects, and favorable medication resistance profiles are more forgiving of ART non-adherence [11]. As a result, there has been a dramatic increase in viral suppression rates in the USA from 32% in 1997 to 86% in 2015 [12]. It is also evident that increasingly greater numbers of stimulant users and those living with other psychiatric comorbidities are able to achieve

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viral suppression [12, 13]. Although many patients receiving effective ART can maintain undetectable viral load in plasma, current treatments are unable to eradicate HIV in immune cells, lymphoid tissue, and organs [14, 15], which is commonly referred to as the latent HIV reservoir.

One prominent theory informing HIV cure research is focused on understanding the mechanisms of HIV latency reversal to inform "wake and kill" approaches to eliminate HIV reservoirs [16, 17]. This includes inducing HIV production in quiescent CD4+ T cells that are infected to facilitate immune clearance [18]. To date, proviral HIV DNA and cell-associated (CA)-HIV RNA are two of the most common biomarkers indexing persistence of a latent HIV reservoir in immune cells. Proviral HIV DNA is the amount of HIV DNA that is integrated into the host DNA. This includes both replication competent and defective virus [19, 20], and proviral HIV DNA is often harbored in central memory T cells displaying checkpoint inhibitors like PD1 that aid with evasion of immune clearance [18, 21]. The clinical relevance of proviral HIV DNA is supported by prior research indicating that greater proviral HIV DNA in monocytes predicts clinically relevant outcomes such as HIV-associated neurocognitive disorders [22]. On the other hand, CA-HIV RNA quantifies the amount of HIV RNA being manufactured inside a CD4+ T cell [20, 23, 24]. CA-HIV RNA is generally thought to index active replication of HIV and consequently is considered to be one marker of HIV latency reversal [23]. Clinical research characterizing the bio-behavioral pathways relevant to HIV persistence would advance our basic understanding of viable targets for latency reversal agents in HIV cure studies.

Trauma and stimulant use could influence HIV persistence in immune cells because both have been shown to predict faster clinical progression among people living with HIV [25]. Traumatic events predict faster all-cause and AIDS-related mortality, even after adjusting for baseline CD4+ T cell count and plasma HIV viral load [2]. Similarly, more frequent stimulant use is also associated with faster clinical HIV progression in both men and women after adjusting for ART non-adherence [26–28]. More research in treated HIV infection is needed to examine the bio-behavioral mechanisms linking PTSD and stimulant use with HIV persistence.

PTSD symptoms are often characterized by increases in hyperarousal (e.g., constantly feeling watchful or on guard; an exaggerated startle response) that lead to chronic activation of the autonomic nervous system (ANS) as well as persistent elevations in norepinephrine (NE) and other catecholamines [29]. For example, people living with PTSD display higher urinary NE when compared to those without PTSD as well as other psychiatric patient populations [30, 31]. The clinical relevance of neuroendocrine dysregulation is supported by findings from one cohort study indicating that higher urinary cortisol and NE independently predicted greater plasma HIV viral load [32]. Findings from Sloan and colleagues [33] also underscore the potential relevance of the ANS for HIV reservoirs such that SIV replication was 3.9-fold greater where sympathetic nerve terminals juncture with primate lymph nodes. Interestingly, there is some evidence that measures of ANS activation during an acute laboratory stressor are associated with increases in CA-HIV RNA, which may reflect HIV latency reversal [34]. Although further research is clearly needed, ANS activation is one biologically plausible pathways whereby PTSD could influence HIV persistence.

Prior research also provides some indication that the use of stimulants could contribute to HIV persistence. One in vitro study by Addai and colleagues [35] showed that cocaine induced increases in proviral HIV DNA integration into host cell DNA. This is supported by findings from a recent cross-sectional study where HIV-positive methamphetamine users with undetectable HIV viral load displayed greater proviral HIV DNA and greater immune exhaustion relative to HIV-positive non-users [36]. Other recent studies with HIV-positive, methamphetamine-using sexual minority men receiving effective HIV treatment observed that those who engaged in recent stimulant use displayed upregulation of genes relevant to HIV persistence, greater monocyte activation, and higher inflammation [37, 38]. Finally, social support for methamphetamine abstinence has previously been associated with lower proviral HIV DNA [39]. Further clinical research is needed to understand whether and how cocaine use is associated with measures of HIV persistence.

This cross-sectional pilot study examined the associations of PTSD and cocaine use with measures of HIV persistence in those with sustained undetectable viral load. We hypothesized that participants with elevated PTSD symptoms would display higher proviral HIV DNA and CA-HIV RNA. Similarly, we hypothesized that cocaine use would be associated with higher proviral HIV DNA and CA-HIV RNA.

Methods

In total, 48 HIV-positive individuals on ART with an undetectable HIV viral load for at least 1 year were recruited from the community and a large public HIV clinic. During a screening visit, informed consent and Health Insurance Portability and Accountability Act (HIPAA) release forms were completed. Inclusion criteria, assessed by reviewing medical records, were (1) 18 years of age or older and (2) evidence of sustained undetectable viral load (HIV viral load < 20 copies/ml) for at least 1 year prior to enrollment. All participants could have no more than one instance of low viremia less than 100 copies/mL during the past year where they displayed sustained undetectable viral load. Individuals with evidence of co-morbid HCV were excluded. Enrolled participants completed an assessment battery of psychosocial measures, on-site urine drug toxicology testing, and a blood draw to gather

relevant HIV biomarkers. All participants received $40 for completing the study visit, and study procedures were approved by the Institutional Review Board at the University of Miami with concurrent approval from Jackson Memorial Hospital.

Measures

PTSD Symptoms The PTSD Checklist for the Diagnostic and Statistical Manual of Mental Disorders–5 (DSM-5) is a validated, 20-item measure examining the severity of PTSD symptoms [40]. Total PTSD symptom severity was calculated (range 0–80) with higher scores indicating greater severity (Chronbach's $\alpha = 0.95$). In addition, sub-scale scores measuring symptom severity within each PTSD symptom cluster for DSM-5 were calculated: Intrusions (Cluster B), Avoidance (Cluster C), Negative Affect (Cluster D), and Hyperarousal (Cluster E).

Cocaine Use Participants provided a urine sample for on-site toxicology testing during the assessment visit using the 4-panel iCup by Alere Toxicology [41] to obtain biological confirmation of recent stimulant use within the past 72 h. Substances included on this panel were cocaine, methamphetamines, tetrahydrocannabinol (THC), and opiates. In addition, the World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) was administered as a validated self-report measure of substance use [42, 43]. Participants who provided a urine sample that was reactive for cocaine metabolites as well as those who reported any cocaine use in the past 3 months on the ASSIST were classified as engaging in recent cocaine use. Four participants who tested positive for cocaine in urine reported no cocaine use in the past 3 months. None of the urine samples provided by participants were reactive for methamphetamine.

HIV-Related Indicators Duration of sustained undetectable HIV viral load (without any instances of low level viremia) up to the assessment visit, time since HIV diagnosis, and CD4+ T cell count were collected via medical chart abstraction.

HIV Persistence Peripheral blood mononuclear cells (PBMCs) were isolated and simultaneously analyzed for total proviral HIV DNA and CA-HIV RNA. Total proviral DNA was purified using AllPrep DNA/RNA kit (Qiagen) according to the manufacturer's protocol. Quantitation of viral DNA was performed by droplet digital polymerase chain reaction (ddPCR) using a Bio-Rad QX200 ddPCR instrument. Following PCR amplification, a flow cytometry analysis was used to determine the fraction of PCR-positive droplets in the original sample. This data was then analyzed using Poisson statistics, implemented in Bio-Rad QuantaSoft v. 1.7.4, to determine the target DNA template concentration in the original sample. Total CA-HIV RNA was also extracted from the PBMCs using the AllPrep Mini Kit from Qiagen (catalog #80204). The total CA-HIV RNA was quantitated using the Superscript III Platinum One Step qRT-PCR Kit Catalog #11732-088 with primers and probe specific for the long terminal repeat sequence.

ART Measures Participants self-reported when they first began ART. Adherence was assessed using a visual analogue scale (VAS) which requires individuals to rate on a line from 0 to 100% the proportion of ART medications that they took in the past 30 days [44, 45].

VACS Index The Veterans Aging Cohort Study (VACS) Index is a validated surrogate marker that predicts all-cause mortality in those living with HIV infection [46, 47]. The VACS Index has been shown to discriminate risk of mortality more effectively than standard HIV disease markers, especially among those with undetectable viral load and people aged 50 years or older [46, 47]. The VACS Index (range 0 to 164) was calculated by summing scores for differentially weighted parameters including age, hemoglobin, HIV disease markers (i.e., CD4+ T cell count and plasma HIV RNA), general indicators of organ system injury, and the presence of HCV antibodies. Higher scores indicate greater health risk. Indicators for the VACS Index were extracted from the medical records in the year prior to study enrollment and obtained from comprehensive metabolic panels conducted as part of this project.

Statistical Analysis Bivariate associations of PTSD and recent cocaine use with measures of HIV persistence were examined using Pearson correlations as well as independent samples t tests, respectively. Informed by results of these analyses, a series of multiple linear regression models were fit to examine total PTSD severity as well as severity within each PTSD symptom cluster as correlates of $\log_{10}$ proviral HIV DNA, controlling for the VACS Index. We chose to control for the VACS Index because it includes measures of multi-organ system damage, which could potentiate pathophysiologic processes (e.g., inflammation) that amplify HIV persistence in immune cells. Results of multiple linear regression models are reported as unstandardized (b) and standardized (β) coefficients. The alpha level for significance was set to less than 0.05 (two-tailed) for each analysis.

Results

The majority of the sample was Black/African-American (77%), male (54%), and heterosexual (74%). Most participants graduated high school (62%) and more than half were currently on disability (58%). Age ranged from 26 to 76 years

Table 1 Participant characteristics ($N = 48$)

	n	(%)	
Race/ethnicity			
Black or African-American, non-Hispanic	37	(77.1%)	
White, non-Hispanic	1	(2.1%)	
Multi-racial/multi-cultural	1	(2.1%)	
Hispanic or Latino	6	(12.5%)	
Afro-Caribbean	3	(6.3%)	
Gender			
Male	26	(54.2%)	
Female	21	(43.8%)	
Transgender female	1	(2.1%)	
Sexual orientation			
Heterosexual	46	(74.4%)	
Gay/lesbian	9	(14.8%)	
Bisexual	6	(9.8%)	
Education			
Did not graduate high school	18	(37.5%)	
High school graduate	16	(33.3%)	
Some college or trade school	9	(18.8%)	
College graduate	5	(10.4%)	
On disability	28	(58.3%)	
Recent cocaine use[a]	24	(50.0%)	
	M	(SD)	Range
Age (years)	51.5	(9.9)	26.2–75.7
Health-related indicators			
BMI	28.6	(6.4)	15.9–42.4
Time since HIV diagnosis (years)	15.2	(8.3)	0.6–32.5
ART adherence (range 0% to 100%)	96.6	(8.5)	50.0–100.0
Years since began ART	13.8	(8.0)	0.6–32.5
CD4+ T-cell count (cells/mm^3)	791.8	(351.3)	204.0–1634.0
Proviral HIV DNA	171.3	(336.6)	0.0–2220.0
Proviral HIV DNA (log10)	1.80	(1.93)	0.0–3.35
Cell-associated HIV RNA	1.47	(5.6)	0.0–36.8
Cell-associated HIV RNA (log10)	− 0.09	(0.5)	− 1.24–1.57
Duration of viral suppression (months)	23.4	(12.3)	1.0–47.9
VACS Index	24.7	(15.9)	0.0–71.0

ART anti-retroviral therapy, *BMI* body mass index, *VACS* Veteran's Aging Cohort Study

[a] Any self-reported cocaine use in the past 3 months or reactive urine toxicology for cocaine

with a mean of 52 (SD = 10). The mean CD4+ T cell count was 791 (SD = 351) cells/mm^3, and participants were highly adherent to ART such that they reported taking a mean of 96.6 (SD = 8.5)% of doses in the past month. One in five participants screened positive for PTSD (21%) and half (50%) were classified as engaging in recent cocaine use. Sample characteristics are presented in Table 1.

As shown in Table 2, we observed a moderate, negative association of higher PTSD symptom severity with lower proviral HIV DNA. However, there were no significant associations of any measure of PTSD symptom severity with CA-HIV RNA. There was a moderate positive association of a greater VACS Index with higher proviral HIV DNA, and a moderate negative association of higher proviral HIV DNA with lower CA-HIV RNA. Finally, time on ART, ART adherence, and duration of sustained undetectable HIV viral load were not significantly associated with either proviral HIV DNA or CA-HIV RNA. As shown in Table 3, recent cocaine users had a significantly shorter duration of sustained undetectable HIV viral load. However, recent cocaine use was not significantly associated with proviral HIV DNA or CA-HIV RNA.

Table 2 Correlates of HIV persistence ($N = 48$)

		1	2	3	4	5	6	7	8	9	10
1	Proviral HIV DNA (Log_{10})	–									
2	Intracellular HIV RNA (Log_{10})	− .357*	–								
3	PTSD total severity	− .297*	.122	–							
4	PTSD Cluster B (intrusions) severity	− .340*	.087	.922**	–						
5	PTSD Cluster C (avoidance) severity	− .302*	.112	.923**	.916**	–					
6	PTSD Cluster D (negative affect) severity	− .132	.112	.907**	.722**	.801**	–				
7	PTSD Cluster E (hyperarousal) severity	− .336*	.136	.882**	.740**	.705**	.738**	–			
8	VACS Index	.300*	− .134	.018	− .100	− .062	.116	.072	–		
9	Time on ART	.087	− .283	− .003	.038	.033	− .014	− .056	.048	–	
10	ART adherence	.021	− .144	.050	.107	− .032	.074	− .025	.049	.107	–
11	Duration of viral suppression	− .057	.152	− .036	− .064	− .093	− .040	.044	.282	.199	.049

ART antiretroviral treatment, *PTSD* post-traumatic stress disorder, *VACS* Veteran's Aging Cohort Study
*$p < 0.05$; **$p < .01$

Results from all multiple linear regression models are presented in Table 4. After adjusting for the VACS Index, greater severity of PTSD cluster B symptoms (intrusions) was significantly associated with lower proviral HIV DNA. This model accounted for 20% of the variance in proviral HIV DNA. Similarly, greater severity of PTSD cluster E symptoms (hyperarousal) was associated with lower proviral HIV DNA after adjusting for the VACS Index. This model accounted for 19% of the variance in proviral HIV DNA.

Discussion

To our knowledge, this study is among the first to examine the relationship between PTSD symptoms and measures of HIV persistence. Interestingly, we observed that greater PTSD symptom severity was associated and lower proviral HIV DNA. Because lower proviral DNA was also associated with higher CA-HIV RNA, it is plausible that decreases in proviral DNA reflect an indirect induction of HIV production in immune cells (wake). Inducing HIV production could facilitate recognition and clearance of infected cells by the immune system (kill). Although greater PTSD symptom severity was associated with higher CA-HIV RNA, this did not reach statistical significance. Further research is needed to replicate and extend these findings by examining the prospective, potentially bi-directional associations of PTSD symptom severity with measures of HIV persistence.

PTSD symptom clusters which are generally thought to be characterized by excessive ANS activation were

Table 3 Correlates of recent cocaine use ($N = 48$)

	Recent cocaine use ($n = 24$)	No recent cocaine use ($n = 24$)		
	M (SD)	M (SD)		p value
Age	52.5 (9.3)	50.2 (10.5)	t[[46]] = − 0.81	0.422
BMI	29.0 (6.8)	28.2 (6.0)	t[[45]] = − 0.44	0.664
Time since HIV diagnosis (years)	16.9 (8.5)	13.4 (7.9)	t[[44]] = − 1.46	0.152
ART adherence (range 0 to 100%)	97.6 (4.3)	95.6 (11.3)	t[[46]] = − 0.83	0.408
Years since began ART	15.0 (8.5)	12.6 (7.5)	t[[45]] = − 1.02	0.311
Proviral HIV DNA (Log10)	1.9 (0.7)	1.7 (0.8)	t[[46]] = − 0.72	0.477
Intracellular HIV RNA (Log10)	− 0.1 (0.5)	− 0.1 (0.6)	$t(46) = 0.21$	0.837
Duration of viral suppression (months)	19.9 (13.0)	26.9 (10.6)	$t(46) = 2.04$	0.047
VACS Index (range 0 to 164 [riskiest])	26.6 (18.7)	22.9 (13.1)	$t(42) = -0.77$	0.447
PTSD total severity	18.0 (15.1)	16.2 (17.4)	$t(46) = -0.40$	0.693
	n (%)	n (%)		
Black/African-American	19 (79.2%)	18 (75.0%)	$\chi^2(1) = 0.12$	0.731
Reactive urine toxicology for cannabis	8 (34.8%)	3 (13.6%)	$\chi^2(1) = 2.72$	0.099

ART antiretroviral treatment, *BMI* Body Mass Index, *PTSD* post-traumatic stress disorder, *VACS* Veteran's Aging Cohort Study

Table 4 Multivariable linear regression analyses examining the associations of PTSD symptoms with proviral HIV DNA ($N = 44$)

	b (SE)	*β*	*p* value
Model 1			
(Intercept)	1.25 (0.41)		
PTSD total severity	0.02 (0.04)	0.06	.693
VACS Index	0.02 (0.01)	0.33	.030
$F(2, 41) = 2.56$, $p = .09$, $R^2 = 0.11$			
Model 2			
(Intercept)	1.66 (0.24)		
PTSD cluster B (intrusions) severity	− 0.04 (0.02)	− 0.30	.038*
VACS Index	0.01(0.01)	0.05	.051
$F(2, 41) = 5.04$, $p = .01$, $R^2 = 0.20$			
Model 3			
(Intercept)	1.62 (0.23)		
PTSD cluster C (avoidance) severity	− 0.09 (0.05)	− 0.28	.055
VACS Index	0.02 (0.01)	0.30	.041
$F(2, 41) = 4.66$, $p = .02$, $R^2 = 0.19$			
Model 4			
(Intercept)	1.47 (0.23)		
PTSD cluster D (negative affect) severity	− 0.02 (0.02)	− 0.12	.409
VACS Index	0.02 (0.01)	0.33	.031
$F(2, 41) = 2.86$, $p = .07$, $R^2 = 0.12$			
Model 5			
(Intercept)	1.72 (0.26)		
PTSD cluster E (hyperarousal) severity	− 0.05 (0.03)	− 0.30	.047*
VACS Index	0.01 (0.01)	0.26	.080
$F(2, 41) = 4.82$, $p = .01$, $R^2 = 0.19$			

SE standard error

*$p < .05$

independently associated with lower proviral HIV DNA. In particular, hyperarousal indexes symptoms of heightened ANS activation such as an exaggerated startle response that are essential for a DSM-5 diagnosis of PTSD. This may partially explain PTSD-associated elevations in NE as well as a blunted cortisol awakening response reported in prior studies [30, 31, 48]. Given that persistent elevations in urinary NE and cortisol have also been shown to predict higher plasma viral load [32], future studies should measure neuroendocrine dysregulation as a plausible biological mechanism whereby PTSD could induce HIV production in immune cells of those receiving effective treatment. Mechanisms linking PTSD and HIV persistence should be examined in longitudinal cohorts as well as randomized controlled trials of exposure-based approaches to PTSD treatment.

Findings from the present study also have potentially meaningful implications for HIV cure research. Informed by the wake and kill theory [16, 17], clinical studies are testing latency reversing agents designed to induce HIV production in latently infected immune cells that could render them vulnerable to being killed by immune mediated clearance or apoptosis [49]. It is especially noteworthy that trials of latency reversal agents have been historically problematic due to concerns related to adverse events [49]. Findings from the present investigation provide some indication that further research is needed to examine if ANS-mediated neuroimmune pathways could be viable targets for the development of latency reversal agents that are safe and tolerable.

Although we observed that recent cocaine users had significantly shorter duration of undetectable HIV viral load, there was no association of cocaine use with measures of HIV persistence. Findings are consistent with prior research documenting that HIV-positive stimulant users are more likely to experience difficulties with ART adherence and display elevated HIV viral load [13, 26, 50, 51]. It is noteworthy that previous clinical studies documenting stimulant-associated alterations in biological processes relevant to HIV pathogenesis enrolled methamphetamine users [36–39]. Methamphetamine is a potent sympathomimetic stimulant with a longer half-life than cocaine. Potential differential effects of methamphetamine and cocaine on HIV persistence should be examined more closely in future studies. Longitudinal and experimental

studies should examine the unique as well as common mechanisms whereby methamphetamine and cocaine use may contribute to HIV persistence.

Another intriguing aspect of the present study was that the negative association between key PTSD symptom clusters and proviral HIV DNA remained even after adjusting for the VACS Index. In this study, greater proviral HIV DNA was associated with higher VACS Index scores. Because the VACS Index predicts all-cause mortality and cause-specific mortality in people living with HIV [46, 47], this provides some indication that higher proviral HIV DNA is linked to clinically relevant outcomes. This positive association could be attributable to a longer duration of untreated HIV infection, lower nadir CD4+ T cell count, and ART regimen differences [52]. Thus, adjusting for the VACS Index in the present study underscores that the negative association of PTSD with proviral HIV DNA does not appear to be merely attributable to confounding. Further longitudinal research is needed to examine the potentially bi-directional relationship between HIV persistence and greater end-organ system damage.

The findings from this study should be interpreted in the context of some limitations. Because this was a cross-sectional pilot study design with a modest sample size, findings should be considered preliminary. Future longitudinal and experimental research is needed to examine the bio-behavioral mechanisms whereby PTSD may influence HIV persistence. Another notable limitation is that there is no universally accepted "gold standard" for measuring the HIV reservoir, which presents major challenges to HIV cure research. Furthermore, although the present study examined important confounders such as this VACS Index, other key confounders such as nadir CD4+ T cell count, duration of untreated HIV infection, and ART regimen should be examined more closely in future studies [53].

Despite these limitations, this study is among the first to observe a relationship between PTSD symptoms and HIV persistence. Findings underscore the possibility that PTSD could be inducing HIV production in immune cells of those receiving effective HIV treatment. Although preliminary, these provocative results represent a crucial first step to support the scientific premise of further longitudinal and experimental research examining the bio-behavioral pathways whereby PTSD could influence HIV persistence.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all participants in this study.

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