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Neopterin Relates to Lifetime Depression in Older Adults With HIV on Suppressive Antiretroviral Therapy

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Background: Chronic inflammation contributes to the pathogenesis of depression in persons with HIV (PWH). Neopterin, a biomarker of HIV-related immune activation that partially normalizes with antiretroviral therapy (ART), correlates with major depressive disorder (MDD) and subclinical depressive symptoms in persons without HIV and acutely infected, young PWH. The sensitivity of neopterin, however, to both lifetime and current depression is poorly understood in older PWH on suppressive ART.

Methods: Participants were 70 PWH and 35 persons without HIV (HIV−) who were at least 50 years old and completed standardized neurobehavioral and neuromedical assessments. Depressive symptoms in the past 2 weeks, measured with the Beck Depression Inventory-II (BDI-II), and lifetime MDD diagnoses, defined as meeting Diagnostic and Statistical Manual of Mental Disorders-IV criteria for a depressive episode at any point in one's lifetime, were separately modeled as a function of plasma neopterin levels in the full sample and by HIV serostatus.

Results: Compared with HIV− adults, PWH had higher neopterin levels ($P < 0.001$) and BDI-II scores ($P < 0.01$) and were more likely to have lifetime MDD ($P < 0.01$). Higher neopterin related to lifetime MDD, but only in PWH, even after controlling for clinically relevant comorbidities and treatment factors in logistic regression (odds ratio = 3.11, $P = 0.002$). Higher neopterin correlated with higher BDI-II scores in the full sample ($r_s = 0.25$; $P = 0.010$), but not within either group (PWH: $r_s = 0.03$, $P = 0.819$; HIV−: $r_s = 0.09$, $P = 0.588$).

Conclusion: Neopterin was associated with lifetime MDD, but not current depressive symptoms in older PWH on suppressive ART. This may reflect a legacy of inflammation-related disruptions to amino acid metabolism and neurotransmitter synthesis, similar to prior observations. Identification of biopsychosocial and resilience factors underlying the null association between neopterin and current depression in older PWH is warranted.

Key Words: aging, HIV, depression, inflammation, neopterin, antiretroviral therapy

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INTRODUCTION

Persons with HIV (PWH) have greater odds of meeting criteria for major depressive disorder (MDD) compared with the general population.[1] Among older PWH, 52% reported depressive symptoms within the previous year,[2] which is markedly higher than the general population (9.1%).[3] In the general population, prevalence of depression tends to decline with age; however, PWH have plateauing, rather than declining, levels of depression with age.[4] Depression in aging PWH is of particular importance given that over half (51%) of PWH in the U.S. and dependent areas are aged 50 year old and older.[5] Underlying causes of the higher prevalence of depression among older PWH are not fully understood, but chronic inflammation plays a role.

Numerous studies link depression to inflammation among persons with chronic diseases, including HIV. For example, central and peripheral inflammation because of immunometabolic dysregulation contributes to MDD risk in patients with metabolic syndrome.[6,7] Similarly, risk of depressive symptoms is elevated among PWH with high levels of the acute phase reactant, C-reactive protein.[8] Increased peripheral blood concentrations of pro-inflammatory cytokines, particularly interleukin-6 (IL-6) and tumor necrosis factor, are also frequently observed in depressed patients with[9] and without HIV.[10] Elevated cerebrospinal fluid (CSF) concentrations of cytokines and tryptophan catabolites may also reflect a transdiagnostic neuroimmune feature of major psychiatric disorders, including schizophrenia, bipolar disorder, and MDD.[11] Understanding the influence of inflammation is clinically relevant because it is associated with treatment-resistant depression.[12] Meta-analysis of randomized controlled trials shows anti-inflammatory treatments may have significant antidepressant effects when compared with placebo.[13]

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Neopterin is a product of guanosine triphosphate metabolism that is produced by macrophages. Its concentrations in blood are reduced by antiretroviral therapy (ART)[14] but can remain elevated years after initiation.[15] Neopterin is synthesized in response to interferon-gamma (IFN-γ), which also induces tryptophan degradation via activation of indoleamine 2,3-dioxygenase.[16] Because tryptophan is a precursor of serotonin, increased neopterin may signal a concurrent reduction in serotonin and vulnerability for depression.[16] Neopterin is increased in individuals experiencing 2 or more episodes of depression compared with others.[17] Consistent with the influence of neopterin on indoleamine 2,3-dioxygenase, people with MDD have lower tryptophan levels and higher IFN-γ.[18] In the limited literature on the association between neopterin and depression among PWH, similar trends have been found.[19–21]

The existing research linking neopterin with depression in PWH has typically evaluated relatively young cohorts with recent HIV diagnosis. It is well established that typical biological aging involves increased inflammation,[22] including elevations in neopterin,[23,24] and the combination of HIV disease and older age may enhance the likelihood of a chronic inflammatory state.[25] As PWH grow older, studying depression and its association with immune function becomes increasingly important. The study reported here investigates the relationship between neopterin in blood plasma and depression, both lifetime MDD and current depressive symptoms, in a cohort of older PWH on suppressive ART. We hypothesized that: (1) older PWH would have higher rates of lifetime MDD and more current depressive symptoms than their HIV− counterparts; (2) older PWH would also exhibit higher plasma neopterin levels; and (3) higher neopterin would relate to higher odds of lifetime MDD and more current depressive symptoms irrespective of HIV serostatus, but these associations would be stronger among PWH.

METHODS

Participants and Procedure

This study examined 70 PWH and 35 persons without HIV (HIV−) adults from the University of California, San Diego HIV Neurobehavioral Research Program's Successfully Aging Seniors with HIV cohort. All participants provided written informed consent and the study protocol was approved by the institutional review board. To be included in this analysis, participants were at least 50 years old and had neopterin measured in blood plasma. All PWH were taking ART and had a plasma HIV RNA $\leq$ 50 copies/mL. All participants underwent standardized neuromedical and psychiatric assessments.

Psychiatric Assessments

Participants were evaluated for lifetime (any point in one's lifetime) and current (last 30 days) MDD and substance use disorder (dependence or abuse) diagnoses using the Composite International Diagnostic Interview,[26] a computerized psychodiagnostic clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders-IV, because study methodology was developed before the release of the Diagnostic and Statistical Manual of Mental Disorders-5. In addition to the diagnostic evaluation, participants were administered the Beck Depression Inventory II (BDI-II)[27] to provide a continuous measure of depressive symptoms (possible range: 0–63) experienced in the past 2 weeks. To preserve statistical power in primary analyses, we chose to model current depression with the continuous total BDI-II score instead of a current MDD diagnosis, because only 10 total study participants had a current MDD diagnosis.

Domain-specific BDI-II scores reflecting cognitive (possible range: 0–27), affective (possible range: 0–12), and somatic (possible range: 0–24) symptoms of depression were computed based on a previous factor analysis of the BDI-II in 1583 PWH.[28]

Neuromedical Assessment

Medical comorbidities and medications were determined by interview. For the group of PWH, additional HIV disease-related variables were collected. These included history of AIDS, estimated duration of HIV disease (years), current $CD4^+$ T-cell count, nadir $CD4^+$ T-cell count, and duration of ART use (years). Current use of efavirenz is reported for the present study given its known associations with neurobehavioral disturbance.[29] HIV RNA level was measured in plasma by reverse transcription polymerase chain reaction (Abbott Diagnostics; lower limit of quantitation 50 copies/mL).

Neopterin Assay

Blood was collected by venipuncture and aliquots were stored at −80C until assayed. Neopterin levels were quantified from the blood by enzyme-linked immunosorbent assay (ALPCO, Salem, NH) and are expressed as nmol/L. Assays were performed in duplicate, and assays for the samples with coefficients of variation greater than 20% or outliers that were more than 4 SDs from the mean were repeated. Assays for 10% of the samples were also repeated to ensure operator and batch consistency.

Statistical Analyses

Univariable HIV serostatus comparisons on demographic, medical, biomarker, and psychiatric data were performed with 2-tailed t test, Wilcoxon rank-sum, or likelihood ratio χ^2 tests, as appropriate. Neopterin was $\log_{10}$ transformed to produce a more normal distribution. Hedge's g (g) statistic for binary predictors and Pearson coefficient (r)/Spearman rho (r_s) for continuous predictors were used to generate effect sizes for predictors of neopterin.

To examine conditions associated with neopterin in our mixed sample of PWH and persons without HIV, multivariable linear regression modeled neopterin levels as a function of HIV serostatus and clinical factors of interest, which included lifetime MDD. Clinical factors were considered based on which variables in Table 1 demonstrated univariable associations with HIV serostatus or neopterin at a critical $\alpha = 0.10$. Stepwise regression models based on Akaike Information Criterion (AIC) were conducted to select the

TABLE 1. Demographic, Medical, and Psychiatric Characteristics of Sample (n = 105)

	HIV− (n = 35)	PWH (n = 70)	*P*
Descriptive demographics			
Age, median [IQR]	59 [54–64]	57 [51–61]	0.19
Education, median [IQR]	14 [12–16]	14 [12–16]	0.96
Male, n (%)	23 (65.7%)	60 (85.7%)	0.02
Non-Hispanic white, n (%)	22 (62.9%)	56 (80.0%)	0.06
Medical comorbidities			
Hyperlipidemia, n (%)*	11 (31.4%)	38 (56.7%)	0.01
Hypertension, n (%)*	14 (40.0%)	28 (41.8%)	0.86
Ever smoker, n (%)*	14 (40.0%)	27 (40.3%)	0.98
Current smoker, n (%)*	9 (25.7%)	24 (35.8%)	0.30
Diabetes mellitus, n (%)*	7 (20.0%)	17 (25.4%)	0.54
Hepatitis C virus, n (%)*	6 (17.1%)	14 (20.9%)	0.65
BMI median [IQR]	28 [23–29]	26 [23–29]	0.24
Current medications			
NSAID, n (%)	8 (22.9%)	21 (30.0%)	0.44
Antihypertensive drug, n (%)	9 (25.7%)	22 (31.4%)	0.54
Lipid-lowering drug, n (%)	8 (22.9%)	28 (40.0%)	0.08
Psychiatric characteristics/diagnoses			
BDI-II, median [IQR]	2 [0–6]	8 [2–16]	0.0001
Cognitive, median [IQR]	0 [0–1]	2 [0–5]	0.0001
Affective, median [IQR]	0 [0–1]	2 [0–3]	0.0005
Somatic, median [IQR]	1 [0–4]	5 [1–8]	0.0003
Current MDD, n (%)†	1 (2.9%)	9 (13.0%)	0.16‡
LT MDD, n (%)	10 (28.6%)	39 (55.7%)	0.008
LT GAD, n (%)	0 (0%)	7 (6.7%)	0.09‡
LT alcohol use disorder, n (%)†	17 (50.0%)	33 (47.1%)	0.78
LT cannabis use disorder, n (%)†	7 (20.6%)	21 (30.0%)	0.30
LT meth use disorder, n (%)†	8 (23.5%)	21 (30.0%)	0.49
LT cocaine use disorder, n (%)†	6 (17.7%)	16 (22.9%)	0.54
Psychotropic medications			
Antidepressant drug, n (%)	4 (11.4%)	30 (42.9%)	0.0006
On SSRI, n (%)	2 (5.7%)	14 (20.0%)	0.04
On SNRI, n (%)	0 (0%)	5 (7.1%)	0.17
On atypicals, n (%)	3 (8.6%)	15 (21.4%)	0.08
On tricyclics, n (%)	0 (0%)	5 (7.1%)	0.17
HIV disease characteristics			
AIDS, n (%)		43 (61.4%)	
Duration of HIV disease (yr), median [IQR]§		20 [11–25]	
Current $CD4^+$ T-cell count, median [IQR]‖		649 [478–835]	
Nadir $CD4^+$ T-cell count, median [IQR]‖		180 [43–300]	
Duration of exposure to ARVs (yr), median [IQR]		11 [6–17]	
On efavirenz, n (%)		17 (16%)	

Group comparisons: Wilcoxon for continuous variables; likelihood ratio test for dichotomous variables.
*n = 102.
†n = 104.
‡*P*-value associated with Fisher exact test.
§n = 69.
‖n = 67.
ARV, antiretroviral; CD4, cluster of differentiation 4; CESD, center for epidemiological studies depression; LT, lifetime; NSAID, nonsteroidal anti-inflammatory drug.

optimal model. The same AIC-based regression approach was used to identify the optimal set of predictors of neopterin among PWH only. Clinical factors were considered for inclusion based on which variables in Table 1 demonstrated univariable associations with neopterin, among PWH only, at a critical $\alpha = 0.10$.

After establishing the clinical factors independently associated with neopterin, primary analyses specifically focused on neopterin as a predictor of depression characteristics. To capture both lifetime and current depression, analyses modeled lifetime MDD diagnoses and BDI-II scores (total and domain scores) as separate outcomes. Based on the

pattern of univariable associations between neopterin and lifetime MDD, a confirmatory AIC-based logistic regression analysis examined lifetime MDD status as a function of neopterin, HIV status, and their interaction, with a follow-up analysis examining the neopterin and lifetime MDD association in PWH only. The pattern of univariable associations between neopterin and BDI-II scores did not indicate a differential association by HIV serostatus and therefore an AIC-based linear regression analysis examined BDI-II scores as a function of neopterin only in the total sample. For each regression analysis, covariates included clinical correlates of neopterin identified in prior analysis and additional psychosocial and treatment covariates univariably associated with lifetime MDD or total BDI-II scores at a critical $\alpha = 0.10$. All analyses were performed using JMP Pro version 14.0.0 (SAS Institute Inc., Cary, NC).

RESULTS

Sample Characteristics

Demographic, medical, and psychiatric characteristics of the sample are summarized in Table 1. The full sample consisted predominantly of middle-aged {median 58 (interquartile range [IQR] 52–62) years}, non-Hispanic white (74.5%) men (79.2%) with some college education [median 14 (IQR 12–16) years]. PWH and HIV− groups were comparable (ie, P values for group differences > 0.05) across many demographic and medical characteristics, except PWH were more likely to be male (85.7% vs. 65.7%, $P = 0.02$) and have hyperlipidemia (56.7% vs. 31.4%, $P = 0.01$). With respect to psychiatric characteristics, PWH had more evidence of historical and current affective distress than the HIV− group. Specifically, the PWH group had higher rates of lifetime MDD (55.7% vs. 28.6%, $P < 0.01$), higher scores on BDI-II [median 8 (IQR 2–16) vs. median 2 (IQR 0–6), $P < 0.01$], and a higher proportion of individuals on any antidepressant medication (42.9% vs. 11.4%, $P < 0.01$) and selective serotonin reuptake inhibitors (20.0% vs. 5.7%, $P = 0.04$). The prevalence of lifetime substance use disorders did not significantly differ by HIV serostatus (p's > 0.29). Among PWH, the median estimated duration of HIV disease was 20.0 years, the median CD4$^+$ T-cell count was 649 cells/mm^3, and the median nadir CD4$^+$ T-cell count was 180 cells/mm^3.

Clinical Predictors of Neopterin

Univariably, PWH had higher levels of plasma neopterin [median = 9.9 nmol/L (IQR 7.6–11.9)] than the HIV− group [median = 6.3 nmol/L (IQR 5.0–7.6); g = 1.25; $P < 0.001$]. With respect to other univariable relationships between neopterin and clinical factors across the entire sample, lifetime MDD (g = 0.56; $P = 0.004$), diabetes (g = 0.50; $P = 0.049$), male sex (g = 0.68; $P = 0.005$), hepatitis C seropositivity (g = 0.43; $P = 0.082$), and lifetime methamphetamine use disorder (g = 0.37; $P = 0.087$) were associated with higher levels of neopterin. In an AIC-based multiple linear regression model ($R^2 = 0.33$; $F_{[5, 96]} = 10.94$; $P < 0.001$, Table 2), higher neopterin was associated with HIV seropositivity ($\beta = 0.14$; $P < 0.001$), male sex ($\beta = 0.07$; $P = 0.028$), lifetime MDD ($\beta = 0.05$, $P = 0.052$), diabetes ($\beta = 0.06$; $P = 0.077$) and hepatitis C ($\beta = 0.06$; $P = 0.082$). In addition to these covariates, a model that was restricted to PWH ($R^2 = 0.38$; $F_{[6, 60]} = 6.14$; $P < 0.001$) also included lifetime cannabis use disorder ($\beta = -0.09$; $P = 0.006$) and efavirenz use ($\beta = -0.07$; $P = 0.040$). Each of these additional covariates were associated with lower neopterin levels.

Neopterin and Lifetime MDD in PWH

As previously noted, higher neopterin was associated with lifetime MDD in PWH compared with those without a history of MDD (g = 0.59; $P = 0.028$), whereas neopterin levels did not significantly differ by lifetime MDD status in the HIV− group (g = −0.19; $P = 0.361$; Fig. 1). A logistic regression testing the interaction between neopterin and HIV serostatus confirmed a significant interaction effect between neopterin and HIV on lifetime MDD [odds ratio (OR) = 4.62, $P = 0.015$]. Thus, a follow-up logistic regression analysis within the PWH group only was conducted to determine whether neopterin uniquely explained lifetime MDD status in PWH after accounting for clinical correlates of neopterin identified in prior analysis (ie, sex, diabetes, hepatitis C, lifetime cannabis use disorder, efavirenz use) and additional

TABLE 2. Multivariable Linear Regression Model Selected Based on AIC to Model Log-Transformed Neopterin as a Function of Clinical Predictors of Interest in the Full Sample and PWH Only

	Full Sample			PWH Only		
Predictor	**β (SE)**	**95% CI**	***P***	**β (SE)**	**95% CI**	***P***
PWH (ref: HIV−)	0.14 (0.03)	0.08 to 0.20	<0.001	—	—	—
Male (ref: female)	0.07 (0.03)	0.01 to 0.14	0.028	0.08 (0.04)	−0.16 to 0.01	0.063
LT MDD (ref: no dx)	0.05 (0.03)	0.00 to 0.11	0.052	0.07 (0.03)	0.01 to 0.14	0.024
Diabetes (ref: no dx)	0.06 (0.03)	−0.01 to 0.12	0.077	0.07 (0.03)	0.00 to 0.14	0.041
Hepatitis C virus (ref: no dx)	0.06 (0.03)	−0.01 to 0.12	0.082	0.08 (0.04)	0.00 to 0.15	0.041
LT cannabis use disorder (ref: no dx)	—	—	—	−0.08 (0.03)	−0.14 to −0.01	0.018
Efavirenz (ref: no efavirenz)	—	—	—	−0.07 (0.04)	−0.15 to −0.00	0.040

dx, diagnosis; LT, lifetime.

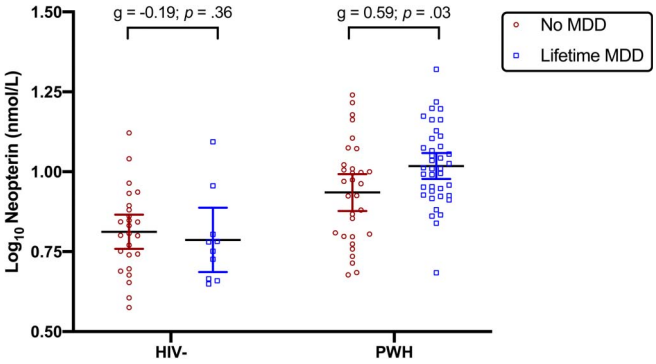

FIGURE 1. Plasma neopterin levels are elevated in PWH and a history of MDD. Caption: PWH [median = 9.9 nmol/L (IQR 7.6–11.9)] had higher levels of plasma neopterin than the HIV-negative group [median = 6.3 nmol/L (IQR 5.0–7.6); g = 1.25; $P < 0.001$]. Lifetime MDD related to significantly higher neopterin levels in PWH (g = 0.59, $P = 0.028$), but not in HIV− individuals (g = −0.19, $P = 0.361$). Statistical analyses conducted on $\log_{10}$ neopterin levels are expressed as mean ± 95% confidence interval. full color online

psychosocial and treatment factors univariably associated with lifetime MDD: non-Hispanic white race/ethnicity (OR = 2.78; $P = 0.09$), current antidepressant use (OR = 2.85; $P = 0.04$), lifetime alcohol use disorder (OR = 3.02, $P = 0.03$), and lifetime methamphetamine use disorder (OR = 2.60; $P = 0.08$). The optimal model was overall significant (pseudo $R^2 = 0.22$; $\chi^2_{[4,\ 65]} = 21.39$; $P < 0.001$) and higher neopterin levels remained significantly associated with lifetime MDD (OR = 3.11 per 1 SD increase in neopterin levels; $P = 0.002$) in PWH. With respect to covariates, the optimal model also contained antidepressant use, lifetime alcohol use disorder, and lifetime cannabis use disorder as predictors of higher odds of lifetime MDD in PWH (Table 3).

Neopterin and BDI-II

To determine the univariable associations between neopterin and current depressive symptoms, a series of Spearman correlations examined relationships between neopterin and BDI-II scores across the full sample and by HIV serostatus (Fig. 2). In the full sample, higher neopterin significantly correlated with higher BDI-II scores ($r_s = 0.25$; $P = 0.010$). Despite the significant correlations between neopterin and BDI-II scores in the full sample, the correlation between neopterin and total BDI-II scores was substantially weaker and did not reach significance within either group (HIV−: $r_s = 0.09$; $P = 0.588$; PWH: $r_s = 0.03$; $P = 0.819$). Thus, a linear regression analysis was conducted in the entire sample only to determine whether neopterin uniquely explained BDI-II scores across the cohort after accounting for clinical correlates of neopterin in the full sample (ie, sex, diabetes, hepatitis C) and additional psychosocial and treatment factors univariably associated with BDI-II scores: non-Hispanic white race/ethnicity (d = 0.42; $P = 0.06$), current antidepressant use (d = 0.76; $P < 0.001$), lifetime alcohol use disorder (d = 0.59, $P < 0.01$), lifetime cannabis use disorder (d = 0.67, $P < 0.01$), and lifetime methamphetamine use disorder (d = 0.47; $P = 0.03$). The optimal model was overall significant ($R^2 = 0.20$; $F_{[4,\ 99]} = 7.42$; $P < 0.001$) and higher neopterin levels remained significantly associated with total BDI-II scores (β = 1.67 per 1 SD increase in neopterin levels; $P = 0.04$). Similar to the lifetime MDD analysis, the optimal model also retained antidepressant use, lifetime alcohol use disorder, and lifetime cannabis use disorder as covariates of higher BDI-II scores (p's < 0.07). With respect to BDI-II subdomains, higher neopterin was significantly associated with higher cognitive ($r_s = 0.27$; $P = 0.006$) and somatic subscale scores ($r_s = 0.22$; $P = 0.022$), and approached statistical significance with higher affective subscale scores ($r_s = 0.17$; $P = 0.091$). Similar to the total BDI-II results, correlations between neopterin and BDI-II domains did not reach significance when stratified by HIV serostatus (HIV−: $r_s < 0.13$; p's > 0.178; PWH: $r_{s;} < 0.08$; p's > 0.550).

TABLE 3. Multivariable Logistic Regression Model Selected Based on AIC to Model Lifetime Major Depressive Disorder as a Function of Log-Transformed Neopterin and Clinical Covariates in PWH

Predictor	Beta (SE)	P	OR	95% CI
$\log_{10}$ neopterin (per 1 SD increase)	1.13 (0.36)	0.002	3.11	1.52 to 6.34
Antidepressant use (ref: no use)	1.41 (0.61)	0.020	4.08	1.24 to 13.38
LT alcohol use disorder (ref: no dx)	1.07 (0.64)	0.095	2.93	0.83 to 10.31
LT cannabis use disorder (ref: no dx)	1.16 (0.75)	0.121	3.19	0.74 to 13.79

dx, diagnosis; LT, lifetime.

DISCUSSION

In a cohort of well-characterized older PWH on suppressive ART and age-matched HIV− adults, HIV disease was related to elevated plasma neopterin levels. In turn, higher plasma neopterin levels related to higher odds of a

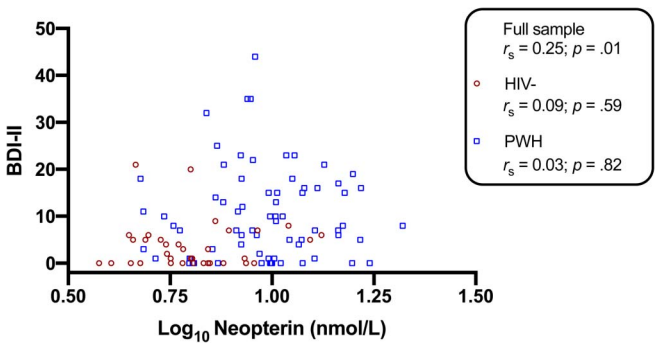

FIGURE 2. Plasma neopterin levels and current depressive symptoms. Higher plasma neopterin correlated with higher BDI-II scores in the full sample ($r_s = 0.25$; $P = 0.010$), but not within either group (PWH: $r_s = 0.03$, $P = 0.819$; HIV−: $r_s = 0.09$, $P = 0.588$). Correlations conducted with Spearman rho. full color online

clinically significant depression history, but only within PWH. Plasma neopterin was also elevated in individuals with comorbid chronic illnesses (ie, diabetes, hepatitis C virus) and was notably lower in PWH with a history of cannabis use disorder and currently taking efavirenz. Neopterin remained robustly sensitive to lifetime MDD after statistical adjustment for these clinical factors and additional depression-related psychosocial and treatment factors. Plasma neopterin levels were also modestly correlated with current depressive symptoms in the full sample, but this relationship was not replicated in analyses stratified by HIV serostatus.

Our findings align with several previous studies that have investigated the relationship between neopterin and depression in PWH. Hellmuth et al reported that higher plasma neopterin correlated with worse initial depression scores in acutely infected PWH,[19] whereas a similar study in ART-naïve PWH found the same relationship only among patients taking antidepressants.[21] Another study reported that higher plasma viral load and lower CD4 counts related to higher urinary neopterin concentrations, and urinary neopterin outperformed these HIV disease indicators as a predictor of BDI scores in multivariable analysis.[20] In contrast, Gold et al,[30] did not detect a relationship between BDI scores and neopterin levels in a male cohort of PWH during primary HIV infection (<1-year duration). These null findings may relate to the observation that most participants self-reported minimal (52%) to mild (17%) depression whereas fewer participants reported moderate (17%) and severe (14%) depression.

Our findings extend the literature on neopterin as a marker of HIV− related immune activation with sensitivity to depression characteristics by characterizing these relationships in ART-treated and virally suppressed older PWH. The mentioned studies focused on younger adults (average/median ages: 28[13], 35.6[14], 36[16], 37.6[15]) compared with this study (median age: 58). In addition, these existing studies investigated a more acutely HIV-infected population (average/median duration of infection: 19.8 days,[13] 103.5 days[16]) compared with our study (median duration of infection: 20 years). In our study, plasma neopterin levels related to presence of lifetime MDD and higher current depressive symptoms, as measured by the BDI-II. However, the association between neopterin and current depressive symptoms was only significant in the total sample and not observed within either of the HIV serostatus groups. Although the severity of self-reported depression symptoms was higher in the PWH group, most participants had subthreshold depression (ie, about 22% of the PWH group had BDI-II total scores >17). Therefore, we have limited power to detect associations between current clinically significant depression and immune activation in this sample.

Based on previous studies, levels of neopterin decline with effective ART.[31,32] The elevated levels of neopterin observed in our sample of older PWH, relative to the HIV− sample, may reflect legacy effects of prior immune compromise [eg, 61.4% of the PWH group were diagnosed with AIDS and median nadir $CD4^+$ T cell count was 180 (IQR: 43–300)].[33,34] PWH who have more advanced disease may also have greater translocation of gut microbes into the blood. Neopterin in blood correlated with an indicator of microbial translocation, (1→3)-β-D-glucan[35] in a cohort of virally suppressed PWH.[36] The association between neopterin and (1→3)-β-D-glucan may be relevant to our findings, because gut dysbiosis has been implicated in depressive disorders.[37] In addition to neopterin, other immune biomarkers such as C-reactive protein and a host of pro-inflammatory cytokines (eg, IFN-γ, IL-6, IL-15, IP-10, tumor necrosis factor-α) may have utility for capturing acute inflammatory changes in PWH that track with neurobehavioral status.[9,38–40] More research is needed to identify biomarkers of inflammation that are sensitive to current depression symptoms versus prior immune responses associated with previous MDD. Such research should use gold-standard measures of depression, such as a structured clinical interview and validated self-report measure such as the BDI-II.[28,41] Of note, the diagnostic value of the BDI-II does not seem to be weakened in the presence of somatic or affective symptom overlap with both depression and HIV.[28] Our observation that neopterin most strongly correlated with the cognitive subscale of the BDI-II, which includes items reflecting negative thought patterns and cognitive distortions[28] (eg, rumination, pessimism), also suggests a link between immune dysfunction and psychological features (versus physical ailments) of depression.

The neurobiological underpinnings of depression with inflammation have yet to be fully elucidated, yet disruptions in amino acid metabolism[42] and neurotransmitter synthesis[43] likely occur. Elevated neopterin is consistently correlated with conversion of tryptophan to kynurenine, resulting in less serotonin synthesis. Plasma and CSF levels of serotonin are reduced in PWH[44–46] and greater tryptophan degradation (indexed by kynurenine/tryptophan ratios) has been linked to depression[20,47] and impulsivity/risk-taking[48] in PWH. In addition to serotonergic deficiencies, neopterin also correlates with decelerated conversion of phenylalanine to tyrosine, resulting in less dopamine synthesis.[42] This concurrent increase in neopterin and decreased dopamine production may reflect oxidative stress-induced reductions in tetrahydrobiopterin (BH_4), a critical cofactor in phenylalanine metabolism.[42] This pathway converges with the robust observation that pro-inflammatory cytokine signaling compromises the synthesis and release of dopamine in cortico-striatal reward pathways.[43,49,50] Consistent with this notion, dopaminergic abnormalities have been widely reported in PWH[51–53] and shown to correlate with depressive symptoms and neurocognitive deficits.[52,54]

HIV disease is hypothesized to accelerate the aging processes in part because of persistent chronic inflammation, even in the presence of suppressive ART.[1] As a result, PWH are at increased risk of developing comorbid diseases that reciprocally enhance inflammation and further accelerate aging in this population. Limiting and managing the accumulation of comorbidities is a central tenant of HIV clinical care. In the present study, PWH with comorbid hepatitis C virus or diabetes (or both) exhibited significantly increased neopterin levels compared with PWH without these comorbidities. Interestingly, a history of lifetime cannabis use disorder was linked to lower neopterin levels. This mirrors prior observations that cannabis possesses anti-inflammatory properties that may mitigate HIV-related gut and

blood–brain-barrier permeability, oxidative stress, and possibly protect against neurocognitive impairment.[55–59] In contrast, we observed that lifetime cannabis use disorder related to increased odds of lifetime MDD within PWH. This underscores the complexity of a disorder-based classification of cannabis use that not only reflects historical exposure levels, but also use-related psychosocial difficulties (eg, interference with occupational functioning) that may correlate with mood. A more surprising clinical factor that also related to lower neopterin levels was use of efavirenz (n = 17), a non-nucleoside reverse transcriptase inhibitor that carries a high central nervous system toxicity risk profile and should be used with caution in older PWH with neuropsychiatric histories.[60,61] Of note, a prospective study observed that switching from efavirenz to the less neurotoxic non-nucleoside reverse transcriptase inhibitor dolutegravir related to increased plasma kynurenine concentrations, but not neopterin or kynurenine/tryptophan ratios.[62] Although efavirenz has been linked to neuropsychiatric disturbances and related to lower neopterin in our sample, it did not influence the unique relationship between neopterin and lifetime MDD.

Our study findings should be considered in light of its limitations. First, our small sample size (N = 105) prohibits more complex analyses requiring greater power to detect small-to-medium effects. Second, our cross-sectional data preclude discussion of temporality among our variables of interest. Therefore, the extent to which levels of neopterin have changed over time and whether elevated levels of neopterin preceded or succeeded episodes of MDD is unknown. Third, the present studied focused on neopterin given it operates within a well-defined biological pathway with putative relevance to depression and HIV. Other immune biomarkers, however, may also be associated with depression in older PWH. Fourth, although blood-based biomarker assays are more feasible and scalable in both research and clinical settings, the absence of CSF neopterin data limit our ability to draw inferences about central nervous system-specific immune activation. Fifth, male sex was associated with neopterin despite our study being underpowered to study sex-specific mechanisms of immune response and depression. Sex may moderate immune and neurobehavioral associations[63] and therefore should be considered in future research. Last, the PWH group consisted of mostly non-Hispanic white men, which is not representative of the demographics of PWH in the United States. Race/ethnicity is important to consider because prior research indicates markers of systemic inflammation are associated with depressive symptoms differentially across race/ethnicity groups.[64]

Taken together, our findings provide important context to the literature on neopterin and depression in HIV disease. As expected, PWH exhibited higher neopterin levels and greater lifetime and current depression characteristics than their HIV− counterparts. Given that plasma neopterin was a more sensitive indicator of a lifetime history of clinical depression rather than current depressive symptoms in the PWH group, these individuals may possess unmeasured biopsychosocial factors that confer resilience against the adverse effects of neopterin on current depression that have been documented in younger and less treated cohorts. Continued monitoring and management of comorbidity burden, exploration of novel anti-inflammatory therapeutics, and identification of positive behaviors and psychological factors may further facilitate successful neurobehavioral aging in this population and inform care for those with more recently acquired HIV and comorbid depression.

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