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Epigenetics in persons living with HIV: trauma, coping, and *FKBP5* and *SLC6A4* methylation

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ABSTRACT

Aim: People living with HIV (PLWH) have an increased risk for lifetime trauma and mental health difficulties. However, no studies have evaluated stress-related genes in relation to early-life adversity, lifetime trauma, or post-traumatic stress disorder (PTSD) in PLWH.

Methods: Using bisulfite pyrosequencing, we evaluated DNA methylation (DNAm) in intron 7 of FKBP5, a glucocorticoid feedback regulator, and in the promoter of SLC6A4, the serotonin transporter gene, in whole blood of a random sample of 70 PLWH recruited from an HIV program, and 51 individuals 2 years later ($n = 48$ at both time points). Exploratory regression analyses were conducted with DNAm in relation to trauma exposure, mental health symptoms, and coping strategies.

Results: Higher DNAm at one site of SLC6A4 was associated with lower levels of anxiety (B = −0.62 (SE = 0.23), $p = 0.0109$), depression (B = −0.06 (SE = 0.03), $p = 0.0435$), and PTSD symptoms at baseline (B = −0.03 (SE = 0.01), $p = 0.0374$). DNAm at FKBP5 was negatively associated with measures of anxiety (B = −0.30 (SE = 0.07), $p = 0.0001$) and depression symptoms (B = −0.2 (SE = 0.10), $p = 0.0103$). Various coping strategies were also associated with sites in both genes across time points, e.g. self-blame and substance use.

Conclusion: Our findings generate intriguing hypotheses linking mental health symptoms and DNA methylation, to be replicated with larger samples.

PLAIN LANGUAGE SUMMARY

Many people living with HIV experience high levels of trauma and mental health difficulties in their lifetime. One way in which this trauma may affect mental health, is through a process called epigenetics, in which chemical changes are made to the DNA in response to different exposures. Small chemical groups called methyl groups are placed onto a cytosine (the C in our DNA), which can modify how available the DNA is to be expressed into a protein. These methylation patterns at stress-related genes can essentially tune up or down a body's response to a stressor. In our study, we examined how these methylation differences at important regulatory locations in stress-related genes may be related to exposure to lifetime histories of trauma, as well as symptoms of depression, anxiety, and perceived stress, and various coping strategies people use to deal with trauma or stress, such as humor, denial, self-blame, or substance use. We found that higher DNA methylation levels at multiple positions in the two studied genes were related to lower levels of symptoms of anxiety, depression, and post-traumatic stress disorder (PTSD) in a population of adults living with HIV. Some of the coping strategies, such as self-blame and substance use, were also related to DNA methylation at both studied genes. These findings indicate that epigenetic differences may contribute to mental health symptoms in people with HIV.

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People living with HIV; stress-related genes; *FKBP5*; *SLC6A4*; depression; anxiety; lifetime trauma; PTSD

1. Introduction

People living with HIV (PLWH) are disproportionately affected by traumatic experiences and are at an elevated risk for mental health difficulties compared to the general population [1,2]. The prevalence of depression among PLWH is nearly twice that of the general population [3–5]. The prevalence of anxiety disorders is also higher among PLWH compared to the general population [6–8]. Previous work has suggested that higher rates of depression and anxiety among PLWH are related to lower levels of social support [9,10], internalized stigma [11], sociodemographic factors [12,13], substance use [14], and health-related fears [15]. Individuals with HIV also face a greater risk of developing PTSD, with global estimates ranging from 25% to 35%, depending on screening or diagnostic tool utilization [11,16]. However, PLWH also benefit from coping strategies that alleviate mental health symptoms [17,18]. Given that lifetime histories of trauma and mental health difficulties are linked to

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Article highlights

- This study investigated relationships between whole-blood DNA methylation of two stress-related genes, *FKBP5* and *SLC6A4*, and different models of trauma exposure, as well as coping and mental health symptoms in people living with HIV (PLWH) at two time points.
- Higher DNAm at one site in the promoter of *SLC6A4* was associated with lower levels of anxiety, depression, and PTSD symptoms at baseline.
- DNAm at intron 7 of *FKBP5* was negatively associated with measures of anxiety and depression symptoms.
- Coping strategies such as self-blame and substance use were also associated with various sites in these genes across both time points.
- Our findings highlight an epigenetic mechanism for the potential embodiment of mental health in PLWH.

health risk behaviors [19], poor medication adherence [20], and HIV progression [21], further developing our understanding of how lifetime trauma, mental health, and coping become embodied in people with HIV is crucial to improving health outcomes for PLWH.

One suggested pathway through which lifetime trauma may affect health and well-being is through the biological mechanism of epigenetics. One commonly studied epigenetic mechanism is DNA methylation (DNAm) usually found at cytosines followed by guanines (CpG sites) in the DNA. DNA methylation can be sensitive to environmental exposures, such as lifetime trauma [22–25]. A growing body of evidence demonstrates that epigenetics may mediate associations between trauma, particularly during childhood, and increase the risk of adverse physical and mental health outcomes [26–29]. Dysregulation of the hypothalamic pituitary adrenal (HPA) axis and serotonergic neurotransmission has been linked to several psychiatric conditions [30–33]. Candidate gene approaches for investigating molecular pathways that mediate relationships between environmental exposures, such as lifetime trauma, and mental health difficulties have primarily focused on DNA methylation at stress-related genes implicated in regulating glucocorticoid signaling and serotonergic neurotransmission, such as *NR3C1* [24,34], *SLC6A4* [35,36], and *FKBP5* [22,37,38]. Directions of effect in these studies are often inconsistent, potentially due to differences in tissue studied or timing of measurements [39,40]. Further, the timing of critical windows of exposure has not been fully resolved, and may vary by exposure, gene region, and disease outcome [41,42].

Despite high levels of trauma among PLWH, coping strategies can help improve health behaviors and overall health outcomes [43,44]. Coping can be broadly defined as minimizing distress associated with adverse life experiences. Coping strategies are often classified in various ways; one way is to group them as dysfunctional or adaptive [45]. Research on the direct relationship between DNAm and coping is limited, but adaptive coping may buffer the effects of depression and anxiety, potentially mitigating stress-related epigenetic changes [34,46,47].

FKBP5 has become a target gene of interest for investigating molecular pathways that mediate the relationship between lifetime trauma and mental health difficulties [22,30], as it is a gene that moderates the glucocorticoid receptor (GR) sensitivity and HPA-axis regulation [48]. Multiple studies have found lower methylation at intron 7 of *FKBP5* in peripheral blood to be associated with childhood trauma and psychiatric diseases [22,49]. In contrast, Harms et al. [50] found that childhood stress was associated with higher *FKBP5* methylation at sites in intron 2 and intron 5 in adult saliva, while a study of Chinese adolescents failed to identify any associations between promoter region methylation and anxiety symptoms [51]. Other studies have found associations between *FKBP5* methylation and depressive symptoms [52], as well as structural changes of the brain in individuals with major depressive disorder [53].

SLC6A4's role in regulating the neurotransmission of serotonin has led it to become a gene of interest for exploring associations between methylation, trauma exposure, and mental health difficulties. A study examining *SLC6A4* methylation in blood drawn from 100 adults of the Detroit Neighborhood Health Study found lower *SLC6A4* promoter methylation mediated the relationship between the number of traumatic events experienced and PTSD [36]. Another study found the opposite direction of effect, such that resilience factors were associated with lower *SLC6A4* promoter methylation in saliva of Latinx mothers and children, while stress factors were associated with higher methylation [47]. The same direction of effect was found in leukocytes of adults reporting childhood adversities, higher perceived stress, and a greater family history of depression had higher *SLC6A4* methylation [35].

Prior epigenetics research with PLWH has primarily focused on identifying differences in epigenome-wide methylation with infection status or viral load [54,55]. These studies have shown that sites near or within immune-related genes were significantly associated with HIV infection [54,55]. While epigenetic aging has been shown to be accelerated with HIV [56–58], no studies have yet investigated the associations between DNAm, lifetime trauma, mental health symptoms, or coping strategies in PLWH. Given the high prevalence of mental health difficulties and higher levels of lifetime trauma among PLWH, it is essential to explore the relationship between DNAm of stress-related genes, trauma, mental health symptoms, and coping in PLWH.

The primary objective of this study was to evaluate associations between DNAm of *FKBP5* and *SLC6A4*, trauma exposure, and mental health symptoms in PLWH using whole blood samples drawn at two time points. Different models of lifetime trauma were used to test different hypotheses on relevant periods of exposure. Furthermore, this study aimed to address the role of coping strategies and their relationship to *FKBP5* and *SLC6A4* DNAm. We hypothesized that childhood trauma would be the most critical period of exposure for epigenetic changes and that higher levels of overall lifetime trauma, along with lower levels of adaptive coping, would be associated with altered DNA methylation. However, given inconsistencies in prior literature, expected directions of effect are difficult to predict.

2. Materials and methods

2.1. Study population

The study sample was drawn from an HIV program in a suburban area using a random sampling procedure. Self-

report survey data were collected at two time points nearly 2 years apart (between 2019 and 2021). The first time point is referred to as the "baseline," and the second as the "follow-up" for the remainder of the study. Whole blood samples were collected at baseline between March 2019 and March 2020, and follow-up whole blood samples were collected between August 2020 and December 2021. The original sample consisted of 70 individuals living with HIV (mean age 50 years, SD = 12.6) at baseline. At the two-year follow-up, 48 of the 70 baseline participants provided an additional sample, and four new participants provided a sample only at follow-up, for a total of 52 samples at the follow-up time point. Baseline self-reported demographic characteristics included age, self-reported sex, and self-reported race (pooled into three categories of Black, White, and Other, based on small sample sizes for other groups). All baseline samples were collected before the COVID pandemic, and all but one sample at follow-up were collected after the COVID-19 pandemic began. All study protocols were approved by the Institutional Review Board at Hofstra/Northwell Health with approval number 18–0660.

2.2. Psychosocial measures

Psychosocial stressors were measured using a variety of assessments administered at baseline and follow-up. Participants completed the Trauma History Questionnaire (THQ), a psychometrically validated instrument [59,60] that covers a wide range of potentially traumatic events that may meet Criterion A1 of the DSM-V-TR [61], required for the diagnosis of PTSD. For this study, investigators operationalized the THQ scale into five different measures. First, a total trauma scale comprised a sum of cumulative traumatic events for participants not missing data for two or more items (Cronbach's alpha = 0.82, indicating high internal consistency). Next, the sum of repeated events (1 if repeated, 0 if not), a sum of recent events (past 5 years), and a sum of childhood events (events occurring <18 years of age) was calculated. For all the summed scales, categorical versions were created, and they were coded as "1" if they had any trauma within each respective category (recent vs. childhood vs. repeated) or "0" if not.

Participants were also administered the most recent version of the Post-Traumatic Stress Disorder Checklist for the DSM-5 (PLC-5) to measure past-month PTSD symptoms [62]. The Posttraumatic Stress Disorder Checklist is a validated and widely used self-report measure for diagnosing PTSD. The National Center for PTSD recommends using a cut-point score between 31 and 33 for an indication of probable PTSD [63]. A cut-point of 31 was used to determine PTSD symptomology; however, the PCL-5 was coded solely as a continuous variable for all analyses.

Symptoms of anxiety and depression were measured using the Patient Health Questionnaire-4 (PHQ-4 [64]). The PHQ-4 consists of anxiety and depression subscales, and the total score reflects the overall symptom burden. Each of the PHQ-4 subscales was analyzed separately.

Stress was measured using the Perceived Stress Scale-10 (PSS), which was developed to measure the extent to which respondents found their lives "unpredictable, uncontrollable, and overloading" [65]. A higher PSS score indicated higher stress levels and was used as a continuous variable.

2.3. Coping strategies

Coping strategies were measured using the Brief-COPE [45]. Each of the 14 dimensions, or coping strategies, was separately assessed for analyses using the Brief-COPE. These include emotion-focused coping (acceptance, emotional support, humor, positive reframing, and religion), problem-focused coping (active coping, planning, and instrumental support), and dysfunctional strategies (self-distraction, denial, venting, substance use, behavioral disengagement, and self-blame).

2.4. Generation of DNAm data

DNA from previously collected whole blood samples was analyzed to determine DNA methylation levels for sample participants. Following standard protocols, DNA was first isolated and purified using Qiagen's QIAamp Blood Midi Kit, and the concentration and purity of the DNA were assessed using a Qubit Fluorometric Quantification System and a Nanodrop Spectrophotometer. Then, 250 ng of DNA were bisulfite converted in duplicate using Zymo's EZ DNA Methylation-Gold™ kit protocols. All bisulfite-treated samples were amplified via polymerase-chain reaction using an EpigenDX™-designed primer for *FKBP5*, which amplifies sites within bin 2 of intron 7 as referenced in Klengel et al [22]. Positive and negative controls were used for each PCR, all assays were validated with known methylation controls prior to use, and gel electrophoresis was used to determine if each sample was amplified successfully and without contamination. Each successfully amplified duplicate for *FKBP5* was pyrosequenced using Qiagen's Pyromark Q24. For assaying methylation at *SLC6A4*, optimized primers were used to amplify the DNA [66], and successfully amplified duplicates for *SLC6A4* were sent to EpigenDX™ for pyrosequencing using the Qiagen Pyromark Q96. Primer sequences and chromosomal locations of assayed sites can be found in Supplementary Figure S1. Of the original 70 baseline and 52 follow-up samples, DNA was successfully assayed for all but one sample at follow-up for *FKBP5* and for 69 samples at baseline and 51 at follow-up for *SLC6A4*, though numbers ranged across CpG sites. The percent methylation values we report are direct estimates from bisulfite pyrosequencing, which are comparable to the Beta values reported in most Illumina microarray studies.

2.5. Data analysis

Summary statistics for each demographic and relevant health factor from each time point were calculated. Because not all variables are normally distributed, non-parametric tests were used to compare mean differences at each time point. We tested for changes between the groups at each time point using primarily unpaired tests due to high loss to follow-up, and non-parametric tests for the non-normally distributed data. Mann–Whitney tests were used to compare mean differences at each time point for continuous variables, and chi-

square tests were used to compare the categorical variables across time points. Wilcoxon signed rank (paired) tests were used to test for stability of methylation data over time within the same individuals. Bivariate Spearman correlations were tested at each time point to explore the relationships between all factors that may influence methylation, including demographics, health factors (e.g., CD4 counts, smoking), coping measures, mental health measures, and trauma measures. Based on these findings, and theoretical considerations of factors that are known to influence methylation (e.g., smoking [67]), we selected covariates to include in the regression models. For example, because HIV-related health variables, such as cell counts or viral load, were not correlated with methylation at either gene (Supplementary Tables S1 and S2), we did not include these in the presented regression models. Similarly, because heavy alcohol use and recreational drug use were not significantly associated with methylation at either gene, we did not include these behaviors in the subsequent analyses (Supplementary Tables S3 and S4). The exploratory multiple linear regressions were conducted with the dependent variable of DNA methylation at each CpG site or the average across sites, controlling for covariates of age, sex (male as the reference group), race (White as the reference group), and current smoking status. Diagnostic plots and normality tests of residuals were run to test for model fit, and all models met the assumptions of linear regressions. Because of the exploratory nature of the paper, and the fact that all tested sites are not independent, we opted not to include multiple testing corrections in this study.

3. Results

3.1. Demographics

Demographic and health characteristics of 70 baseline and 51 follow-up samples are shown in Table 1. At baseline, the mean age of the sample was 50.5 years; 24% were female, the majority were born in the U.S. (72%), most participants had a household income of less than $93,000. Regarding health characteristics at baseline, 40% of the sample had a history of AIDS, but only 6% had a detectable viral load, with similar proportions at follow-up. At both time points, 18% screened positive for PTSD upon completion of the PCL-5. Current smoking (19% baseline vs 10% follow-up), heavy alcohol use (monthly or more frequent, 7% vs 9%), and recreational drug

Table 1. Sample characteristics at baseline and follow-up.

Characteristics	Baseline ($n = 70$)	Follow-up ($n = 51$–53)	P-value[†]
Demographics			
Age, years, mean(SD)	50.5 (12.63, 25–77)	54.61 (11.95, 27–78)	**0.0492**
Female, N(%)	24 (0.34)	14 (0.27)	0.4238
Race, N(%)			0.7887
Black,	30 (0.43)	19 (0.37)	–
White	30 (0.43)	23 (0.45)	–
Other Race	10 (0.14)	9 (0.18)	–
Ethnicity, N(%)			
Latinx	10 (0.14)	12 (0.24)	0.1930
Born in the US, N(%)	50 (0.72)	39 (0.76)	0.5346
Health-Related Variables			
Smoking(current), N(%)	13 (0.19)	5 (0.10)	
Heavy Alcohol Use,* N(%)			0.2169
Never	41 (0.40)	39 (0.73)	
Once or Twice	24 (0.34)	9 (0.17)	
Monthly	4 (0.06)	3 (0.06)	
Weekly	0 (0.00)	1 (0.02)	
Daily/almost daily	1 (0.01)	1 (0.02)	
Recreational Drug Use, N(%)			0.9689
Never	53 (0.78)	30 (0.79)	
Once or Twice	5 (0.07)	2 (0.05)	
Monthly	2 (0.03)	1 (0.03)	
Weekly	2 (0.03)	2 (0.05)	
Daily/almost daily	6 (0.09)	3 (0.08)	
AIDS status, N(%)	28 (0.40)	21 (0.41)	1
Viral Load detected, N(%)	4 (0.06)	3 (0.07)	
PTSD Score, mean(SD)	13.21 (15.58, 0–57)	12.97 (20.04, 0–68)	0.4286
PTSD Scored ≥ 31, N(%)	12 (0.18)	7 (0.18)	1
PSS Score, mean(SD)	12.94 (7.94, 0–32)	12.13 (7.66, 0–30)	0.5760
PHQ-4 Anxiety Score, mean (SD)	1.10 (1.79, 0–6)	1.31 (2.07,0–6)	0.6798
PHQ-4 Depression Score, mean (SD)	0.88 (1.58,0–6)	0.85 (1.58, 0–6)	0.9727
Lifetime History of Trauma			
Trauma Sum Score, mean(SD)	4.62 (3.89, 0–18)	–	–
Child Trauma, N(%)	31 (0.44)	–	–
Child Trauma continuous, mean(SD)	1.01 (1.52, 0–6)	–	–
Recent, N(%)	33 (0.47)	–	–
Recent continuous, mean(SD)	0.91 (1.41, 0–8)	–	–
Repeated, N(%)	39 (0.56)	–	–
Repeated continuous, mean(SD)	1.43 (1.79, 0–7)	–	–

[†]P-values derived from the Wilcoxon rank-sum test for continuous variables, and the Chi-square test for categorical variables.
*Heavy alcohol use indicates 5 or more drinks for men or 4 or more drinks for women in a single setting in the past year.
Significant p-values <0.05 are bolded.

use (weekly and/or daily, 9% vs 3.8%) were similar at baseline and follow-up time points.

Lifetime Trauma History data are shown in Table 1 and Supplementary Table S5. At baseline, 44% reported experiences of childhood trauma (<18 years old), 47% reported experiencing a recent traumatic event (within 5 years), and 56% reported repeated exposure to any traumatic event. The most frequently reported types of trauma were receiving news of a serious injury, life-threatening illness, or unexpected death of someone close (53%) and ever having a serious or life-threatening illness (47%).

3.2. Methylation levels over time

Mean methylation values were very similar across time points in both measured genes (Table 2). Values at *FKBP5* sites were high (>90%), while values at *SLC6A4* sites were relatively low (<10%), consistent with expected levels based on prior studies in blood at both genes [22,66].

3.3. Correlations among study variables

There were numerous correlations of key study variables with DNA methylation at both time points in *SLC6A4*, but only at the follow-up time point within *FKBP5* (Supplementary Tables S6 and S7). Specifically, at baseline, methylation at various sites within *SLC6A4* was negatively correlated with PTSD, PSS, anxiety, and depression symptoms, and some coping mechanisms, including humor and self-blame. At follow-up, sites within *FKBP5* correlated negatively with anxiety and the coping strategy of acceptance. In contrast, various sites within *SLC6A4* correlated positively with overall trauma, repeated trauma, and acceptance coping but negatively with depression and self-blame coping (Supplementary Table S7).

3.4. Baseline regression results for FKBP5

In linear regression models at baseline, adjusted for the covariates of age, sex, self-identified race, and smoking status, we identified no significant associations between methylation at *FKBP5* and lifetime history of trauma, regardless of how it was modeled (i.e., recent vs. childhood vs. repeated vs. accumulated). There was a significant negative association between humor and *FKBP5* methylation at CpG1 [B: −0.31 (0.15), $p = 0.0394$; adj $R^2 = 0.102$], such that those who used humor more often as a coping strategy had lower DNAm at this site. None of the demographics or smoking covariates were associated with methylation at this gene region.

Table 2. Methylation levels over time.

Methylation Levels *FKBP5*	Baseline ($n = 70$)	Follow-up (n's range 50–51)	p-value†
CpG1	95.9	96.0	0.8614
CpG2	92.6	92.5	0.7514
Methylation Levels *SLC6A4*	Baseline (n's range 60–69)	Follow-up (n's range 38–51)	
CpG1	10.2	9.46	0.1098
CpG2	5.23	4.86	0.2918
CpG3	3.15	3.05	0.8666
CpG4	2.91	2.51	0.3152
CpG5	3.00	3.42	0.6036
CpG6	4.17	3.78	0.1370

†P-values represent results from paired Wilcoxon signed rank tests comparing means between those in the study at both time points.

3.5. Baseline regression results for SLC6A4

In linear regression models at baseline, adjusted for the same demographics as in models of *FKBP5*, we identified significant negative associations between average *SLC6A4* methylation and depressive symptoms [B: −0.35 (0.13), $p = 0.0082$], PTSD symptoms [B: −0.03 (0.01), $p = 0.0374$], perceived stress [B: −0.06 (0.03), $p = 0.0435$], and coping strategies of self-blame [B: −0.43 (0.19), $p = 0.0344$] and humor [B: −0.43 (0.21), $p = 0.0151$] (Supplementary Figure S2). These associations were also significant at individual CpG sites, including CpG 1, 2, 4, and 6 (Table 3). Total repeat trauma was also negatively associated with methylation only at CpG4 [B: −0.22 (0.11), $p = 0.0423$], and anxiety was negatively associated with methylation only at CpG 1 [B:-0.62 (0.23), $p = 0.0109$]. Of the covariates included, only smoking status was associated with methylation at baseline.

3.6. Follow-up regression results for FKBP5

In linear regression models, none of the trauma variables were associated with *FKBP5* methylation at either site or across the average of sites (Table 4). Methylation across the average of both CpG sites was negatively associated with anxiety symptoms [B: −0.30 (0.07), $p = 0.0001$], depression symptoms [B: −0.26 (0.10), $p = 0.0103$], and the coping strategy of self-blame [B: −0.36 (0.16), $p = 0.0287$] (Supplementary Figure S3). Significant negative associations were also identified at individual CpG sites with these same variables, as well as with various coping strategies, including substance use, acceptance, and self-distraction (Table 4). The only covariate associated with methylation at this time point was sex.

3.7. Follow-up regression results for SLC6A4

We identified positive associations between the average *SLC6A4* methylation in linear regression models and any repeated trauma (B: 1.31 (0.49), $p = 0.0149$, Table 5, Supplementary Figure 4). We also found associations with trauma scales at individual sites within *SLC6A4*, including between CpG3 and any childhood trauma [B: 1.16 (0.55), $p = 0.0444$] and any repeat trauma models [B: 1.19 (0.57), $p = 0.0441$], (Table 5). Cumulative trauma was also significantly associated with methylation at CpG4, but not after removing one influential outlier. Methylation at CpG1 is marginally negatively associated with depression symptoms [B: −0.71 (0.35), $p = 0.0494$]. Methylation at CpG3 is marginally negatively associated with venting [B: −0.71 (0.35), $p = 0.0497$]. The only covariate associated with methylation at this time point was race.

Table 3. Baseline models of stress, mental health, trauma, coping and *SLC6A4* methylation.

	CpG1		CpG2		CpG4		CpG6		Avg CpGs (1–6)	
	B(SE) p-value	Adj. R^2	B(SE) p-value	Adj. R^2	B(SE) p-value	Adj. R^2	B(SE) p-value	Adj. R^2	B(SE) p-value	Adj. R^2
Stress, Mental Health, and Trauma Variables										
PHQ-4 Anxiety	−0.62 (0.23) 0.0109	0.0588								
PHQ-4 Depression	−0.63 (0.26) 0.0176	0.0436							−0.35 (0.13) 0.0082	0.0826
PSS									−0.06 (0.03) 0.0435	0.0135
PTSD					−0.03 (0.01) 0.0209	0.1336			−0.03 (0.01) 0.0374	0.0199
Total Repeat Trauma					−0.22 (0.11) 0.0423	0.1196				
Coping Variables										
Self-Blame	−0.88 (0.40) 0.0314	0.0313					−0.34 (0.16) 0.0368	0.0621	−0.43 (0.19) 0.0344	0.0277
Self-Distraction			−0.69 (0.22) 0.0034	0.1940						
Humor			−0.48 (0.23) 0.0470	0.1167					−0.43 (0.21) 0.0464	0.0151
Substance Use			−0.76 (0.31) 0.0159	0.1483						

Each model included covariates of self-reported sex, age, race, and current smoking status. Only significant findings at p-value<0.05 are presented.

Table 4. Follow-up models of stress, mental health, trauma, coping, and *FKBP5* methylation.

	CpG1		CpG2		AVG.	
Stress, Mental Health, and Trauma Variables	B(SE) *p*-value	Adj. R^2	B(SE) *p*-value	Adj. R^2	B(SE) *p*-value	Adj. R^2
PHQ-4 Anxiety	−0.23 (0.10) 0.0319	0.0930	−0.36 (0.09) 0.0005	0.3043	−0.30 (0.07) 0.0001	0.3559
PHQ-4 Depression			−0.40 (0.12) 0.0018	0.2555	−0.26 (0.10) 0.0103	0.1869
Coping						
Self-Distraction	−0.52 (0.22) 0.0213	0.1202				
Self-Blame					−0.36 (0.16) 0.0287	0.2026
Acceptance	−0.45 (0.20) 0.0260	0.1119	0.47 (0.22) 0.0381	0.1918		
Substance Use	−0.85 (0.40) 0.0403	0.0935				

Each model included covariates of self-reported sex, age, race, and current smoking status. Only significant findings at p-value<0.05 are presented.

Table 5. Follow-up models of stress, mental health, trauma, coping, and *SLC6A4* methylation.

	CpG1		CpG3		Average CpG1-CpG6	
Stress, Mental Health, and Trauma	B(SE) *p*-value	Adj. R^2	B(SE)	Adj. R^2	B(SE) *p*-value	Adj. R2
PHQ-4 Depression	−0.71 (0.35) 0.0494	−0.0117				
Any Childhood Trauma			1.16 (0.55) 0.0444	0.1582		
Any Repeat Trauma			1.19 (0.57) 0.0441	0.1585	1.31 (0.49) 0.0149	0.2690
Coping						
Venting			−0.71 (0.35) 0.0497	0.1643		

Each model included covariates of self-reported sex, age, race, and current smoking status. Only significant findings at p-value<0.05 are presented.

4. Discussion

This study explored the relationships between DNA methylation at two stress-related genes (*FKBP5* and *SLC6A4*) and various stress, trauma, resilience, and health factors. To our knowledge, this is the first study to investigate *SLC6A4* and *FKBP5* methylation in PLWH and the first to explore the relationship between coping strategies and methylation at these genes. This study also represents a unique opportunity for

investigation of lifetime trauma and its mental health and epigenetic correlates, as PLWH tend to report high levels of trauma and high mental health risk [1,2], as was identified in our study as well. Associations were found between methylation at both genes and mental health symptoms, including depression and anxiety, and various coping strategies, including self-blame, humor, and substance use. Additional associations were also identified with *SLC6A4* methylation and various measures of trauma. While many of these associations were not always consistent across time points, potentially due to small sample sizes at follow-up, these findings point to a role for methylation in the embodiment of trauma and mental health in PLWH.

Below, we further describe the implications of these exploratory findings, how they relate to similar studies on the epigenetics of stress, trauma, and resilience, and how this study contributes to the hypothesis that epigenetic differences have a role in contributing to the impact of stress and trauma on health.

4.1. Stress, trauma, and mental health

Though *FKBP5* methylation was not associated with trauma at either time point, we identified several associations with *SLC6A4* methylation and various trauma models at both time points. At baseline, we found reduced methylation associated with greater levels of repeated trauma, PTSD, and perceived stress, which are consistent with prior findings by Koenen and colleagues [36], who found lower methylation at this gene in blood mediated the relation of traumatic events with PTSD, and lower methylation was also found in maternal leukocytes and cord blood in mothers with depression during pregnancy [66]. However, some prior studies have also found opposite directions of effect, when measured across different tissues and populations [35,47]. Interpretation of our findings is limited by small sample sizes, particularly at follow-up.

It was also intriguing that mental health symptoms of depression and anxiety were associated with methylation at both genes and across time points at *SLC6A4*. The negative associations between *FKBP5* methylation and depression and anxiety symptoms at follow-up are consistent with prior findings of decreased *FKBP5* methylation at these same loci in association with greater exposure to trauma or childhood adversity [22,68,69], and higher expression has been linked with greater levels of depression [70], and PTSD [22]. Because cortisol binding can lead to decreased methylation levels at the regulatory element in intron 7 of *FKBP5*, thereby increasing the expression of this gene, this mechanism can ultimately dampen the feedback regulation of the HPA axis [48,71].

At both time points, we identified a negative association between *SLC6A4* methylation and depression symptoms, which was also in the same direction as identified in prior studies [36]. *SLC6A4* is responsible for producing the serotonin transporter (5-HTT) that removes serotonin (5-HT) from the synaptic cleft [72]. Methylation at *SLC6A4* is an important biological mechanism for regulating serotonin transporter availability, which is well established as relevant to mental health outcomes [31,72].

4.2. Coping strategies

To our knowledge, no prior studies have investigated the relationship between coping strategies outlined in the Brief-COPE and methylation at any stress-related genes. We identified several associations between various sites in each gene and multiple-coping strategies across time points, including emotion-focused coping strategies, such as humor and acceptance, and avoidance-focused coping strategies, such as self-distraction and substance use. While these findings provide valuable insights, it is important to note that the results varied across CpG sites and time points, and directions of effect were not always as expected. However, associations with coping may simply result from more frequent experiences of trauma or stress that facilitate the use of different coping strategies, and thus, the association with coping may simply be a byproduct of high levels of trauma. Prior studies have also shown that seemingly adaptive or positive strategies may not always yield straightforward or positive health outcomes, such as higher blood pressure has been found with greater vigilance among African Americans [73]. More research is needed to distinguish the effects of trauma and coping on methylation.

4.3. HIV-Related potential confounders

Previous research has shown that HIV infection is associated with an increased epigenetic age [56–58]. Medication adherence has also been associated with slower epigenetic aging [74]. While these studies are beneficial for understanding the pathogenesis and treatment of HIV, changes in epigenetic aging could also be related to higher levels of inflammation resulting from higher levels of stress [75,76]. Additionally, prior studies among PLWH have primarily focused on CpGs near or within immune-related genes and have identified associations between methylation at these loci and HIV infection [54,55]. However, no studies have yet investigated methylation at stress-related genes in people living with HIV. We found no associations between HIV-related health variables and methylation at either gene, even after adjusting for potential confounding factors that may occur with active infections (e.g., white blood cell counts). This outcome was unexpected, given that HIV typically alters immune cell levels. However, 94% of the participants in our study had undetectable levels of viral load, and 93% had high adherence to antiretroviral medications, which may have reduced their relevance in this sample. Further, these variables may not be especially relevant at the stress-related genes examined in this study.

Our study time points encompassed the COVID-19 pandemic, yet we did not detect significant differences over time in measures of methylation, mental health, or perceived stress. This suggests that the impact of COVID-19 may not have been relevant to these measures in our population.

4.4. Strengths and limitations

Our study examines DNA methylation in relation to lifetime histories of trauma, mental health, and coping in people living with HIV. This population is uniquely vulnerable to mental health challenges, both in the context of disease acquisition and in living with

a highly stigmatized disease. The comprehensive inclusion of measurements of trauma, PTSD, stress, anxiety, depression, and coping strengthens the study. For example, we tested various models of lifetime trauma history – childhood, cumulative, recent, and repeated trauma – to examine their relationships with epigenetic data. However, our findings did not favor any single model over the others. Additionally, by employing the THQ to assess trauma history, we adopted a broad definition encompassing crime-related events, general disasters and trauma, and both physical and sexual abuse across the lifespan. This contrasts with the more limited focus of commonly used measures (e.g., ACEs), which primarily assess childhood abuse and household dysfunction [77]. Moreover, though heavy alcohol use and substance use did not associate with methylation at either gene, these factors are often underreported, especially in stigmatized populations [78]. Our hypothesis-driven approach, which focuses on select candidate genes, is also critical for understanding how particular genes contribute to the physiological response to stress and trauma, especially in studies with smaller sample sizes where genome-wide approaches may not be suitable.

There are several limitations to this study. Our study may be the first to analyze stress-related methylation in PLWH, but our findings should be interpreted cautiously due to small sample sizes, particularly at follow-up, which may contribute to inconsistencies in the direction of effects across CpG sites and time points. While the literature tends to show early life stress to associate with methylation in adulthood, our findings were less consistent, and we believe it may be that our measures of lifetime stress were prone to significant recall bias. Participants did not always answer questions about early life stress consistently or with similar levels of detail, nor did they report the severity of the traumas. It is also possible that the coping mechanisms helped mitigate effects of the earlier traumas for some individuals, but we were not able to test this hypothesis given the small sample size that precluded interaction analyses. Additionally, our examination of DNA methylation in whole blood complicates interpretations because of its heterogeneous nature and potential for confounding from cell composition effects [79]. However, we partially addressed this issue by including individual blood cell count measures, which did not influence our findings. The occasional inconsistencies in our results are in line with findings from other large studies that have struggled to identify consistent associations with trauma or early life stress using genome-wide approaches [80,81]. Moreover, it remains possible that blood may not be the optimal tissue for assessing trauma effects, and stronger associations may be found in other tissues. Finally, there is a possibility that the HIV infection itself masked associations with trauma, but this was unlikely to be a significant contributor, as all individuals in our study had very low viral loads, and we attempted to account for immune response differences by adjusting for cell counts, which had no effect in our analyses.

5. Conclusions

Our study identified many associations between methylation at stress-related genes and anxiety and depression, highlighting a biological mechanism for the potential embodiment of mental health at the molecular level in PLWH. Conversely, the associations with coping strategies indicate a potential buffering role for these factors in people with high levels of trauma or mental health symptoms. However, further research is needed to test for interactions and gather more detailed measures to disentangle coping strategies from trauma exposures. Though lifetime histories of trauma (childhood, recent, or repeated) did not associate consistently across sites or time points in either gene, future studies with larger samples are needed to test these hypotheses of critical windows of trauma exposure fully. Future research could also examine other candidate genes of interest (*OXTR, BDNF, NR3C1)* or expand to genome-wide searches in studies with much larger sample sizes and across other tissues.

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Author contributions

Cassidy J. Tomlinson, Amy L. Non, and Rebecca M. Schwartz conceived of the study, and participated in its design. Cassidy J. Tomlinson and Amy L. Non generated and analyzed the epigenetic data. Cassidy J. Tomlinson drafted the original manuscript, and Cassidy J. Tomlinson, Amy L. Non, Rebecca M. Schwartz, Laura Ryniker, and Haley M. Cook, participated in the interpretation of the data and critically revised the manuscript. All the authors read and approved the final manuscript.

Amy L. Non is a member of the Epigenomics Editorial Board. They were not involved in any editorial decisions related to the publication of this article, and all author details were blinded to the article's peer reviewers as per the journal's double-anonymized peer review policy.

Disclosure

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Ethical declaration

All study protocols were approved by the Institutional Review Board at Hofstra/Northwell Health under approval #18–0660. The participants all provided their written informed consent to participate in this study.

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Data availability statement

The data in the current study are available from the corresponding author upon request.

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