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BRIEF REPORT

Psychosocial Correlates of Monocyte Activation and HIV Persistence in Methamphetamine Users

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Abstract

This cross-sectional study investigated the associations of psychosocial factors relevant to recovery from substance use disorders with monocyte activation and HIV persistence in a sample of 84 HIV-positive, methamphetamine-using sexual minority men with undetectable HIV viral load (<40 copies/mL). We examined if psychosocial factors were associated with decreased soluble CD14 (sCD14) and lower proviral HIV DNA. Multiple linear regression models adjusted for age, anti-retroviral therapy regimen, and CD4+ T-cell count. Time on ART was also included in models examining proviral HIV DNA. Greater self-efficacy for managing methamphetamine triggers and higher social support for abstinence were independently associated with lower sCD14. Greater social support for abstinence was also independently associated with lower proviral HIV DNA. Psychosocial factors relevant to recovery from substance use disorders are associated with lower monocyte activation and decreased proviral HIV DNA. Findings underscore the need for longitudinal research to identify plausible mechanisms linking psychosocial factors and substance use with biological processes relevant to HIV pathogenesis.

Keywords HIV persistence · Immune activation · Methamphetamine · Self-efficacy · Social support

Introduction

The use of methamphetamine and other stimulants has consistently been linked to faster clinical Human Immunodeficiency Virus (HIV) progression (Carrico 2011; Adams et al. 2017). This may be partially due to the fact that stimulant users are more likely to experience difficulties with anti-retroviral therapy (ART) adherence that contribute to higher viral load (Ellis et al. 2003; Carrico et al. 2011). However, the associations of stimulant use with faster clinical HIV progression often remain after adjusting for ART adherence and viral load (Cook et al. 2008; Carrico et al. 2014). Further clinical research is needed to elucidate plausible biological pathways whereby stimulant use may accelerate clinical HIV progression.

Autonomic nervous system (ANS) dysregulation is one of many biologically plausible pathways that could partially account for stimulant-associated immune dysregulation in HIV. Methamphetamine use is associated with reduced heart rate variability and lower parasympathetic tone (Henry et al. 2012). Methamphetamine administration also increases salivary alpha amylase, a peripheral biomarker of ANS activation (Haile et al. 2013). In HIV-positive persons, greater ANS activity before starting ART and higher urinary norepinephrine predict poorer suppression of HIV viral load (Cole et al. 1998; Ironson et al. 2015). Because sympathetic nerve terminals juncture with lymphoid tissue, this could have important implications for HIV persistence. This is partially supported by prior research that observed markedly higher levels of Simian Immunodeficiency Virus (SIV) replication where lymph nodes juncture with sympathetic nerve terminals (Sloan et al. 2006).

Although the persistence of a latent reservoir in treated HIV infection is a major barrier to finding an HIV cure, there is currently no widely accepted 'gold standard' for measuring the HIV reservoir that persists in immune cells and

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lymphoid tissue (Richman et al. 2009). To date, studies have focused extensively on quantifying the amount of integrated proviral HIV DNA and cell-associated HIV RNA in immune cells. Integrated proviral HIV DNA is thought to persist in resting CD4+ memory T-cells, and it has generally been considered to be an archival variant that does not index active HIV replication (Avettand-Fènoël et al. 2016). However, the potential relevance of measuring proviral HIV DNA is supported by prior research where greater proviral DNA and a higher ratio of cell-associated HIV RNA to proviral HIV DNA were correlated with a measure of viral outgrowth (Eriksson et al. 2013). Furthermore, greater proviral HIV DNA has also been linked to clinically relevant outcomes, including HIV-associated neurocognitive disorders (Valcour et al. 2010).

There is some preliminary evidence from human studies that ANS dysregulation and methamphetamine use may contribute to HIV persistence among those who are virally suppressed. Greater sympathetic nervous system activation has been associated with greater intracellular HIV RNA but not higher proviral HIV DNA (Hecht et al. 2015). Although one prior study observed that methamphetamine users displayed higher proviral HIV DNA compared to non-users (Massanella et al. 2015), findings were not significant after adjusting for ART regimen. In another study with treated methamphetamine users, recent stimulant use was associated with the upregulation of genes and pathways relevant to HIV latency and immune activation (Carrico et al. 2018). Further research is needed to examine substance-associated elevations in measures of HIV persistence.

Because the parasympathetic nervous system innervates the intestinal tract, methamphetamine and other stimulant use could potentiate microbial translocation (commonly referred to as the leaky gut). The translocation of microbial products such as lipopolysaccharide (LPS) is partially attributable to intestinal damage by HIV early in infection (Brenchley et al. 2006; Sandler and Douek 2012). Translocation of LPS and other microbial products drives immune activation and inflammation despite effective ART (Tien et al. 2010; Hunt 2012; Lederman et al. 2013). Previous research by Irwin et al. (2007) with HIV-negative cocaine users observed that cocaine infusion decreased LPS-stimulated monocyte expression of tumor necrosis factor – alpha (TNF-α) and interleukin-6 (IL-6). Concurrent cocaine-induced ANS dysregulation was associated with decreased TNF-α expression on monocytes. Similarly, findings from a cross-sectional study with virally suppressed methamphetamine users observed that recent stimulant use and greater substance use severity are associated with higher soluble CD14 (sCD14), which partially reflects LPS stimulation (Carrico et al. 2018).

This present study examined if psychosocial factors relevant to recovery from substance use disorders are associated with monocyte activation and HIV persistence in virally suppressed methamphetamine users. We hypothesized that greater self-efficacy for managing methamphetamine triggers and higher social support for abstinence would be associated with lower sCD14 as well as decreased proviral HIV DNA. Consistent with our prior research documenting the association of substance abuse severity with higher sCD14 (Carrico et al. 2018), we also hypothesized that greater substance use severity would be associated with higher proviral HIV DNA.

Methods

HIV+ sexual minority men with biologically confirmed recent methamphetamine use were recruited from HIV medical clinics, Acquired Immune Deficiency Syndrome (AIDS) service organizations, substance abuse treatment programs, the community, and referrals from active participants for a randomized controlled trial (Carrico et al. 2016b). Participants then signed an informed consent at an in-person screening visit that included consent for specimen banking. The inclusion criteria for all enrolled participants were: 1) 18 years of age or older; 2) report anal sex with man in the past 12 months; 3) have documentation of HIV+ serostatus (i.e. letter of diagnosis or ART medications other than Truvada matched to photo identification); and 4) provide a urine or hair sample that was confirmed to be reactive for methamphetamine.

Once participants were enrolled, they were asked to complete a separate baseline assessment approximately one week after enrollment that included a detailed battery of psychosocial measures, a urine sample for on-site toxicology testing, and peripheral venous blood sample to measure HIV disease markers. Participants also provided an additional two 10 mL EDTA tubes for specimen banking (i.e., plasma and extracted leukocyte DNA). Only 84 participants with undetectable HIV viral load (< 40 copies/mL) were included in the present study.

Measures

Demographics and Health Status The participants completed a demographic questionnaire that assed age and race/ethnicity. They also reported their current ART regimen, time since starting ART, and ART adherence during the past 30 days using the visual analogue scale (Giordano et al. 2004). HIV viral load testing was performed to detect plasma HIV RNA using the Abbott Real Time HIV-1 assay (Abbott Molecular, Inc.; Des Plaines, IL). This assay has a lower limit of detection of 40 copies/mL. CD4+ T-cell count was measured with

whole blood using flow cytometry, and assays were performed by Quest Diagnostics.

Psychosocial Factors Participants completed a measure of self-efficacy that indexes perceived ability to resist methamphetamine use in high-risk situations (Breslin et al. 2000). The social support measure assesses the extent to which participants have social relationships that are supportive of abstinence (Prochaska et al. 1994). Prior research with methamphetamine-using sexual minority men receiving substance abuse treatment observed that these measures of self-efficacy and social support were most strongly associated with less stimulant use (Carrico et al. 2013).

Psychiatric Comorbidities The Addiction Severity Index (ASI) was administered to assess the severity of alcohol and other substance use (McLellan et al. 1992). Depression was assessed using the 20-item Centers for the Epidemiologic Study - Depression (CES-D) scale, using a cutoff of ≥27 to indicate severe depression (Reisner et al. 2009). Post-Traumatic Stress Disorder (PTSD) symptoms were measured with the PTSD Checklist – Civilian Version (PCL-C), using a validated algorithm to determine whether participants screed positive for PTSD (Ruggiero et al. 2003).

sCD14 Higher sCD14, a marker that partially reflects LPS-induced monocyte activation, was also measured in this study. The plasma levels were determined by the use of Human Quantikine Immunoassay (R&D Systems, Minneapolis, MN) following the manufacturer's instructions. For sCD14 measurement, samples were diluted 400-fold and results were expressed in ng/ml.

Proviral HIV DNA Quantitation of viral DNA was performed on extracted leukocyte DNA by digital droplet PCR (ddPCR) using a Bio-Rad QX200 ddPCR instrument (Bio-Rad Laboratories, Inc., Hercules, CA). Primers and probe bind to the LTR sequence with an amplicon length of 185 base pairs and are based on the HIV_{LAI} clone (Genbank accession number K02013). The forward primer sequence is LAI^{8981} *ctg cat ccg gag tac ttc aag aac tg*, the reverse primer sequence is LAI^{9166} *tcc cag gct caa atc tgg tct a* and that of the fluorogenic reporter probe is LAI^{9081}*56-FAM agt ggc gag/ZEN/ccc tca gat gct gc 3IABkFQ* (Integrated DNA Technologies). To perform ddPCR, the DNA target, fluorescently-labeled probe, and the ingredients for PCR reaction were partitioned into 20,000 droplets by the QX200 Droplet Generator (BioRad). PCR amplification of the template molecules occurred in each individual droplet. Following PCR amplification, each droplet was analyzed for fluorescent signal in the QX200 droplet reader to determine the fraction of PCR-positive droplets in the original sample. The dynamic range of detection for ddPCR is from 1 to $1X10^5$ copies (Bizouarn 2014). The single-copy human CCR5 gene was quantified to measure the number of cell equivalents in DNA samples for standardization purposes (Sharkey et al. 2000).

Statistical Analyses

Multiple linear regression analyses examined the independent associations of self-efficacy and social support with the outcomes after adjusting for age, ART, and CD4+ T-cell count. Consistent with our previously published work on sCD14 (Carrico et al. 2018), a multiple linear regression analysis examined the independent association of substance use severity with proviral HIV DNA. Time on ART was also included in all models examining proviral HIV DNA as an outcome.

Results

Participant age ranged from 24 to 59 years, with a mean of 43.3 (*SD* = 8.7). Half of participants were Caucasian (49%), 29% were Hispanic/Latino, 11% were African American, and 11% were other ethnic minorities or multicultural. The median CD4+ T-cell count was 645 (Interquartile Range = 449–829) cells/mm^3 and all participants had an HIV viral load less than 40 copies/mL. Approximately 43% of participants screened positive for severe depression and over half (55%) screened positive for PTSD.

As shown in Table 1, bivariate associations indicated that psychosocial factors and the ASI drug score were inversely associated with sCD14. However, only social support was inversely associated with proviral HIV DNA. In multiple linear regression analyses, there was a significant, independent association of higher self-efficacy (standardized beta = −0.40; $p = 0.0002$) as well as greater social support (standardized beta = −0.29; $p = 0.008$) with lower sCD14 (see Table 2). As shown in Table 3, greater social support (standardized beta = −0.25; $p = 0.032$) was independently associated with lower proviral HIV DNA. However, there were no significant associations of self-efficacy for managing methamphetamine triggers (standardized beta = −0.02; $p = 0.899$) and the ASI Drug Score (standardized beta = −0.07; $p = 0.449$) with proviral HIV DNA. Findings were unchanged after adjusting for ART adherence.

Discussion

This study is among the first to observe that psychosocial factors relevant to recovery from substance use disorders are

Table 1 Bivariate associations among psychosocial variables, sCD14, and proviral HIV DNA

	1	2	3	4	5	6	7
sCD14	–						
HIV DNA (log_{10})	0.09	–					
Social Support	−0.28**	−0.33**	–				
Self-Efficacy	−0.43**	−0.04	0.23*	–			
ASI Drug Score	0.35**	−0.04	−0.10	−0.49**	–		
Depressive Symptoms	0.07	0.09	−0.10	−0.21	0.41**	–	
PTSD Symptoms	0.06	0.17	−0.10	−0.14	0.26*	0.72**	–

($N = 84$)

sCD14 soluble CD14, *ASI* Addiction Severity Index, *PTSD* Post-Traumatic Stress Disorder

* $p < .05$; ** $p < .01$

associated with lower monocyte activation and decreased HIV persistence. There were small-moderate associations of greater self-efficacy and social support with lower SCD14 and higher social support with lower proviral HIV DNA. Self-efficacy and substance use severity were not significantly associated with proviral HIV DNA. Taken together, these results provide preliminary support for further research to examine the bio-behavioral mechanisms whereby substance use could alter HIV pathogenesis.

Social support and self-efficacy have previously been identified as important psychosocial processes that could support recovery among methamphetamine-using sexual minority men (Carrico et al. 2013). Although findings from the present study underscore the potential relevance of these psychosocial change processes for HIV pathogenesis, it remains unclear whether these associations are attributable to decreased substance use. Further research is needed to determine if these associations are due to psychosocial factors or if these psychosocial factors are serving as a proxy for lower addiction severity. Future studies should also examine if evidence-based substance abuse interventions such as cognitive-behavioral therapy and contingency management reduce monocyte activation and proviral HIV DNA by decreasing stimulant use (Carrico et al. 2016a).

Findings indicated that greater social support for abstinence was associated with lower proviral HIV DNA. This is consistent with prior findings from our team where recent stimulant use was associated with upregulation of single genes and two-directional perturbation of pathways relevant to HIV latency and immune activation (Carrico et al. 2018). It is noteworthy, however, that other research has not observed significant differences in proviral HIV DNA between methamphetamine users and non-users (Massanella et al. 2015). Further clinical research that includes measures

Table 2 Associations of psychosocial factors with sCD14 ($N = 84$)

Model 1: Self-Efficacy	β	95% CI	Standardized β	*p*-value
Age (years)	9.88	(−1.09, 20.84)	0.18	0.077
Prescribed a Protease Inhibitor	256.20	(24.56, 487.84)	0.24	0.031
Prescribed Efavirenz	199.60	(−261.48, 660.67)	0.09	0.391
CD4+ Count	0.38	(0.004, 0.75)	0.21	0.047
Self-Efficacy	−1.17	(−1.76, 0.58)	−0.40	0.0002
Adjusted $R^2 = 0.232$				
Model 2: Social Support	β	95% CI	Standardized β	*p*-value
Age (years)	7.42	(−4.29, 19.13)	0.13	0.211
Prescribed a Protease Inhibitor	317.25	(77.02, 557.47)	0.29	0.010
Prescribed Efavirenz	480.21	(9.82, 950.59)	0.21	0.046
CD4+ Count	0.40	(0.005, 0.79)	0.23	0.047
Social Support	−23.04	(−0.29, −39.75)	−0.29	0.008
Adjusted $R^2 = 0.160$				

Table 3 Associations of psychosocial factors and substance use severity with proviral HIV DNA (log_{10}) (N =84)

Model 1: Self-Efficacy	β	95% CI	Standardized β	*p*-value
Age (years)	0.02	(−0.01, 0.04)	0.18	0.183
Prescribed a Protease Inhibitor	−0.11	(−0.56, 0.34)	−0.06	0.619
Prescribed Efavirenz	−0.26	(−1.12, 0.61)	−0.07	0.561
CD4+ Count	−0.00068	(−0.001, 0.00004)	−0.23	0.063
Time on ART	0.006	(−0.03, 0.04)	0.05	0.741
Self-Efficacy	0.0001	(−0.001, 0.001)	0.02	0.899
Adjusted $R^2 = 0.037$				
Model 2: Social Support	β	95% CI	Standardized β	*p*-value
Age (years)	0.01	(−0.01, 0.04)	0.14	0.280
Prescribed a Protease Inhibitor	−0.12	(−0.55, 0.31)	−0.06	0.587
Prescribed Efavirenz	−0.18	(−1.00, 0.64)	−0.05	0.658
CD4+ Count	−0.0006	(−0.001, 0.0002)	−0.19	0.128
Time on ART	0.003	(−0.03, 0.03)	0.02	0.877
Social Support	−0.03	(−0.06, −0.003)	−0.25	0.032
Adjusted $R^2 = 0.094$				
Model 3: ASI Drug Score	β	95% CI	Standardized β	*p*-value
Age (years)	0.02	(−0.01, 0.04)	0.19	0.165
Prescribed a Protease Inhibitor	−0.10	(−0.55, 0.35)	−0.06	0.654
Prescribed Efavirenz	−0.25	(−1.09, 0.60)	−0.07	0.561
CD4+ Count	−0.00069	(−0.001, 0.00006)	−0.23	0.070
Time on ART	0.004	(−0.03, 0.04)	0.04	0.800
ASI Drug Score	−0.81	(−2.95, 1.32)	−0.07	0.449
Adjusted $R^2 = 0.0326$				

of active viral replication such as cell-associated HIV RNA are clearly needed to examine the bio-behavioral mechanism(s) whereby substance use could alter HIV persistence. Identifying these pathways could identify novel targets for HIV cure interventions.

Findings from this cross-sectional study should be interpreted in context of some important limitations. Findings should be considered preliminary due to the small sample size and cross-sectional design. This study also focused exclusively on enrolling sexual minority men, and further research with women is clearly needed. This study relied on the biologically confirmed presence of any stimulant use for inclusion, and future research should assess methamphetamine and cocaine concentrations through quantitative toxicology measures as well as include a comparison group of non-users. Because peripheral blood mononuclear cells were not banked in this study we were unable to measure cell-associated HIV RNA and HIV DNA in specific immune cell subsets, which could provide a more nuanced understanding of the HIV reservoir. It is also unclear the extent to which these associations are attributable to psychosocial factors, decreased stimulant use, or distinct patterns of polysubstance use. Although depressive and PTSD symptoms were not associated with sCD14 or proviral HIV DNA, future research should examine these psychiatric comorbidities as potential moderators. Finally, we did not test for Hepatitis C Virus (HCV) co-infection or measure liver functioning, both of which are important possible confounders that should be measured in future studies.

Despite these limitations, the findings from this study provide some of the first evidence for psychosocial factors relevant to recovery from substance use disorders are associated with lower monocyte activation and decreased proviral HIV DNA. These results support the scientific premise of further clinical research to examine the bio-behavioral pathways whereby substance use may amplify monocyte activation and alter HIV persistence.

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Compliance with Ethical Standards

This study was approved by University of California San Francisco, University of Miami, and Northwestern University Institutional Review Boards. The participants signed a written consent form for enrollment into this study.

Conflict of Interest The Authors have no conflicts of interest to report.

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