Title

Multiple substance use, inflammation and cardiac stretch in women living with HIV

Authors

Riley, Elise D

Kizer, Jorge R

Tien, Phyllis C

et al.

Publication Date

2022-09-01

DOI

10.1016/j.drugalcdep.2022.109564

Peer reviewed

HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2023 September 01.

Published in final edited form as:

Drug Alcohol Depend. 2022 September 01; 238: 109564. doi:10.1016/j.drugalcdep.2022.109564.

Multiple substance use, inflammation and cardiac stretch in women living with HIV

Elise D. Riley, PhD, MPH[1], **Jorge R. Kizer, MD, MSc**[2,3], **Phyllis C. Tien, MD**[1], **Eric Vittinghoff, PhD**[3], **Kara L. Lynch, PhD**[4], **Alan H.B. Wu, PhD**[4], **Phillip O. Coffin, MD**[1,5], **Gabriele Beck-Engeser, BS**[6], **Carl Braun, BS**[1], **Peter W. Hunt, MD**[1,6]

[1]University of California, San Francisco, School of Medicine, Department of Medicine, Division of HIV, Infectious Diseases and Global Medicine, San Francisco, California, USA.

[2]San Francisco VA Health Care System, Division of Cardiology, San Francisco, California, USA.

[3]University of California, San Francisco, School of Medicine, Department of Epidemiology and Biostatistics, San Francisco, California, USA.

[4]University of California, San Francisco, School of Medicine, Department of Laboratory Medicine, San Francisco, California, USA.

[5]San Francisco Department of Public Health, San Francisco, California, USA.

[6]University of California, San Francisco, School of Medicine, Department of Experimental Medicine, San Francisco, California, USA

Abstract

BACKGROUND: Cardiovascular disease (CVD) and heart failure (HF) are disproportionately high in people living with HIV and differ by sex. Few CVD-related studies focus on drug use, yet it is common in low-income women living with HIV (WLWH) and increases cardiac dysfunction.

SETTING: We recruited unsheltered and unstably housed WLWH from San Francisco community venues to participate in a six-month cohort study investigating linkages between drug use, inflammation, and cardiac dysfunction.

METHODS: Adjusting for CVD risk factors, co-infections, medications, and menopause, we examined the effects of toxicology-confirmed drug use and inflammation (C-reactive protein, sCD14, sCD163 and sTNFR2) on levels of NT-proBNP, a biomarker of cardiac stretch and HF.

RESULTS: Among 74 WLWH, the median age was 53 years and 45% were Black. At baseline, 72% of participants had hypertension. Substances used included tobacco (65%), cannabis (53%), cocaine (49%), methamphetamine (31%), alcohol (28%), and opioids (20%). Factors significantly associated with NT-proBNP included cannabis use (Adjusted Relative Effect [ARE]: −39.6%) and sTNFR2 (ARE: 65.5%). Adjusting for heart failure and restricting analyses to virally suppressed persons did not diminish effects appreciably. Cannabis use was not significantly associated with sTNFR2 and did not change the association between sTNFR2 and NT-proBNP.

Corresponding author: Elise Riley, 1001 Potrero Ave., UCSF Mailbox 0874, San Francisco, CA 94143-0874, Elise.Riley@UCSF.edu.

CONCLUSIONS: Among polysubstance-using WLWH, NT-proBNP levels signaling cardiac stretch were positively associated with sTNFR2, but 40% lower in people who used cannabis. Whether results suggest that cardiovascular pathways associated with cannabis use mitigate cardiac stress and dysfunction independent of inflammation in WLWH who use multiple substances merits further investigation.

Keywords

HIV; Women; substance use; NT-proBNP; inflammation; sTNFR2

1. Introduction

HIV and substance use are both known to increase the risks of cardiac dysfunction and cardiovascular events common to overdose (e.g., heart attack and stroke), particularly in some high-risk populations. For example, substance use among unsheltered and unstably housed women living with, and at risk for, HIV is common (>50% prevalence) (Riley et al., 2015), and cocaine-related overdose is a common cause of death in this population (Riley et al., 2013). However, most large-scale HIV studies regarding cardiovascular disease and cardiac dysfunction do not account for substance use. The extent to which ongoing substance use contributes to chronic cardiac dysfunction is therefore unknown.

Monitoring NT-proBNP, a biomarker which signals volume overload and cardiac stretch, provides an opportunity to monitor cardiac dysfunction, improve targeting of individuals with increased cardiovascular risk, and optimize strategies for primary and secondary prevention of cardiovascular disease (Campbell, 2008). A better understanding of factors that are associated with or influence NT-proBNP could contribute to more effective strategies for improving cardiovascular health (Manzano-Fernandez et al., 2009). Such improvements are especially important in women, particularly racial/ethinic minority women, for whom heart failure (HF) is a foremost cardiovascular disorder (Nayak et al., 2020). The heterogeneity of women with HF has led to recent calls for gender-specific research to inform care strategies specific to women of all races and ethnicities, many who are not in consistent care (Carlson et al., 2020).

PLWH have higher NT-proBNP levels than age-matched people living without HIV (Berg et al., 2007; Secemsky et al., 2015). Consistent with research from the general population, the higher NT-proBNP levels found in PLWH are associated with cardiovascular dysfunction (Secemsky et al., 2015), and represent one of several serum biomarkers used to classify individuals into separate risk categories that predict mortality independent of cardiac structure and function (Gingo et al., 2015; Scherzer et al., 2018). Research conducted specifically in women living with HIV (WLWH) confirms that NT-proBNP is an independent marker of mortality (Gingo et al., 2015). While WLWH have higher NT-proBNP levels than women living without HIV, the differences have been linked to non-HIV factors such as kidney disease, anemia and HCV coinfection (Mansoor et al., 2009), reflecting the contributions of comorbidities to cardiac volume regulation in the setting of HIV infection (Mansoor et al., 2009). Given that PLWH are at higher risk for non-AIDS co-morbidities and shorter life expectancy than those without HIV, even in the

modern era of effective antiretroviral therapy (Antiretroviral Therapy Cohort, 2008), the conditions contributing to these risks, such as substance use, and their association with potential pathways signaled by NT-proBNP, warrant attention.

Cardiac risks among PLWH are due to multiple factors outside of substance use, paramount among them being inflammation, which persists during effective antiretroviral treatment (Hsue et al.). For example, research shows associations between markers of general inflammation, such as C-reactive protein (CRP), and cardiovascular outcomes (Gilotra and Geraci, 2017). In addition, higher sCD163 (a biomarker of innate monocyte/macrophage activation) and sTNFR2 (a biomarker of inflammatory TNF-signaling) levels are among the strongest predictors of myocardial infarction in antiretroviral therapy (ART)-suppressed PLWH (Tenorio et al., 2014). Furthermore, sCD14 is related to risk of incident HF in older adults (Al-Kindi et al., 2020), and in association with stimulant use, predicts mortality in treated HIV infection (Carrico et al., 2018; Hunt et al., 2014; Sandler et al., 2011). A more nuanced treatment of human studies examining the associations of substance use with markers of immune activation and inflammation in HIV is needed (Slawek et al., 2021). The simultaneous consideration of inflammatory factors alongside substance use could provide a more accurate understanding of how each influences cardiac dysfunction. We therefore determined associations of substance use and markers of inflammation with NT-proBNP levels in unsheltered and unstably housed WLWH, as well as the extent to which alterations in immune activation and inflammation mediate associations between significantly influential substances and NT-proBNP levels.

2. Material and Methods

2.1. Study design

Polysubstance Use and Health Outcomes Evaluation (PULSE) is a prospective study of unsheltered and unstably housed women living in San Francisco. Between June 2016 and January 2019, study participants made monthly visits for six consecutive months to examine the influences of substance use on markers of cardiac dysfunction, including NT-proBNP. Two-hundred forty-five women (172 HIV- and 77 HIV+) were recruited from homeless shelters, free meal programs, low-income single room occupancy (SRO) residential hotels), street encampments, the Zuckerberg San Francisco General Hospital HIV clinic (“Ward 86”), and from provider and participant referrals. The current analysis was restricted to WLWH who had available biomarker data (n=74).

Inclusion criteria were female sex at birth, age ≥ 18 years and a history of housing instability (i.e., slept in public or a homeless shelter, or stayed with a series of associates because there was no other place to sleep [“couch-surfed”]). HIV antibody testing was conducted at screening. All study procedures reported here were approved by the Institutional Review Board at the University of California, San Francisco (IRB Study #14–13868).

2.2. Data Collection

Participants completed confidential study visits consisting of an interview, blood draw, urine collection and vital sign assessment. Measures were assessed at all visits with the

exception of inflammatory biomarkers, which were only assessed at two of the six study visits. Data for the current study were therefore restricted to the two study visits where all measures were available. Given that substances and combinations of substances used change over time, we included information from both visits to increase heterogeneity in substance exposure. Questionnaires and study procedures were pilot tested to ensure appropriateness for the target population.

2.3. Dependent Outcome Measures

We used serum samples from two study visits per participant to evaluate the level of NT-proBNP (Roche NT-proBNP; cutoff for HF in a non-acute setting for individuals younger than 75 years >125 pg/mL) (Farnsworth et al., 2018).

2.4. Independent Exposure Measures

The primary exposure assessed was toxicology-confirmed substance use (Table 1). We tested for the presence of substances as well as pharmaceutical drugs in hydrolyzed urine samples using a qualitative liquid chromatography-high resolution mass spectrometry (LC-HRMS) method. Data acquisition and generation of mass spectra took place using an SCIEX 5600 TripleTOF® LC-HRMS system. Data were acquired using HRMS full scan mode with information-dependent acquisition of HRMS product ion spectra, which were searched against a mass spectral library for positive identification of each substance. The methodology has proven sensitive and specific for the detection of these compounds in urine (Thoren et al., 2016), using standardized detection limits for each analyte (Thoren et al., 2016). To increase cannabis test sensitivity, we conducted separate urine THC screening, which uses a liquid chromatography tandem mass spectrometry (LC-MS/MS) method to detect THC−COOH (>0.5 ng/mL) and THC-COOH-glucuronide (2.5 ng/mL) (Benowitz et al., 2019a). Additional substance and pharmaceutical drug metabolites included the following: cocaine, cocaethylene, amphetamine, methamphetamine, heroin, additional opioids, fentanyl, methadone, buprenorphine, naloxone, lidocaine, benzodiazepines, cotinine (>10 pg/ml, a marker of smoking (Benowitz et al., 2019b), ethyl glucuronide (a marker for alcohol), beta blockers, calcium channel blockers, diuretics, nitrates, antihypertensive agents, statins, vasodilators, antithrombotic agents and acetaminophen (Table 1).

Additional exposures from the same two study visits included age, race, ethnicity, menopausal status (>12 months since last menstrual period), estradiol (Enhanced Estradiol Assay: eE2, Siemens ADVIA® Centaur XP), chronic health conditions, CVD risk factors and inflammatory markers. Chronic health conditions included HIV antibody status, as well as self-reported conditions including hepatitis C infection, diabetes, prior myocardial infarction and prior stroke. Additional CVD risk factors were measured in a standardized fashion, including body mass index (BMI), calculated as weight in kilograms and height as meters squared (kg/m^2), systolic blood pressure and diastolic blood pressure. We assessed blood pressure according to a standardized protocol, with participants sitting upright and both feet planted on the floor after a five-minute period of rest and silence. An Omron™ wrist blood pressure monitor was used for obese participants based on research staff discretion, and an Omron™ upper arm blood pressure monitor was used for all other participants. Inflammatory markers included high sensitivity C-reactive protein

(CardioPhase™ High-Sensitivity CRP, Siemens ADVIA® Chemistry XPT). In addition, sTNFR2, sCD163 and sCD14 were selected as a panel of inflammatory biomarkers due to their associations with cardiac dysfunction and/or substance use (Al-Kindi et al., 2020; Carrico et al., 2018; Hunt et al., 2014; Sandler et al., 2011; Tenorio et al., 2014). All three analytes have relatively low within-subject-variability, supporting their utility in studies with modest sample sizes. Plasma levels of sCD14, sCD163, and sTNFR2 were all assessed in duplicate using commercial ELISA kits (all R&D Systems). The coefficients of variation for all ELISAs were <5% and measures were log-transformed for analysis to meet assumptions of normality.

2.5. Analysis

We used linear mixed models to estimate unadjusted and adjusted associations between exposure measures and log-transformed NT-proBNP from two study visits per participant. Beginning with the subset of exposures associated at $p<0.1$ with NT-proBNP in unadjusted analysis, we used backwards deletion to select final models. In a final step, we added markers of HIV inflammation, allowing for a crude assessment of potential mediation. To avoid potential confounding by recent heart failure, we adjusted estimates among individuals with available electronic health record data for heart failure noted at any point during the study, or up to two years prior. To assess influences from substance use without potential residual confounding by viral load, we also conducted a sensitivity analysis in which only virally suppressed persons were included. All analyses were done using Stata Version 15.0 (Stata Corp., College Station, TX).

3. Results

The sample population included 74 out of 77 (96%) PULSE participants living with HIV who had available biomarker data. Among participants with biomarker data, 60 had available data from two study visits, while the remaining 14 had available data from one study visit, resulting in 134 observations. The median participant age was 53 years (range: 25.5–68; IQR: 41–59) and 73% were racial or ethnic minority women (Table 2). Median BMI was 28.8, which is regarded as “overweight” (Sahakyan et al., 2015), 12% of participants reported a previous diabetes diagnosis, and 46% reported hepatitis C infection. Two-thirds (66%) of study participants were virally suppressed. Prior physician-diagnosed MI and stroke were self-reported by 8% and 11% of participants, respectively. At baseline, 72% had blood pressures that met criteria for hypertension (i.e., systolic >120 mm Hg or diastolic>80 mm Hg) (Table 2).

The prevalence of toxicology-confirmed substances at any study visit included cotinine/nicotine (65%); cannabis (53%); cocaine (49%); methamphetamine (31%); alcohol (28%); non-heroin opioids (20%); cocaethylene (16%); and heroin (3%) (Table 2). Seventy-seven percent of participants had evidence of more than one substance (polysubstance use) at one or more study visits (Table 3). Toxicology-confirmed use of CVD-related pharmaceutical drugs was rare (1.4% hypertensive agents, 4.1% calcium channel blockers, 10.8% beta blockers and 0% statins) (Table 2).

Median levels of inflammatory markers included sCD14 (Median=3.44 ng/ml; IQR=2.93, 3.93), sCD163 (Median=168 ng/ml; IQR=1.2, 2.39) and sTNFR2 (Median=1.21 pg/ml; IQR: 0.84–1.75). Inflammatory markers were not highly correlated (Pearson's Correlation ≤ 0.56 for each permutation).

3.1. NT-proBNP

At baseline, the median level of NT-proBNP was 78.8 pg/mL (IQR: 38.1, 158). A level of NT-proBNP exceeding 125 pg/mL (the cutoff for HF for individuals younger than 75 years in a non-acute setting (Farnsworth et al., 2018)) was observed in 33 participants (45%) during at least one of the two study visits. Table 4 shows that, after adjusting for other significant variables, including age and race/ehtnicity, cannabis was the only substance significantly associated with NT-proBNP. NT-proBNP levels were 40% lower among women who were toxicology positive for cannabis (Adjusted Relative Effect: −39.6%; 95% CI: −56.1%, −17.0%). In addition, effects from combinations of drugs that included cannabis were largely similar to effects from cannabis only (data not shown), and the overall heterogeneity of variables for all models including drug combinations was significant.

Each inflammatory marker was positively associated with NT-proBNP in unadjusted analysis, though only sCD14 (Adjusted Relative Effect per standard deviation [SD]: 33.3%; 95% CI: 10.2%, 61.2%) and sTNFR2 (Adjusted Relative Effect per SD: 59.8%; 95% CI: 33.0%, 92.1%) reached levels of significance. Adjusting for age, race/ethnicity and cannabis use, a similar level of association was maintained for each inflammatory marker. When adjusted estimates included age, race/ethnicity, cannabis use and all inflammatory markers simultaneously, sTNFR2 effects were maintained; however, sCD14 was no longer significant and sCD163 effects reversed direction (Adjusted Relative Effect per SD: −20.9%; 95% CI: −34.9%, −4.0%).

Analyses restricted to virally suppressed individuals (n=54) were not appreciably different, though the magnitude of association between sTNFR2 and NT-proBNP doubled (data not shown).

Analyses restricted to individuals with available electronic health record data (n=55) showed a similar cannabis effect (Adjusted Relative Effect: −40.3%; 95% CI: −59.2%, −12.7%), which changed to a limited degree after adjusting for heart failure, but was still statistically significant (Adjusted Relative Effect: −34.7; 95% CI: −56.7%, −1.7%). Likewise, associations were significant when analyses were restricted to virally suppressed individuals with electronic health record data (n=51), even after adjusting for each inflammatory marker (data not shown). The exception was that the cannabis effect diminished substantially when all inflammatory markers were included in the same model and that model was restricted to virally suppressed people with electronic health records, at which point the magnitude of effect for cannabis was reduced to −19.5% (95% CI: −43.8%, 15.4%).

4. Discussion

In this community-recruited sample of unsheltered and unstably housed WLWH, almost 80% used multiple substances and 45% had NT-proBNP levels above the normal range for non-acute settings over a six-month study period. This finding confirms unsheltered and unstably housed WLWH as a group at especially high risk for cardiac dysfunction. Among 19 substances and pharmaceutical drugs tested, cannabis was the only one significantly, and negatively, associated with NT-proBNP level. Effects from drug combinations including cannabis were similar to cannabis only and overall heterogeneity of models assessing drug combinations were significant, reinforcing the idea that the effect from each individual substance was distinct, and the effect from cannabis was in fact due to cannabis rather than a combined effect. In addition, HIV viral load and hepatitis C co-infection were not significantly associated with NT-proBNP levels. Likewise, several CVD risk factors (e.g., prior MI, prior stroke, diabetes, cotinine and alcohol) did not reach levels of significance in this sample population. Prior research suggests that cannabis contributes to an anti-inflammatory profile in people living without HIV (e.g., lower systemic TNF-α in cannabis users)(Ribeiro et al., 2021), as well as in people living with HIV (Costiniuk and Jenabian, 2019) (e.g., lower levels of monocyte activation [CD14++CD16+] in people living with HIV) (Castro et al., 2019; Manuzak et al., 2018; Rizzo et al., 2018). However, the combined use of cannabis and cocaine lead to an increased proinflammatory status (Ribeiro et al., 2021). Here we found no evidence of potential mediation of cannabis effects on NT-proBNP by inflammatory markers including sTNFR2, indicating independent contributions by each. Our findings suggest that, in high-risk polysubstance-using WLWH, markers of cardiac stretch are higher in those with higher levels of sTNFR2 and lower in people who use cannabis. While further research is needed to confirm these findings from a single, modest-sized sample, results suggest that mechanisms of cardiac stretch may be influenced by protective effects of cannabis use independent of sTNFR2 in WLWH who use substances.

While some studies report associations between cannabis use and acute coronary syndromes (Richards et al., 2019), recent reviews point to large prospective studies that have failed to show significant associations between cannabis use and cardiovascular events, concluding that the relationship is still unclear (Alfulaij et al., 2018; Ghosh and Naderi, 2019). Results presented here contribute prospective evidence to this ongoing dialog in finding that, among polysubstance-using WLWH, the toxicology-confirmed presence of cannabis is negatively associated with a biomarker of cardiac stretch. Possible mechanisms and pathways are unclear, but deserve consideration. Some prior studies suggest that cannabis has beneficial health effects, including among PLWH (Bredt et al., 2002; Manuzak et al., 2018); however, the relationship is complicated. For example, cannabis activation of the endocannabinoid receptor 1 (CB_1R) can lead to adverse cardiovascular effects through a variety of mechanisms (e.g., endothelial dysfunction, cell death, tissue injury, oxidative stress, smooth muscle proliferation)(Pacher et al., 2018), whereas activation of CB_2R (expressed primarily in immune cells) exerts anti-inflammatory effects (Pacher et al., 2018). The association we observed between cannabis use and lower NT-proBNP levels did not appear to be explained by lower levels of inflammatory markers, suggesting that factors independent of TNF-α signaling may account for this inverse association. However, it is

possible that cannabis was influencing inflammatory markers other than those studied here. Complicating these relationships is the potential effect modification by the concentration of Δ9−tetrahydrocannabinol (THC) found in cannabis, which may have an atheroprotective effect at low doses (Steffens et al., 2005). However, dramatic increases in the THC content of available cannabis over the past decade have complicated the assessment of its impact (Pacher et al., 2018). Future studies that not only qualitatively assess the presence of each drug, but quantitatively assesses drug concentration, may provide a more complete understanding of these initial associations. Another potential mechanism linking cannabis with lower levels of NT-proBNP is weight gain from increased appetite, which could lead to higher neprilysin breakdown of NT-proBNP (Packer, 2018); however, BMI was not significant here, suggesting that this is not a significant contributing factor.

While the inflammatory marker hsCRP is predictive of HF in the general population (Anand et al., 2005), we did not find an association between hsCRP and NT-proBNP levels in our study of WLWH. Since CRP is synthesized in the liver and both HIV and viral hepatitis are often associated with hepatic synthetic dysfunction, CRP may be less reflective of the inflammatory state in HIV and less predictive of cardiovascular outcomes than in the general population.(Reingold et al., 2008; Ronit et al., 2018) Nevertheless, we found that the inflammatory marker sTNFR2, which is increased in treated HIV infection and strongly predicts cardiovascular events and mortality in this setting,(Tenorio et al., 2014) was strongly and independently associated with higher NT-proBNP levels. Interestingly, higher sCD163 levels, which have been associated with vascular inflammation (Subramanian et al., 2012) and subsequent myocardial infarction in some but not all prior studies (Hoenigl et al., 2019; Knudsen et al., 2013), were associated with paradoxically lower NT-proBNP levels in our study. While this association was no longer significant after restricting to ART-suppressed participants (and hence was not as robust an association as sTNFR2), this was a surprising finding without an obvious explanation. sCD163 is associated with M2 macrophage activation in tissues, which is associated with the fibrotic responses often observed in HF, and higher plasma sCD163 has been linked to HF with preserved ejection fraction in a prior study of individuals without HIV (Glezeva et al., 2015). Why we found the opposite association in a sample of WLWH is unclear, and needs to be confirmed in future studies. Nevertheless, an important clue may be that we only revealed a negative correlation between sCD163 and NT-proBNP after simultaneously adjusting for sTNFR2 levels; in unadjusted analyses, we found no evidence for a negative correlation. One potential explanation for this phenomenon is that CD163-expressing “M2” macrophages may be induced in response to inflammation (and hence are associated with sTNFR2), but they often secrete IL-10, which can decrease inflammation (Crayne et al., 2019). Thus, adjusting for the degree of inflammation (i.e., sTNFR2), might unmask anti-inflammatory properties associated with sCD163.

Consistent with a recent study by Al-Kindi et al., which found a significant association between sCD14 and HF in adults over age 65 (Al-Kindi et al., 2020), we found a significant association between sCD14 and NT-proBNP; however, we observed that the association was no longer significant after adjusting for sTNFR2.The *Health ABC Study* did not find a significant association between sTNFR2 level and incident HF among adults in their 70s (average age=74 years), but did document significant associations between sTNFR1 and HF.

Whether differences between this study and the ABC study are due, at least in part, to the 20 year age difference between sample populations, the difference in the proportion of female, unsheltered or minority study participants, or the difference in sTNFR2 measurement (because cytokine receptors are known to be more stable and longer lasting in circulation than cytokines themselves) is unknown. Moreover, whether the difference can be explained by the fact that the *ABC Study* was not composed of participants living with HIV is unclear. It is plausible that the contributions of inflammatory responses to cardiac dysfunction are qualitatively different in individuals living with an immune deficiency syndrome.

Analyses reported here suggest no significant association between NT-proBNP and viral load, which is similar to reports by the Women's Interagency HIV Study (WIHS) (Mansoor et al., 2009). However, our results are dissimilar in that the WIHS observed strong associations between NT-proBNP and chronic hepatitis C infection, but but we did not find an association between NT-proBNP and self-reported hepatitis C infection. While we adjusted for prior hepatitis C treatment, we did not have data on sustained virologic response (SVR). It is unclear whether differences in results between studies can be accounted for by such measurement differences, the absence of kidney function in our model, the absence of substance use in the WIHS models, or general differences in the study populations. Compared to the WIHS, participants from the current study were older (53 vs. 42), more likely to smoke tobacco (65% vs. 48%), have Stage 2 hypertension (40% vs. 27%) and more likely to have HCV infection (46% vs. 26%). Regardless of the specific differences between methodologies and data, both studies confirm that among ART-treated women, NT-proBNP levels are not discernably related to HIV disease severity, but rather to non-HIV factors.

Our study has several potential limitations. First, results may not be generalizable to men since NT-proBNP concentrations differ by sex (Leosdottir et al., 2011). Second, the number of comparisons made was large and the sample was modest. Third, while the number of factors considered was substantial, it did not include serum creatinine or hemoglobin due to the absence of available data. Future studies with larger and more diverse populations, which include these measurements, will help elucidate the initial findings reported here. Fourth, as is true in every study, it is possible that unmeasured factors are confounding results. For example, we did not find significant associations between NT-proBNP and several socioeconomic factors (income, education, insurance status); however, it is possible that people who use cannabis may have other resources associated with better cardiac health. Fifth, findings reported here are from a small sample. Replicating results in larger cohorts will increase the evidence-base and ensure reliability of findings. However, while additional studies will address issues of generalizability, it will be important to consider the possibility that results may not be generalizable to all WLWH, but rather to other popualtions of people who use substances and higher-risk individuals. This possibility could have implications for targeted interventions or adaptations to risk assessment tools in very high-risk populations like this, rather than all WLWH.

Study strengths include a community-based sample of polysubstance-using women, over 70% of whom were women of color. Our community-based sampling allowed us to reduce the bias of only including people seeking care, which would result in a sample with clinically apparent conditions and those with access to health care. In addition, the

all-women sample allowed for the estimation of women-specific results, and the longitudinal nature of the study allowed for data collection at multiple time points. Lastly, we not only included a comprehensive list of substances, as well as commonly prescribed pharmaceutical drugs, but each was confirmed by mass spectrometry.

5. Conclusion

NT-proBNP levels signaling cardiac stretch are positively associated with sTNFR2, but 40% lower in WLHW who use cannabis. Cardiovascular pathways associated with cannabis use may mitigate cardiac stress and dysfunction in WLWH, particularly those with high levels of substance and polysubstance use. Whether this protective effect is generalizable to other WLWH, and the conditions in which it is more likely, merit further investigation.

Acknowledgements

The authors thank the research team and study participants for their efforts in completing this study.

This research was supported by the National Institutes of Health (R01 DA037012; R01 DA049648; K24 DA039780).

References

Al-Kindi SG, Buzkova P, Shitole SG, Reiner AP, Garg PK, Gottdiener JS, Psaty BM, Kizer JR, 2020. Soluble CD14 and Risk of Heart Failure and Its Subtypes in Older Adults. J Card Fail 26, 410–419. [PubMed: 32165348]

Alfulaij N, Meiners F, Michalek J, Small-Howard AL, Turner HC, Stokes AJ, 2018. Cannabinoids, the Heart of the Matter. J Am Heart Assoc 7.

Anand IS, Latini R, Florea VG, Kuskowski MA, Rector T, Masson S, Signorini S, Mocarelli P, Hester A, Glazer R, Cohn JN, Val-He FTI, 2005. C-reactive protein in heart failure: prognostic value and the effect of valsartan. Circulation 112, 1428–1434. [PubMed: 16129801]

Antiretroviral Therapy Cohort C., 2008. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 372, 293–299. [PubMed: 18657708]

Benowitz N, Nardone N, St Helen G, Addo N, Jacob P 3rd, Liakoni E, Jain S, Hooshfar S, Lynch K, 2019a. Quantitative biochemical screening for marijuana use and concordance with tobacco use in urban adolescents. Drug Alcohol Depend 205, 107583 [Epub ahead of print]. [PubMed: 31600618]

Benowitz NL, Bernert JT, Foulds J, Hecht SS, Jacob P, Jarvis MJ, Joseph A, Oncken C, Piper ME, 2019b. Biochemical Verification of Tobacco Use and Abstinence: 2019 Update. Nicotine Tob Res.

Berg T, Zdunek D, Stalke J, Dupke S, Baumgarten A, Carganico A, Hess G, 2007. N-terminal pro-B-type natriuretic peptide (NT-proBNP) in HIV-1 infected individuals on HAART. Eur J Med Res 12, 152–160. [PubMed: 17509959]

Bredt BM, Higuera-Alhino D, Shade SB, Hebert SJ, McCune JM, Abrams DI, 2002. Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients. J Clin Pharmacol 42, 82S–89S. [PubMed: 12412840]

Campbell DJ, 2008. Can measurement of B-type natriuretic peptide levels improve cardiovascular disease prevention? Clin Exp Pharmacol Physiol 35, 442–446. [PubMed: 18307738]

Carlson B, Hoyt H, Kunath J, Bratzke LC, 2020. Gender Differences in Hispanic Patients of Mexican Origin Hospitalized with Heart Failure. Womens Health Issues 30, 384–392. [PubMed: 32660828]

Carrico AW, Cherenack EM, Roach ME, Riley ED, Oni O, Dilworth SE, Shoptaw S, Hunt P, Roy S, Pallikkuth S, Pahwa S, 2018. Substance-associated elevations in monocyte activation among methamphetamine users with treated HIV infection. AIDS 32, 767–771. [PubMed: 29369159]

Castro FOF, Silva JM, Dorneles GP, Barros JBS, Ribeiro CB, Noronha I, Barbosa GR, Souza LCS, Guilarde A, Pereira A, Guimaraes RF, Oliveira TF, Oliveira SEF, Peres A, Romao PRT, Pfrimer IAH, Fonseca SGD, 2019. Distinct inflammatory profiles in HIV-infected individuals under ART using cannabis, cocaine or cannabis plus cocaine. AIDS.

Costiniuk CT, Jenabian MA, 2019. Cannabinoids and inflammation: implications for people living with HIV. AIDS 33, 2273–2288. [PubMed: 31764093]

Crayne CB, Albeituni S, Nichols KE, Cron RQ, 2019. The Immunology of Macrophage Activation Syndrome. Front Immunol 10, 119. [PubMed: 30774631]

Farnsworth CW, Bailey AL, Jaffe AS, Scott MG, 2018. Diagnostic concordance between NT-proBNP and BNP for suspected heart failure. Clin Biochem 59, 50–55. [PubMed: 30111510]

Ghosh M, Naderi S, 2019. Cannabis and Cardiovascular Disease. Curr Atheroscler Rep 21, 21. [PubMed: 30980200]

Gilotra TS, Geraci SA, 2017. C-Reactive Protein as an Independent Cardiovascular Risk Predictor in HIV+ Patients: A Focused Review of Published Studies. J Clin Med Res 9, 891–899. [PubMed: 29038665]

Gingo MR, Zhang Y, Ghebrehawariat KB, Jeong JH, Chu Y, Yang Q, Lucht L, Hanna DB, Lazar JM, Gladwin MT, Morris A, 2015. Elevated NT-pro-brain natriuretic peptide level is independently associated with all-cause mortality in HIV-infected women in the early and recent HAART eras in the Women's Interagency HIV Study cohort. PLoS One 10, e0123389. [PubMed: 25811188]

Glezeva N, Voon V, Watson C, Horgan S, McDonald K, Ledwidge M, Baugh J, 2015. Exaggerated inflammation and monocytosis associate with diastolic dysfunction in heart failure with preserved ejection fraction: evidence of M2 macrophage activation in disease pathogenesis. J Card Fail 21, 167–177. [PubMed: 25459685]

Hoenigl M, Moser CB, Funderburg N, Bosch R, Kantor A, Zhang Y, Eugen-Olsen J, Finkelman M, Reiser J, Landay A, Moisi D, Lederman MM, Gianella S, Adult Clinical Trials Group, N.s.t., 2019. Soluble Urokinase Plasminogen Activator Receptor Is Predictive of Non-AIDS Events During Antiretroviral Therapy-mediated Viral Suppression. Clin Infect Dis 69, 676–686. [PubMed: 30418519]

Hsue PY, Deeks SG, Hunt PW, 2012. Immunologic basis of cardiovascular disease in HIV-infected adults. J Infect Dis 205 Suppl 3, S375–382. [PubMed: 22577211]

Hunt PW, Sinclair E, Rodriguez B, Shive C, Clagett B, Funderburg N, Robinson J, Huang Y, Epling L, Martin JN, Deeks SG, Meinert CL, Van Natta ML, Jabs DA, Lederman MM, 2014. Gut epithelial barrier dysfunction and innate immune activation predict mortality in treated HIV infection. J Infect Dis 210, 1228–1238. [PubMed: 24755434]

Knudsen A, Moller HJ, Katzenstein TL, Gerstoft J, Obel N, Kronborg G, Benfield T, Kjaer A, Lebech AM, 2013. Soluble CD163 does not predict first-time myocardial infarction in patients infected with human immunodeficiency virus: a nested case-control study. BMC Infect Dis 13, 230. [PubMed: 23692821]

Leosdottir M, Willenheimer R, Hall C, Tjora S, Malm J, Melander O, Nilsson PM, 2011. Age and gender differences in the association between Nt-proBNP and glucometabolic disturbances. Scand Cardiovasc J 45, 294–300. [PubMed: 21604967]

Mansoor A, Althoff K, Gange S, Anastos K, Dehovitz J, Minkoff H, Kaplan R, Holman S, Lazar JM, 2009. Elevated NT-pro-BNP levels are associated with comorbidities among HIV-infected women. AIDS Res Hum Retroviruses 25, 997–1004. [PubMed: 19803714]

Manuzak JA, Gott TM, Kirkwood JS, Coronado E, Hensley-McBain T, Miller C, Cheu RK, Collier AC, Funderburg NT, Martin JN, Wu MC, Isoherranen N, Hunt PW, Klatt NR, 2018. Heavy Cannabis Use Associated With Reduction in Activated and Inflammatory Immune Cell Frequencies in Antiretroviral Therapy-Treated Human Immunodeficiency Virus-Infected Individuals. Clin Infect Dis 66, 1872–1882. [PubMed: 29471387]

Manzano-Fernandez S, Boronat-Garcia M, Albaladejo-Oton MD, Pastor P, Garrido IP, Pastor-Perez FJ, Martinez-Hernandez P, Valdes M, Pascual-Figal DA, 2009. Complementary prognostic value of cystatin C, N-terminal pro-B-type natriuretic Peptide and cardiac troponin T in patients with acute heart failure. Am J Cardiol 103, 1753–1759. [PubMed: 19539088]

Nayak A, Hicks AJ, Morris AA, 2020. Understanding the Complexity of Heart Failure Risk and Treatment in Black Patients. Circ Heart Fail 13, e007264. [PubMed: 32787445]

Pacher P, Steffens S, Hasko G, Schindler TH, Kunos G, 2018. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. Nat Rev Cardiol 15, 151–166. [PubMed: 28905873]

Packer M, 2018. Leptin-Aldosterone-Neprilysin Axis: Identification of Its Distinctive Role in the Pathogenesis of the Three Phenotypes of Heart Failure in People With Obesity. Circulation 137, 1614–1631. [PubMed: 29632154]

Reingold J, Wanke C, Kotler D, Lewis C, Tracy R, Heymsfield S, Tien P, Bacchetti P, Scherzer R, Grunfeld C, Shlipak M, 2008. Association of HIV infection and HIV/HCV coinfection with C-reactive protein levels: the fat redistribution and metabolic change in HIV infection (FRAM) study. J Acquir Immune Defic Syndr 48, 142–148. [PubMed: 18344877]

Ribeiro CB, Castro FOF, Dorneles GP, de Sousa Barros JB, Silva JM, Tavares C, Carvalho HR, Carlos da Cunha L, Nagib P, Hoffmann C, Peres A, Torres Romao PR, Pfrimer IAH, Fonseca SGD, 2021. The concomitant use of cannabis and cocaine coexists with increased LPS levels and systemic inflammation in male drug users. Cytokine 141, 155472. [PubMed: 33618152]

Richards JR, Bing ML, Moulin AK, Elder JW, Rominski RT, Summers PJ, Laurin EG, 2019. Cannabis use and acute coronary syndrome. Clin Toxicol (Phila) 57, 831–841. [PubMed: 30964363]

Riley ED, Cohen J, Shumway M, 2013. Overdose fatality and surveillance as a method for understanding mortality trends in homeless populations. JAMA Intern Med 173, 1264.

Riley ED, Shumway M, Knight KR, Guzman D, Cohen J, Weiser SD, 2015. Risk factors for stimulant use among homeless and unstably housed adult women. Drug Alcohol Depend 153, 173–179. [PubMed: 26070454]

Rizzo MD, Crawford RB, Henriquez JE, Aldhamen YA, Gulick P, Amalfitano A, Kaminski NE, 2018. HIV-infected cannabis users have lower circulating CD16+ monocytes and IFN-gamma-inducible protein 10 levels compared with nonusing HIV patients. AIDS 32, 419–429. [PubMed: 29194121]

Ronit A, Sharma S, Baker JV, Mngqibisa R, Delory T, Caldeira L, Ndembi N, Lundgren JD, Phillips AN, International Network for Strategic Initiatives in Global, H.I.V.T.S.T.o.A.T.S.G., 2018. Serum Albumin as a Prognostic Marker for Serious Non-AIDS Endpoints in the Strategic Timing of Antiretroviral Treatment (START) Study. J Infect Dis 217, 405–412. [PubMed: 29244111]

Sahakyan KR, Somers VK, Rodriguez-Escudero JP, Hodge DO, Carter RE, Sochor O, Coutinho T, Jensen MD, Roger VL, Singh P, Lopez-Jimenez F, 2015. Normal-Weight Central Obesity: Implications for Total and Cardiovascular Mortality. Ann Intern Med 163, 827–835. [PubMed: 26551006]

Sandler NG, Wand H, Roque A, Law M, Nason MC, Nixon DE, Pedersen C, Ruxrungtham K, Lewin SR, Emery S, Neaton JD, Brenchley JM, Deeks SG, Sereti I, Douek DC, Group, I.S.S., 2011. Plasma levels of soluble CD14 independently predict mortality in HIV infection. J Infect Dis 203, 780–790. [PubMed: 21252259]

Scherzer R, Shah SJ, Secemsky E, Butler J, Grunfeld C, Shlipak MG, Hsue PY, 2018. Association of Biomarker Clusters With Cardiac Phenotypes and Mortality in Patients With HIV Infection. Circ Heart Fail 11, e004312. [PubMed: 29615435]

Secemsky EA, Scherzer R, Nitta E, Wu AH, Lange DC, Deeks SG, Martin JN, Snider J, Ganz P, Hsue PY, 2015. Novel Biomarkers of Cardiac Stress, Cardiovascular Dysfunction, and Outcomes in HIV-Infected Individuals. JACC Heart Fail 3, 591–599. [PubMed: 26164679]

Slawek DE, Arnsten J, Sohler N, Zhang C, Grossberg R, Stein M, Cunningham CO, 2021. Daily and near-daily cannabis use is associated with HIV viral load suppression in people living with HIV who use cocaine. AIDS Care 33, 1350–1357. [PubMed: 32748649]

Steffens S, Veillard NR, Arnaud C, Pelli G, Burger F, Staub C, Karsak M, Zimmer A, Frossard JL, Mach F, 2005. Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice. Nature 434, 782–786. [PubMed: 15815632]

Subramanian S, Tawakol A, Burdo TH, Abbara S, Wei J, Vijayakumar J, Corsini E, Abdelbaky A, Zanni MV, Hoffmann U, Williams KC, Lo J, Grinspoon SK, 2012. Arterial inflammation in patients with HIV. JAMA 308, 379–386. [PubMed: 22820791]

Tenorio AR, Zheng Y, Bosch RJ, Krishnan S, Rodriguez B, Hunt PW, Plants J, Seth A, Wilson CC, Deeks SG, Lederman MM, Landay AL, 2014. Soluble markers of inflammation and coagulation but not T-cell activation predict non-AIDS-defining morbid events during suppressive antiretroviral treatment. J Infect Dis 210, 1248–1259. [PubMed: 24795473]

Thoren KL, Colby JM, Shugarts SB, Wu AH, Lynch KL, 2016. Comparison of Information-Dependent Acquisition on a Tandem Quadrupole TOF vs a Triple Quadrupole Linear Ion Trap Mass Spectrometer for Broad-Spectrum Drug Screening. Clin Chem 62, 170–178. [PubMed: 26453698]

Highlights

- Cannabis use is negatively associated with NT-proBNP in women living with HIV
- The cannabis effect is retained after adjusting for viral suppression and heart failure
- sTNFR2 is positively associated with NT-proBNP in women living with HIV
- Cannabis use is not significantly associated with sTNFR2 in women living with HIV

Table 1.

Substances Assessed

Drug or Drug Class	Individual Drugs and Drug Metabolites
Nicotine	Cotinine, Nicotine
Alcohol	Ethyl Glucuronide
Cannabis (THC)	Tetrahydrocannabinol (THC), THC−COOH and THC−COOH glucuronide
Cocaine	Benzoylecgonine, Cocaine, Ecgonine methyl ester, Norcocaine
	Cocaethylene
	Levamisole
Amphetamines	Methamphetamine, methamphetamine, MDMA
Heroin	6-Monoacetylmorphine, Heroin
Fentanyl	Fentanyl, Norfentanyl
Opioids	6-Monoacetylmorphine, Heroin, Morphine, Codeine, Hydrocodone, Hydromorphone, Dihydrocodeine, Glucuronide, Codeine Glucuronide, Oxycodone, Oxymorphone
Methadone	Methadone, EDDP
Opioid antagonist	Buprenorphine, Norbuprenorphine
Naloxone	Naloxone
Benzodiazepines	Clonazepam, Diazepam, Lorazepam, Nordiazepam, Temazepam, Oxazepam, Alprazolam alpha-hycroxyalprazolam, Flurazepam, 2-Hydroxyethlflurazepam, Desalkylflurazepam, Flunitrazepam, 7-aminto flueflunitrazepam, N-Desmethylflunitrazepam, Midazolam, 7aminotrazepam, Etizolam
Beta Blockers	Metoprolol, Atenolol, Carvedilol, Labetalol
Calcium Channel Blockers	Amlodipine, Diltiazem, Verapamil
Antiarrhythmic	Lidocaine
Diuretic	Furosemide, Hydrochlorothiazide
Other Antihypertensive Agents	Clonidine, Lisinopril, Losartan
Statins	Atorvastatin, Pravastatin, Simvastatin
phosphodiesterase-5 inhibitors (Vasodilator)	Sildenafil
Anticoagulant	Coumadin
Nitrate	Isosorbide mononitrate
Analgesic	Acetaminophen

Drug Alcohol Depend. Author manuscript; available in PMC 2023 September 01.

Table 2.

Baseline Characteristics of unsheltered and unstably housed women living with HIV by substance use[1] (N=74)

Study Characteristic	Median (IQR) or Proportion (%) Total (N=74)	Median (IQR) or Proportion (%) Alcohol Users (n=21)	Median (IQR) or Proportion (%) Cannabis Users (n=39)	Median (IQR) or Proportion (%) Stimulant Users (n=46)	Median (IQR) or Proportion (%) Opioid Users (n=21)	p-value◊
SOCIOECONOMIC FACTORS						
Age (years)	Median=53.2 (40.9, 58.9)	Median=58.0 (52.3–61.7)	Median=52.3 (38.4–58.0)	Median=53.4 (44.5–59.5)	Median=51.2 (38.4–54.5)	0.08
Race/Ethnicity						0.052
White	20 (27.0%)	3 (14.3%)	11 (28.2%)	14 (30.4%)	5 (23.8%)	
Black/African American	33 (44.6%)	13 (61.9%)	15 (38.5%)	21 (45.7%)	7 (33.3%)	
Latina(Ł)	11 (14.9%)	3 (14.3%)	6 (15.4%)	5 (10.9%)	6 (28.6%)	
Multiracial	5 (6.8%)	0 (0.0%)	4 (10.3%)	5 (10.9%)	1 (4.8%)	
Other	5 (6.8%)	2 (9.5%)	3 (7.7%)	1 (2.2%)	2 (9.5%)	
High school graduate	47 (63.5%)	15 (71.4%)	26 (66.7%)	31 (67.4%)	12 (57.1%)	0.70
Monthly income	Median=$907 (867–1025)	Median=$900 (839–1170)	Median=$900 (654–1000)	Median=$938 (889–1112)	Median=$889 (800–979)	0.11
Consistent health insurance	72 (97.3%)	21 (100%)	39 (100%)	44 (95.7%)	21 (100%)	<0.001*
Post-menopausal¶	49 (66.2%)	17 (81.0%)	23 (59.0%)	32 (69.6%)	13 (61.9%)	0.06
Estradiol (pg/mL) *Post-menopausal reference range: ND-32.2 pg/mL*	Median=24.3 (17.6, 55)	Median=21.2 (17.6, 39.8)	Median=23.7 (17.2, 77.0)	Median=23.0 (17.3, 72.8)	Median=28.1 (19.0, 39.8)	0.26
CLINICAL FACTORS						
Body Mass Index (BMI) *Reference range*: *22.0 normal* *27.5 overweight* *33.0 obese*	Median=28.8 (22.5, 34.7)	Median=27.2 (22.3, 31.5)	Median=27.1 (22.3, 31.7)	Median=24.3 (21.2, 32.5)	Median=29.6 (23.0, 33.3)	<0.001*
Systolic Blood Pressure	Median=125 (112, 141)	Median=123 (112, 140)	Median=117 (108, 138)	Median=126.5 (110, 141)	Median=127 (110, 142)	0.37
Diastolic Blood Pressure	Median=84 (76, 92)	Median=83 (76, 90)	Median=82 (75, 92)	Median=84.5 (76, 93)	Median=84 (76, 91)	0.32
Hypertension						
No hypertension	21 (28.4%)	8 (38.1%)	14 (35.9%)	12 (26.1%)	7 (33.3%)	0.39

Study Characteristic	Median (IQR) or Proportion (%) Total (N=74)	Median (IQR) or Proportion (%) Alcohol Users (n=21)	Median (IQR) or Proportion (%) Cannabis Users (n=39)	Median (IQR) or Proportion (%) Stimulant Users (n=46)	Median (IQR) or Proportion (%) Opioid Users (n=21)	p-value◊
Elevated blood pressure *(systolic ≥120 mm Hg or diastolic ≥80 mm Hg)*	4 (5.4%)	1 (4.8%)	1 (2.6%)	2 (4.3%)	1 (4.8%)	
Stage 1 hypertension *(systolic ≥130 mm Hg or diastolic ≥80 mm Hg)*	19 (25.7%)	5 (23.8%)	10 (25.6%)	12 (26.1%)	5 (23.8%)	
Stage 2 hypertension *(systolic ≥140 mm Hg or diastolic ≥90 mm Hg)*	29 (39.2%)	7 (33.3%)	13 (33.3%)	19 (41.3%)	8 (38.1%)	
Hypertensive crisis *(systolic ≥180 mm Hg or diastolic ≥120 mm Hg)*	1 (1.4%)	0 (0.0%)	1 (2.6%)	1 (2.2%)	0 (0.0%)	
Diabetes *[3]*	9 (12.2%)	3 (14.3%)	4 (10.3%)	2 (4.3%)	3 (14.3%)	0.17
Prior myocardial infarction *[3]*	6 (8.1%)	1 (4.8%)	5 (12.8%)	4 (8.7%)	0 (0.0%)	0.24
Prior stroke *[3]*	8 (10.8%)	1 (4.8%)	5 (12.8%)	5 (10.9%)	3 (14.3%)	0.46
HCV-positive *[3]*	34 (45.9%)	10 (47.6%)	17 (43.6%)	23 (50.0%)	12 (57.1%)	0.53
HIV viral load						
<50 copies/mL (ref)	49 (66.2%)	9 (42.9%)	24 (61.5%)	28 (60.9%)	12 (57.1%)	0.034 *
50–199 copies/mL	5 (6.8%)	3 (14.3%)	2 (5.1%)	2 (4.3%)	2 (9.5%)	
200–499 copies/mL	4 (5.4%)	2 (9.5%)	2 (5.1%)	3 (6.5%)	1 (4.8%)	
500–999 copies/mL	4 (5.4%)	2 (9.5%)	2 (5.1%)	4 (8.7%)	1 (4.8%)	
1000+ copies/mL	12 (16.2%)	5 (23.8%)	9 (23.1%)	9 (19.6%)	5 (23.8%)	
INFLAMMATORY BIOMARKERS						
High-sensitivity C-Reactive Protein (mg/L) *Reference range, cardiovascular risk* *< 1.0 Low* *1.0–3.0 Moderate* *3.1–10.0 High*	Median=2.95 (0.8, 8.9)	Median=1.3 (0.5, 3.6)	Median=2.5 (0.7, 7.5)	Median=1.6 (0.7, 7.5)	Median=7.8 (2.5, 16.6)	0.07 <0.001 * 0.10
sCD14 (ng/ml) *[2]* *Reference range*: 1200–2600 ng/mL	Median=1982 (1686, 2262)	Median=1957 (1727, 2418)	Median=1957 (1612, 2418)	Median=1957 (1727, 2302)	Median=1900 (1727, 2188)	0.66
sCD163 (ng/ml) *[2]* *Reference range*: 186–996 ng/ml	Median=1009 (720, 1436)	Median=1263 (842, 1684)	Median=962 (662, 1383)	Median=1022 (722, 1443)	Median=1022 (782, 1564)	0.054
sTNFR2 (pg/ml) *[2]* *Reference range: 829–2262 pg/mL*	Median=3798 (2635, 5505)	Median=4089 (2831, 5347)	Median=3460 (2516, 5033)	Median=3460 (2516, 5347)	Median=4718 (2831, 6920)	0.27
SUBSTANCE AND MEDICATION USE						

Study Characteristic	Median (IQR) or Proportion (%) Total (N=74)	Median (IQR) or Proportion (%) Alcohol Users (n=21)	Median (IQR) or Proportion (%) Cannabis Users (n=39)	Median (IQR) or Proportion (%) Stimulant Users (n=46)	Median (IQR) or Proportion (%) Opioid Users (n=21)	p-value◊
Cotinine/Nicotine [5]	48 (64.9%)	15 (71.4%)	28 (71.8%)	35 (76.1%)	15 (71.4%)	0.51
Alcohol [5]	21 (28.4%)	21 (100%)	14 (35.9%)	14 (30.4%)	4 (19.0%)	n/a
Cannabis (THC) [5]	39 (52.7%)	14 (66.7%)	39 (100%)	24 (52.2%)	12 (57.1%)	n/a
Cocaine [5]	36 (48.6%)	13 (61.9%)	18 (46.2%)	36 (78.3%)	6 (28.6%)	0.06
Cocaethylene	12 (16.2%)	8 (38.1%)	4 (10.3%)	12 (26.1%)	0 (0.0%)	<0.001*
Levamisole [5]	24 (32.4%)	9 (42.9%)	11 (28.2%)	24 (52.2%)	3 (14.3%)	0.11
Methamphetamine [5]	23 (31.1%)	4 (19.0%)	14 (35.9%)	23 (50.0%)	8 (38.1%)	0.17
Heroin/Monoacetylmorphine-6 [5]	2 (2.7%)	1 (4.8%)	2 (5.1%)	2 (4.3%)	2 (9.5%)	0.005*
Fentanyl/Norfentanyl [5]	3 (4.1%)	0 (0.0%)	2 (5.1%)	3 (6.5%)	3 (14.3%)	0.003*
Additional opioids [5]	15 (20.3%)	4 (19.0%)	12 (30.8%)	9 (19.6%)	21 (100%)	n/a
Methadone [5]	18 (24.3%)	6 (28.6%)	10 (25.6%)	12 (26.1%)	10 (47.6%)	0.18
Buprenorphine/Norbuprenorphine [5]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	⫤
Naloxone [5]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	⫤
Benzodiazepine [5]	11 (14.9%)	3 (14.3%)	4 (10.3%)	6 (13.0%)	4 (19.0%)	0.31
Beta blocker [5]	8 (10.8%)	0 (0.0%)	5 (12.8%)	4 (8.7%)	2 (9.5%)	0.68
Calcium channel blocker [5]	3 (4.1%)	0 (0.0%)	0 (0.0%)	3 (6.5%)	0 (0.0%)	<0.001*
Antiarrhythmic [5]	12 (16.2%)	8 (38.1%)	6 (15.4%)	12 (26.1%)	1 (4.8%)	0.026*
Diuretic[5]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	⫤
Antihypertensive [5]	1 (1.4%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	<0.001
Statin [5]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	⫤
Vasodialator [5] (Sildenafil)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	⫤
Anticoagulant [5]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	⫤
Nitrate ([5]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	⫤

Study Characteristic	Median (IQR) or Proportion (%) Total (N=74)	Median (IQR) or Proportion (%) Alcohol Users (n=21)	Median (IQR) or Proportion (%) Cannabis Users (n=39)	Median (IQR) or Proportion (%) Stimulant Users (n=46)	Median (IQR) or Proportion (%) Opioid Users (n=21)	p-value◊
Acetaminophen [5]	20 (27.0%)	5 (23.8%)	5 (12.8%)	9 (19.6%)	9 (42.9%)	<0.001 *

◊ p-value for association between baseline covariate and substance

* <0.01

ת >1 year since last menstrual period

(Ł) All participants reporting Latina ethnicity regardless of other racial categories mentioned

[1] Substance use categories not mutually exclusive (i.e., polysubstance users are represented in all columns reflecting the individual's use)

[2] ELISA test results

[3] Self-reported

[5] Positive toxicology results

n/a Included as part of the outcome

≠ Zero cell value precludes estimate

Table 3.

Polydrug use in unsheltered and unstably housed women living with HIV (N=74)

	Any	**This drug only**	**This drug + Cotinine/ Nicotine****	**This drug + Alcohol****	**This drug + Cannabis****	**This drug + cocaine****	**This drug + Meth amphetamine****	**This drug + Opioids****
Cotinine/Nicotine *[5]*	48 (64.9%)	4 (5%)	--	15 (20%)	28 (38%)	27 (37%)	19 (26%)	12 (16%)
Alcohol *[5]*	21 (28.4%)	1 (1%)	--	--	14 (19%)	13 (18%)	4 (5%)	4 (5%)
Cannabis (THC) *[5]*	39 (52.7%)	3 (4%)	--	--	--	18 (24%)	14 (19%)	11 (15%)
Cocaine *[5]*	36 (48.6%)	2 (3%)	--	--	--	--	13 (18%)	5 (7%)
Meth-amphetamine *[5]*	23 (31.1%)	1 (1%)	--	--	--	--	--	7 (9%)
Opioids *[5]*	15 (20.3%)	1 (1%)	--	--	--	--	--	--

** Proportions include people who may have been toxicology-positive for additional substances

[5] Positive toxicology results

Table 4.

Associations between Study Factors and log-transformed NT-proBNP (ng/L) in unsheltered and unstably housed women living with HIV (N=74; 134 obsersations)

	Unadjusted Effects (95% CI)	**Adjusted Effects (95% CI) Final Model Without Inflammatory Markers**	**Adjusted Effects (95% CI) Final Model With sCD14**	**Adjusted Effects (95% CI) Final Model With sCD163**	**Adjusted Effects (95% CI) Final Model With sTNFR2**	**Adjusted Effects (95% CI) Final Model With all Inflammatory Markers**
SOCIOECONOMIC FACTORS						
Age (per 10 years)	32.1% (7.0%, 63.1%) *	33.7% (9.3%, 63.4%) *	27.1% (4.5%, 54.6%) *	31.8% (7.1%, 62.2%))	24.6% (4.2%, 48.9%))	28.5% (7.9%, 53.1%))
Race/Ethnicity						
White	(ref)					
Black/African American	−43.7% (−67.0%, −4.2) *	−49.1% (−68.5%, −17.7%) *	−45.4% (−65.6%, −13.3%) *	−48.2% (−68.1%, −15.9%) *	−30.9% (−55.5%, 7.3%)	−29.4% (−53.6%, 7.3%)
Latina[Ł]	−50.2% (−75.4%, 0.8%)	−40.9% (−69.0%, 12.5%)	−37.1% (−66.0%, 16.4%)	−41.2% (−69.1%, 11.9%)	−30.1% (−60.3%, 23.2%)	−23.8% (−55.7%, 31.2%)
Multiracial	0.1% (−61.0%, 156.9%)	27.3% (−46.2%, 201.5%)	23.3% (−45.8%, 180.4%)	29.3% (−45.5%, 206.5%)	48.4% (−30.3%, 216.1%)	42.4% (−30.8%, 193.0%)
Other	18.0% (−54.6%, 206.4%)	18.2% (−50.0%, 179.3%)	−2.8% (−57.9%, 124.5%)	14.5% (−51.9%, 172.5%)	35.7% (−36.4%, 189.4%)	52.0% (−29.0%, 225.6%)
High school graduate	−23.5% (−52.4%, 23.0%)					
Monthly income (per $100)	0.0% (−4.3%, 4.5%)					
Consistent health insurance	63.7% (−42.8%, 368.2%)					
Post-menopausal [π]	42.3% (−10.4%, 126.2%)					
Estradiol, (pg/mL) (per 10 units)	−1.0% (−2.8%, 0.9%)					
CLINICAL FACTORS						
Body Mass Index (BMI)	−0.5% (−3.4%, 2.4%)					
Systolic Blood Pressure	5.6% (−2.4%, 14.2%)					
Diastolic Blood Pressure	0.6% (−10.8%, 13.5%)					
Diabetes [3]	−19.2% (−57.4%, 53.2%)					
Prior myocardial infarction [3]	7.9% (−50.3%, 134.3%)					

Drug Alcohol Depend. Author manuscript; available in PMC 2023 September 01.

	Unadjusted Effects (95% CI) [U]	Adjusted Effects (95% CI) Final Model Without Inflammatory Markers	Adjusted Effects (95% CI) Final Model With sCD14	Adjusted Effects (95% CI) Final Model With sCD163	Adjusted Effects (95% CI) Final Model With sTNFR2	Adjusted Effects (95% CI) Final Model With all Inflammatory Markers
Prior stroke [3]	30.2% (−37.4%, 171.0%)					
HCV-negative [3]	(Ref)					
HCV-positive, treated	42.3% (−16.0%, 140.9%)					
HCV-positive, untreated	33.9% (−15.0%, 110.9%)					
HIV viral load						
<50 copies/mL (ref)						
50–199 copies/mL	20.0% (−40.4%, 141.7%)					
200–499 copies/mL	17.3% (−43.6%, 143.9%)					
500–999 copies/mL	−8.9% (−53.2%, 77.1%)					
1000+ copies/mL	4.1% (−35.4%, 67.7%)					
INFLAMMATORY FACTORS						
High-sensitivity C-Reactive Protein (mg/L)	0.2% (−0.5%, 1.0%)					
sCD14, per SD (575.7 ng/ml) [2][6]	33.3% (10.2%, 61.2%) *		25.5% (4.6%, 50.6%) *			6.8% (−11.6%, 29.2%)
sCD163, per SD (601.4 ng/ml) [2][6]	14.5% (−6.8%, 40.8%)			5.4% (−13.0%, 27.7%)		−20.9% (−34.9%, −4.0%) *
sTNFR2, per SD (3145.4 pg/ml) [2][6]	59.8% (33.0%, 92.1%) *				49.5% (25.6%, 78.0%) *	65.5% (33.1%, 105.8%) *
SUBSTANCE USE AND MEDICATION						
Cotinine/Nicotine [5]	−28.4% (−52.3%, 7.4%)					
Alcohol [5]	−14.5% (−41.3%, 24.4%)					
Cannabis (THC) [5]	−40.8% (−57.6%, −17.2%) *	−39.6% (−56.1%, −17.0%) *	−41.4% (−57.2%, −19.9%) *	−39.9% (−56.3%, −17.3%) *	−40.3% (−55.7%, −19.5%) *	−39.6% (−54.8%, −19.1%) *
Cocaine [5]	−3.4% (−32.5%, 38.5%)					
Cocaethylene	5.2% (−36.1%, 73.1%)					
Levamisole [5]	5.5% (−27.7%, 54.0%)					

	Unadjusted[U] Effects (95% CI)	Adjusted Effects (95% CI) Final Model Without Inflammatory Markers	Adjusted Effects (95% CI) Final Model With sCD14	Adjusted Effects (95% CI) Final Model With sCD163	Adjusted Effects (95% CI) Final Model With sTNFR2	Adjusted Effects (95% CI) Final Model With all Inflammatory Markers
Methamphetamine [5]	−12.1% (−41.5%, 31.9%)					
Heroin/Monoacetylmorphine-6 [5]	−40.3% (−82.1%, 99.0%)					
Fentanyl/Norfentanyl [5]	−15.4% (−61.1%, 84.2%)					
Additional opioids [5]	−4.0% (−38.0%, 48.6%)					
Methadone [5]	22.9% (−26.9%, 106.6%)					
Buprenorphine/Norbuprenorphine [5]	(not detected)					
Naloxone [5]	(not detected)					
Benzodiazepine [5]	7.0% (−31.9%, 68.2%)					
Beta blocker [5]	12.0% (−40.2%, 109.9%)					
Calcium channel blocker [5]	−10.4% (−56.7%, 85.8%)					
Antiarrhythmic [5]	−3.5% (−36.5%, 46.8%)					
Diuretic [5]	(not detected)					
Antihypertensive [5]	132.4% (−72.0%, 1830.0%)					
Statin [5]	(not detected)					
Vasodilator [5]	(not detected)					
Anticoagulant [5]	(not detected)					
Nitrate ([5]	(not detected)					
Acetaminophen	15.6% (−16.0%, 59.1%)					

[U] Adjusted for visit only

[*] p<0.05

[^] >1 year since last menstrual period

[Ł] All participants reporting Latina ethnicity regardless of other racial categories mentioned

[2] ELISA test results,

Author Manuscript

Author Manuscript

Author Manuscript

[3]Self-reported,

[5]Positive toxicology results,

[6]change in cTnI assessed per standard deviation [SD]