Published in final edited form as:

AIDS. 2020 November 01; 34(13): 1959–1963. doi:10.1097/QAD.0000000000002617.

Syndemic burden and systemic inflammation, HIV health status, and blood pressure among women with unsuppressed HIV viral loads in the Women's Interagency HIV Study

Deborah L. Jones¹, Violeta J. Rodriguez^{1,2}, Maria Luisa Alcaide¹, Adam Carrico¹, Margaret A. Fischl¹, Natalie E Chichetto³, Carlos J. Rodriguez⁴, Michael A. Welsch⁵, Rachael Farah-Abraham⁶, Adaora A. Adimora⁷, Gypsyamber D'Souza⁸, Mardge H. Cohen⁹, Sanyog Shitole¹⁰, Daniel Merenstein¹¹, Jason Lazar¹²

¹University of Miami Miller School of Medicine

²University of Georgia

³Vanderbilt University Medical Center

⁴Einstein University

⁵University of Mississippi

⁶Emory University

⁷University of North Carolina at Chapel Hill

⁸Johns Hopkins University

⁹Chicago-Cook County

¹⁰University of California San Francisco

¹¹Georgetown University Medical Center

¹²SUNY Downstate Health Sciences University

Abstract

Introduction.—Smoking, low education, obesity, and depressive symptoms are all associated with HIV health status, increased blood pressure, and inflammation, and constitute a syndemic burden that may contribute to poor health outcomes. The current study examined syndemic burden and health outcomes among women living with HIV (WLHIV).

Methods.—Women were participants enrolled in the Women's Interagency HIV Study (WIHS). Outcomes included blood pressure, HIV health status (HIV-1 RNA viral load and CD4 T-cell counts), and interleukin-6. Syndemic burden was defined as a count variable of low education, obesity, cigarette use, and depressive symptoms.

Corresponding Author: Deborah L Jones, PhD, M.Ed., Professor, Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Dominion Towers Suite 404, 1400 NW 10th Avenue, Miami, Florida 33136, 305-243-2601, Fax 305-243-2126., Djones3@med.miami.edu.

Conflicts of Interest: The authors have declared that no competing interests exist.

Results.—Women ($N = 131$) were an average of 60.54 years of age ($SD = 8.86$), and 49% were non-Hispanic Black. In multivariable analyses, syndemic burden was not significantly associated with systolic ($p = .342$) or diastolic blood pressure ($p = .763$), interleukin-6 ($p = .168$), or CD4 count ($p = .846$). However, syndemic burden was associated with increased viral load (age adjusted $\beta = .35$, $p < .001$). Comparing women with high versus low syndemic burden, also controlling for women's age, women with high syndemic burden had higher diastolic blood pressure and HIV viral load.

Discussion.—Syndemic burden appeared to play an important role in HIV health status and could potentially increase the risk of HIV transmission. High syndemic burden, defined as at least two syndemic conditions, had the greatest effects of HIV viral load and diastolic blood pressure. Targeted interventions to address syndemic burden may help improve health outcomes in WLHIV as well as reduce the risk of hypertension and HIV transmission.

Keywords

HIV; women; syndemic; WIHS

Introduction

Hypertension is one of the leading causes of death worldwide, and is more common among people living with HIV (PLWH; 35%) than among HIV-uninfected adults (30%) [1]. Increasing rates of obesity [2] and factors such as smoking and mental health conditions contribute to chronic inflammation among PLWH and likely exacerbate hypertension [3–7]. The negative impact of smoking among PLWH may also exacerbate the already higher risk of hypertension associated with HIV [8, 9]. Depression globally affects 31% of PLWH and is a well-established risk factor for hypertension [10–12]. The clustering of two or more diseases or conditions (i.e., biological, social, or psychological conditions) is referred to as a syndemic, which may exacerbate the burden of negative health outcomes [13]. The syndemic of other health and demographic factors, such as obesity, psychiatric disorders, and less education, likely contribute to smoking behavior and poor health outcomes in this population [14, 15]. Additionally, there is a reduction in ART effectiveness in the presence of multiple syndemic factors, which act to increase HIV disease burden [16, 17]. These syndemic factors may also increase inflammation, which is associated with increased blood pressure [18].

It is unclear how syndemic factors (cigarette smoking, low education, obesity, and depressive symptoms) collectively affect HIV outcomes and hypertension, particularly among older women living with HIV (WLHIV) who are vulnerable to the development of increased blood pressure, chronic inflammation, and poor HIV health status (viral load and CD4 count). This study examined syndemic factors (cigarette smoking, low education, obesity, and depressive symptoms), as predictors of HIV disease markers, hypertension, and inflammation among WLHIV in the Women's Interagency HIV Study (WIHS). We hypothesized that those with a greater number syndemic factors would be associated with poorer HIV disease markers (i.e., higher viral load and lower CD4 count), increased blood pressure and inflammation, compared to those with a lower number of syndemic factors.

This study contributes to the understanding of associations among common syndemics and HIV-related health and chronic disease outcomes among PLWH.

Methods

Participants and Sample Collection

The Women's Interagency HIV Study (WIHS) is a prospective cohort of WLHIV or at risk for acquiring HIV in the US, whose methods have been previously described [19]. Systemic inflammation (via plasma interleukin-6 [IL-6]) was assessed in a subset of WIHS participants during visit cycle 33; all women in the IL-6 subset were experiencing virologic failure. The current analysis is a cross-sectional study among women who completed visit cycle 33 (October 1, 2010 to March 31, 2011) of the WIHS, had syndemic factors assessed, and were tested for systemic inflammation; thus, only 131 women were eligible and included in these analyses.

Measures

Demographic Assessment and Current ART Regimen.—Demographic factors included age, education (number of years), race, and ethnicity. Current ART regimens were determined from self-report.

Syndemic Factors

Syndemic Burden.—Syndemic burden was defined as the sum of the counts for each of the syndemic factors. Syndemic factors were defined as low education (1 = High School degree or less), obesity (1 = BMI ≥ 30) [20], cigarette use (1 = Yes), and depressive symptoms (1 = CES-D score ≥ 27) [21].

Outcomes: HIV Health Status, Blood Pressure, and Inflammation

CD4 Count, HIV Viral Load, Blood Pressure, and Interleukin-6.—CD4 counts and HIV-1 RNA levels (HIV-1 RealTime System; Abbott Molecular, Des Plaines, IL), measures of HIV health status, were determined by commercial laboratories. Blood pressure was measured as the average of five systolic and diastolic blood pressure measurements. Systemic inflammation was examined from IL-6 levels, detected using the enzyme-linked immunosorbent assay (ELISA, Q6000B, R&D Systems, Minneapolis, MN). IL-6 was selected given that it is a proinflammatory cytokine frequently associated with atherosclerosis and CVD, and is a strong predictor of CVD-related events and mortality [22].

Results

Descriptive Statistics of Key Study Variables

Table 1 describes means and standard deviations for key study variables, and correlations among variables for $N = 131$ in the WIHS participants included in this study. Overall, 12% ($n = 16$) of women had 0 syndemic factors, 44% ($n = 57$) had one syndemic factor, 30% ($n = 39$) had two syndemic factors, and 13% ($n = 17$) had three syndemic factors; only $n = 2$ women (2%) had four syndemic factors. Lifetime drug use was only available in a subset of

participants ($n = 115$). In these participants, $n = 16$ (12% reported life marijuana use, $n = 1$ (1%) heroin use, $n = 0$ (0%) methadone use, $n = 3$ (2%) crack use, and $n = 0$ (0%) cocaine use.

Antiretroviral therapy regimens were only available in a subset of women ($n = 89$; 68%). Most women were on a combination of 2 Nucleoside Reverse Transcriptase Inhibitor (NRTI) based regimen and other ART group. Among those reporting ART, $n = 22$ (25%) were on Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) based regimens (NRTIs + NNRTIs); $n = 13$ (15%) on Integrase Strand Transfer Inhibitors (INSTIs) based regimens (NRTIs + INSTIs), and $n = 49$ (55%) on a Protease Inhibitors (PIs) based regimen (NRTI + PI). Two women were complex regimens consisting of PIs + NNRTIs + INSTIs, suggesting history of ART resistance; one woman was on an INSTI + PI regimen. NRTIs reported were TDF ($n = 45$; 51%) and abacavir ($n = 29$; 33%).

Associations between syndemic burden and HIV health status, blood pressure, and inflammation

Women with a high syndemic burden had higher diastolic blood pressure ($M = 79.28$), compared with women with a low syndemic burden ($M = 73.50$), after controlling for age, $p = .043$). Women with a high syndemic burden also had higher viral load ($M = 4.63 \log_{10}$) compared with women with a low syndemic burden ($M = 3.88 \log_{10}$), after controlling for age, $p = .015$). Systolic blood pressure ($p = .343$), CD4 count ($p = .955$), and IL-6 ($p = .380$) were not associated with level of syndemic burden, after controlling for age. In unadjusted analyses, syndemic burden was not associated with CD4 ($p = .956$), systolic blood pressure ($p = .567$), or IL-6 ($p = .640$).

The results of the multivariable regression models are presented in Table 2. Level of syndemic burden was associated with increased HIV viral load ($\beta = .36$, $p = .002$). The syndemic burden explained 17.3% of the variance in systolic blood pressure ($R^2 = .17$, $F(2,126) = 13.14$, $p < .001$), and 11.6% of the variance in diastolic blood pressure ($R^2 = .12$, $F(2,126) = 8.23$, $p = .001$), after adjustment for age. No significant associations were noted between the syndemic burden and IL-6, or with CD4 Count.

Discussion

This study examined syndemic factors (cigarette smoking, low education, obesity, and depressive symptoms) as predictors of HIV health status, blood pressure, and inflammation among WLHIV. Consistent with the Multicenter AIDS Cohort Study (MACS) [16], the collective syndemic burden in participants of the WIHS was significantly associated with HIV viral load, and in the current study, women with high syndemic burden had HIV viral loads as well as greater diastolic blood pressure. Data suggest that syndemic factors may play a role in HIV health status, thereby contributing to an increased risk of transmission. Additionally, the accumulation of syndemic burden may increase the risk of hypertension. These findings, if replicated in a larger sample, support the development of targeted programs to reduce the overall syndemic burden in WLHIV.

Cigarette smoking and depression predict poor HIV outcomes and CVD risk [23], and this study is the first to attempt to measure the contribution of these factors as part of syndemic burden and its relationship with HIV health status, blood pressure, and inflammation. Consistent with previous reports, this study highlights the deleterious effect of depressive symptoms on health outcomes for WLHIV, and the importance of addressing mental health conditions among WLHIV. In addition, the confirmation that syndemic burden is associated with HIV viral load and diastolic blood pressure highlights the importance of understanding clustering conditions that affect the mutual course of the disease trajectory [16]. The current findings may further guide programmatic decision-making for interventions aimed at mitigating the effects of psychosocial factors that could lower the risk of HIV transmission and potentially improving health outcomes in this population. In fact, interventions have previously showed that the social context, including social support and housing arrangements, of patients living with HIV highly influences ART adherence and HIV outcomes [24, 25].

Surprisingly, syndemic burden was not associated with IL-6, although individual factors used to determine syndemic burden are known contributors to elevated inflammation [26]. This may indicate that the constituents of syndemic burden in this study may not be sensitive or specific to inflammatory markers or may be due to the overall higher level of systemic inflammation in this sample of women with uncontrolled HIV infection. Importantly, the current study confirmed that IL-6 levels were negatively related to CD4 count, and positively associated with viral load and BMI. These findings suggest a syndemic burden between obesity, inflammation, and HIV health status. It is likely that excess weight may affect the metabolism of antiretroviral drug levels given that with increased weight, there is an increased volume of distribution. Future studies with large sample sizes should examine how immune function and drug levels are differentially affected by body mass.

Limitations

Given the small sample of WLHIV used in this study, findings from this study may not generalize to other WLHIV. The examination of the relationship of syndemic factors to viral load was limited as the entire resulting sample had detectable viral load, which necessitated a comparison of higher and lower viral load that may not be clinically significant. It is possible, for instance, that the association between syndemic burden and viral load may be mediated by a lack of antiretroviral adherence, which was not considered in the current study. Syndemic burden may not have such a pronounced effect on viral load among adherent participants, given that nonadherence or drug resistance may stimulate viral load increases that are not related to syndemic factors, although inadequate adherence or drug resistance usually result in low level viremia. Detectable viremia, though known to be associated with systemic inflammation, may yield different results when evaluating a population of virologically suppressed individuals. In addition, IL-6 was the only marker used to evaluate systemic inflammation; there are other established biomarkers of systemic inflammation, immune activation, HIV health status, and CVD risk, such as T lymphocytes and myeloid cells, that could have yielded different results that were not available. Finally, the number of cigarettes per day or pack-years smoked were not evaluated.

Conclusion

Despite these limitations, this study contributes to our knowledge and understanding of the syndemic factors that may contribute to HIV health status, hypertension, and inflammation among WLHIV. These findings also lend support to the increasing utility and importance of syndemic theory in the study of HIV. Risk factors do not exist in isolation, nor do the risk processes that create them. Studying risk and risk processes together may therefore help contribute to the development of multilevel interventions focused on improving multiple health outcomes among WLHIV.

Sources of Funding:

Data in this manuscript were collected by the Women's Interagency HIV Study, now the MACS/WIHS Combined Cohort Study (MWCCS). The contents of this publication are solely the authors' responsibility and do not represent the official views of the National Institutes of Health (NIH). WIHS (Principal Investigators): Atlanta CRS (Ighovwerha Ofotokun, Anandi Sheth, and Gina Wingood), U01-HL146241-01; Baltimore CRS (Todd Brown and Joseph Margolick), U01-HL146201-01; Bronx CRS (Kathryn Anastos and Anjali Sharma), U01-HL146204-01; Brooklyn CRS (Deborah Gustafson and Tracey Wilson), U01-HL146202-01; Data Analysis and Coordination Center (Gypsyamber D'Souza, Stephen Gange and Elizabeth Golub), U01-HL146193-01; Chicago-Cook County CRS (Mardge Cohen and Audrey French), U01-HL146245-01; Chicago Northwestern CRS (Steven Wolinsky), U01-HL146240-01; Connie Wofsy Women's HIV Study, Northern California CRS (Bradley Aouizerat and Phyllis Tien), U01-HL146242-01; Los Angeles CRS (Roger Detels and Otoniel Martinez-Maza), U01-HL146333-01; Metropolitan Washington CRS (Seble Kassaye and Daniel Merenstein), U01-HL146205-01; Miami CRS (Maria Alcaide, Margaret Fischl, and Deborah Jones), U01-HL146203-01; Pittsburgh CRS (Jeremy Martinson and Charles Rinaldo), U01-HL146208-01; UAB-MS CRS (Mirjam-Colette Kempf and Deborah Konkle-Parker), U01-HL146192-01; UNC CRS (Adaora Adimora), U01-HL146194-01. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Xu Y, Chen X, Wang K, Global prevalence of hypertension among people living with HIV: a systematic review and meta-analysis. *J Am Soc Hypertens*, 2017 11(8): p. 530–540. [PubMed: 28689734]
2. Crum-Cianflone NF, et al., Increasing rates of obesity among HIV-infected persons during the HIV epidemic. *PLoS ONE*, 2010 5(4).
3. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW, From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature reviews neuroscience*, 2008 9(1): p. 46. [PubMed: 18073775]
4. Felger JC, Lotrich FE, Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. *Neuroscience*, 2013 246: p. 199–229. [PubMed: 23644052]
5. Kiecolt-Glaser JK, Derry HM, Fagundes CP, Inflammation: depression fans the flames and feasts on the heat. *Am J Psychiat*, 2015 172(11): p. 1075–1091. [PubMed: 26357876]
6. Miller GE, Blackwell E, Turning up the heat: Inflammation as a mechanism linking chronic stress, depression, and heart disease. *Current Directions in Psychological Science*, 2006 15(6): p. 269–272.
7. Raison CL, Capuron L, Miller AH, Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*, 2006 27(1): p. 24–31. [PubMed: 16316783]
8. Galai N, et al., Effect of smoking on the clinical progression of HIV-1 infection. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 1997 14(5): p. 451–458.
9. Lima MAC, et al., Systemic Arterial Hypertension in people living with HIV/AIDS: integrative review. *Rev Bras Enferm*, 2017 70(6): p. 1309–1317. [PubMed: 29160495]
10. Van der Kooy K, et al., Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry*, 2007 22(7): p. 613–26. [PubMed: 17236251]
11. Cohen BE, Edmondson D, Kronish IM, State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. *Am J Hypertens*, 2015 28(11): p. 1295–302. [PubMed: 25911639]

12. Rezaei S, et al., Global prevalence of depression in HIV/AIDS: a systematic review and meta-analysis. *BMJ supportive & palliative care*, 2019 9(4): p. 404–412.
13. Singer M, Bulled N, Ostrach B, Mendenhall E, Syndemics and the biosocial conception of health. *The Lancet*, 2017 389(10072): p. 941–950.
14. Vijayaraghavan M, et al., Disparities in receipt of 5As for smoking cessation in diverse primary care and HIV clinics. *Preventive medicine reports*, 2017 6: p. 80–87. [PubMed: 28271025]
15. Crum-Cianflone NF, Tejidor R, Medina S, Barahona I, Ganesan A, Obesity among patients with HIV: the latest epidemic. *AIDS patient care and STDs*, 2008 22(12): p. 925–930. [PubMed: 19072098]
16. Friedman MR, et al., Effects of syndemics on HIV viral load and medication adherence in the multicenter AIDS cohort study. *AIDS (London, England)*, 2015 29(9): p. 1087.
17. Pool ERM, Dogar O, Lindsay RP, Weatherburn P, Siddiqi K, Interventions for tobacco use cessation in people living with HIV and AIDS. *Cochrane Database Syst Rev*, 2016(6).
18. Granger JP, An emerging role for inflammatory cytokines in hypertension. *Am J Physiol Heart Circ Physiol*, 2006 290(3): p. H923–4. [PubMed: 16467462]
19. Barkan SE, et al., The women's interagency HIV study. WIHS collaborative study group. *Epidemiology*, 1998 9(2): p. 117–125. [PubMed: 9504278]
20. Prevention CfDCA, Defining Adult Overweight and Obesity. 2017.
21. Reisner SL, et al., Clinically significant depressive symptoms as a risk factor for HIV infection among black MSM in Massachusetts. *AIDS BEHAV*, 2009 13(4): p. 798–810. [PubMed: 19462228]
22. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH, Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation*, 2000 101(15): p. 1767–1772. [PubMed: 10769275]
23. Hessol NA, et al., Smoking cessation and recidivism in the women's interagency human immunodeficiency virus study. *Am J Prev Med*, 2014 47(1): p. 53–69. [PubMed: 24746376]
24. Mayer KH, Stone VE, Strategies for optimizing adherence to highly active antiretroviral therapy: lessons from research and clinical practice. *Clinical Infectious Diseases*, 2001 33(6): p. 865–872. [PubMed: 11512092]
25. Hawk M, Davis D, The effects of a harm reduction housing program on the viral loads of homeless individuals living with HIV/AIDS. *AIDS care*, 2012 24(5): p. 577–582. [PubMed: 22103666]
26. Yusuf S, et al., Modifiable risk factors, cardiovascular disease, and mortality in 155 722 individuals from 21 high-income, middle-income, and low-income countries (PURE): a prospective cohort study. *The Lancet*, 2019 395(10226).

Table 1.

Bivariate correlations among key individuals syndemic factors

Variables	Age	Education	CES-D	Systolic	Diastolic	Viral Load	Interleukin-6	CD4 Count
Age	—							
Education	0.060	—						
CES-D	0.006	-.189*	—					
Systolic	.415**	0.045	0.091	—				
Diastolic	.309**	0.052	.190*	.684**	—			
Viral Load	0.086	-.0172	.303**	-.0004	0.033	—		
Interleukin-6	0.112	0.007	0.043	-.0038	0.026	.217*	—	
CD4 Count	0.044	0.034	-.195*	0.137	0.100	-.396**	-.298**	—
<i>M(SD)</i>	60.54	48	16.09	115.72	74.31	4.01	6.21	281.77
<i>n (%)</i>	(8.86)	(36.6%)	(12.72)	(17.11)	(11.11)	(1.17)	(27.46)	(234.94)

Note. Depressive symptoms were significantly and positively associated with diastolic blood pressure ($r = .190$) and viral load ($r = .303$), and negatively related to CD4 count ($r = -.195$; $p < .05$). CD4 count was inversely related to HIV viral load ($r = -.396$) and IL-6 ($r = -.298$; $p < .05$). In bivariate analyses, cigarette use, and depressive symptoms were the primary associations with HIV health status and blood pressure. Finally, IL-6 levels were positively associated with BMI and viral load, and inversely related to CD4 count.

* $p < .05$

** $p < .01$

*** $p < .001$

Table 2

Summary of Multivariable Regression Models Predicting CVD markers and Immunological Functioning (N = 131)

Variable	Systolic BP			Diastolic BP			HIV Viral Load			CD-4 Count			IL-6		
	β	<i>t</i>	<i>p</i>	β	<i>t</i>	<i>p</i>	β	<i>t</i>	<i>p</i>	β	<i>t</i>	<i>p</i>	β	<i>t</i>	<i>p</i>
# of Syndemics	-.48	-0.32	.749	1.71	1.69	.094	.36	3.22	.002	.03	.55	.764	-.02	-0.53	.598
Age	.799	5.13	< .001	.38	3.60	< .001	.01	.81	.420	.01	.47	.615	.01	1.30	.198
<i>R</i> ²		.17			.12			.09			.00			.02	
Model <i>F</i>		13.14	***		8.23	***		5.64	**		0.27			0.95	

Note. BP = Blood Pressure. IL-6 = Interleukin-6. The syndemic burden was associated with increased viral load ($\beta = .36$, $p = .002$). The syndemic burden explained 17.3% of the variance in systolic blood pressure ($R^2 = .17$, $F(2,126) = 13.14$, $p < .001$), and 11.6% of the variance in diastolic blood pressure ($R^2 = .12$, $F(2,126) = 8.23$, $p = .001$), but only with age included in the model. No significant associations were noted between the syndemic burden and IL-6, or with CD-4 Count.

* $p < .05$.

** $p < .01$.

*** $p < .001$.