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Systemic inflammation is elevated among both HIV-uninfected and -infected young men who have sex with men

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Summary

Evidence suggests that systemic inflammation increases due to HIV infection. C-reactive protein (CRP), IL-6, and TNF-α values were compared between HIV+ and HIV- young men who have sex with men and transgender women. CRP values were >3mg/L among 49.8% of participants. HIV status was not significantly associated with CRP nor IL-6. TNF-α was significantly higher among HIV+ participants. These results suggest further study of causes and health consequences of elevated systemic inflammation among this population.

Keywords

HIV; inflammation; YMSM; C-reactive protein; cytokines

Introduction

Young men who have sex with men (YMSM; aged 18–29) account for nearly 70% of all new HIV diagnoses among adolescents and young adults in the US.[1] They also represent the demographic group with the highest rate of new HIV diagnoses.[2,3] Elevated levels of inflammatory immune response factors in HIV-uninfected individuals, such as pro-inflammatory cytokines and C-reactive protein (CRP), are associated with HIV infection in other HIV risk groups.[4–6] Higher plasma CRP is also associated with HIV disease progression and death among infected persons, as well as cardiovascular disease risk among uninfected persons.[10–12] Little research to date, however, has assessed within group variation of systemic inflammation among sexual and gender minorities. To address this dearth of research, we analyzed data from a large cohort of YMSM and transgender women (TGW) in order to determine whether systemic inflammation was more elevated among those diagnosed with HIV compared to uninfected participants. We hypothesized that, based on

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Conflict of interest

The authors have no conflicts of interest to declare.

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data from older populations, those diagnosed with HIV would have more elevated systemic inflammation.

Methods

Data were collected as part of RADAR, a NIDA-funded longitudinal cohort study of YMSM and TGW living in the Chicago metropolitan area. Participants were between 16 and 29 years of age, assigned male at birth, spoke English, and had a sexual encounter with a man in the previous year or identified as gay, bisexual or transgender. Systemic inflammation was assessed using the MESO QuickPlex SQ 120 electrochemiluminescence immunoassay platform (Meso Scale Discovery, MSD) by measuring plasma levels of CRP (MSD V-PLEX Plus Human CRP kit [dynamic range: 0.001–49.6 mg/L]) as well as cytokines that can induce CRP, namely, IL-6 and TNF-α (MSD V-PLEX Custom Proinflammatory Panel 1 [human] kit [IL-6 dynamic range: 0.06–488 pg/mL; TNF-α dynamic range: 0.04–248 pg/mL]). Assays for CRP, IL-6, and TNF-α were run on all HIV-infected participants (n=148), 63 (42.6%) of whom had a viral load <40 copies/mL. For CRP, participants who tested HIV-negative across visits (n=147) were matched on age, race, and gender. One individual was found to be a duplicate enrollee therefore their second set of data was retroactively removed. For IL-6 and TNF-α, a subset of HIV-negative participants was randomly selected from among those with available CRP data (n = 89; limited due to availability of assay kits), no significant group differences (age, race, and gender) existed between those selected and not selected. Additionally, cytokine data were selected only from among those who self-reported any sexual activity in prior 6 months. The final analytic dataset included CRP data on 295 participants and cytokine data on 239 participants.

Results

CRP results were higher than expected for age and median BMI of this group, with 49.8% of participants above 3 mg/L. Median CRP values were 2.96 mg/L, 2.81 mg/L, and 3.28 mg/L among all participants, HIV-positive participants, and HIV-negative participants, respectively. Because these values were higher than anticipated, we tested another aliquot of the same plasma from a random subset of subjects (n=10) using a different assay method (hsCRP by particle enhanced immunoturbidimetric assay) at a different laboratory. The correlations were very high across the two different assay methods ($r = .99$, $p < 0.001$).

No significant differences were observed by HIV status with regards to unadjusted CRP, log-transformed CRP, and IL-6 (Table 1). Nor did this differ based on whether participant HIV viral load was detectable or not (data not shown). These results continued to be observed when adjusting for demographic characteristics in multivariable linear regression. HIV-positive participants did have significantly higher levels of TNF-α in both bivariate ($p<0.001$) and demographic-adjusted models ($p<0.001$). Significant associations were observed between unadjusted CRP values and IL-6 ($p<0.001$) and TNF-α ($p=0.010$), but not BMI ($p=0.113$). Significant associations were observed between log-transformed CRP and BMI ($p<0.001$), IL-6 ($p<0.001$), and TNF-α ($p<0.001$). Finally, no significant differences were observed in CRP values by gender identity, marijuana use (self-report or urine

toxicology screen), STI diagnosis (gonorrhea or chlamydia), tobacco use, season of sample collection (e.g. winter), nor body temperature (indicating possible acute infection).

Discussion

Among a racially/ethnically diverse cohort of YMSM and TGW who are now the highest HIV-risk demographic in the US, nearly 50% of participants had plasma CRP levels above 3 mg/L, a threshold associated with a three-fold increased risk of cardiovascular disease among older adults.[13] Correlations between CRP results from the same plasma specimens determined using two different, independent assay platforms validated that the observed high levels of CRP were not due to use of a sensitive assay method with a broad dynamic range. Further, IL-6 and TNF-α were each significantly correlated with both unadjusted and log-transformed CRP values, biologically consistent with the well-defined induction of CRP by these cytokines.

Contrary to our hypothesis that HIV infection would augment CRP values, no significant association was observed between CRP levels (either unadjusted or log-transformed values) and HIV status. Similarly, plasma levels of the cytokine most tightly causally linked to CRP induction, IL-6, was not associated with HIV status. Although many studies have reported that high CRP increased risks of death and some co-morbidities among HIV-infected subjects,[10] the lack of association of CRP level with HIV infection was also reported earlier in one study.[14] Increased TNF-α among the HIV-infected suggests that there may indeed be an additional HIV infection-related pathogenetic mechanism driving systemic inflammation in MSM, in addition to the as-yet undefined mechanism not associated with HIV status. These technical and biological validations support this independent evidence of increased systemic inflammation among YMSM and TGW[15,16] enabling a conclusion that systemic inflammation is common among both uninfected and HIV-infected YMSM. This warrants further research, including longitudinal assessments of both possible temporal fluctuations and long-term outcomes, to determine if YMSM may be at increased lifetime risk of cardiovascular disease or other adverse health consequences associated previously with elevated plasma CRP (including diabetes[17] and cancer[18]).

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References

1. Centers for Disease Control and Prevention. HIV surveillance in adolescents and young adults 2010.
2. Centers for Disease C, Prevention. Diagnoses of HIV Infection in the United States and Dependent Areas 2013.

3. Prejean J, Song R, Hernandez A, et al. Estimated HIV incidence in the United States, 2006–2009. PLoS One 2011; 6(8): e17502. [PubMed: 21826193]

4. Chege D, Chai Y, Huibner S, et al. Blunted IL17/IL22 and pro-inflammatory cytokine responses in the genital tract and blood of HIV-exposed, seronegative female sex workers in Kenya. PLOS ONE 2012; 7(8): e43670. [PubMed: 22928014]

5. Kaul R, Prodger J, Joag V, et al. Inflammation and HIV tranmisison in sub-Saharan Africa. Current HIV/AIDS Reports 2015; 12(2): 216–22. [PubMed: 25877253]

6. Khale E, Bolton M, Hughes JP, Donnell D, Celum C. Plasma Cytokine Levels and Risk of HIV Type 1 (HIV-1) Transmission and Acquisition: A Nested Case-Control Study Among HIV-1–Serodiscordant Couples. The Journal of Infectious Diseases 2014; 211(9): 1451–60. [PubMed: 25389306]

7. Hope TJ. Inflammation weakens HIV prevention. Nat Med 2018; 24(4): 384–5. [PubMed: 29634687]

8. Naranbhai V, Abdool Karim SS, Altfeld M, et al. Innate immune activation enhances hiv acquisition in women, diminishing the effectiveness of tenofovir microbicide gel. J Infect Dis 2012; 206(7): 993–1001. [PubMed: 22829639]

9. McKinnon LR, Liebenberg LJ, Yende-Zuma N, et al. Genital inflammation undermines the effectiveness of tenofovir gel in preventing HIV acquisition in women. Nat Med 2018; 24(4): 491–6. [PubMed: 29480895]

10. Lau B, Sharrett A, Kingsley L, et al. C-Reactive Protein Is a Marker for Human Immunodeficiency Virus Disease Progression. Arch Intern Med 2006; 166: 64–70. [PubMed: 16401812]

11. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. The New England journal of medicine 1997; 336(14): 973–9. [PubMed: 9077376]

12. Feldman JG, Goldwasser P, Holman S, DeHovitz J, Minkoff H. C-reactive protein is an independent predictor of mortality in women with HIV-1 infection. J Acquir Immune Defic Syndr 2003; 32(2): 210–4. [PubMed: 12571532]

13. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, Aspirin, and the Risk of Cardiovascular Disease in Apparently Healthy Men. New England Journal of Medicine 1997; 336(14): 973–9. [PubMed: 9077376]

14. Floris-Moore M, Howard AA, Lo Y, Schoenbaum EE, Arnsten JH, Klein RS. Hepatitis C infection is associated with lower lipids and high-sensitivity C-reactive protein in HIV-infected men. AIDS Patient Care STDS 2007; 21(7): 479–91. [PubMed: 17651029]

15. Everett B, Rosario M, McLaughlin K, Bryn Austin S. Sexual Orientation and Gender Differences in Markers of Inflammation and Immune Functioning. Ann Behav Med 2014; 47(1): 57–70. [PubMed: 24347405]

16. Hatzenbuehler M, McLaughlin K, Slopen N. Sexual Orientation Disparities in Cardiovascular Biomarkers Among Young Adults. Am J Prev Med 2013; 44(6): 612–21. [PubMed: 23683979]

17. Pradhan A, Manson J, Rifai N, Buring J, PM R. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001; 286(3): 327–34. [PubMed: 11466099]

18. Erlinger T, Platz E, Rifai N, Helzlsouer K. C-Reactive Protein and the Risk of Incident Colorectal Cancer. JAMA 2004; 291(5): 585–90. [PubMed: 14762037]

Table 1.

Demographic characteristics, stratified by HIV status, RADAR, Chicago 2015–2017

Characteristic	Total (N=295)		HIV Positive (n=148)		HIV Negative (n=147)[2]		p-value
Age, mean (SD) [1]	24.3 (4.2)	–	24.4 (4.1)	–	24.2 (4.3)	–	0.695
Race/Ethnicity, n (%)[1]							0.996
Black	194	65.8	98	66.2	96	65.3	
White	10	3.4	5	3.4	5	3.4	
Hispanic/Latinx	62	21.0	31	20.9	31	21.1	
Other	29	9.8	14	9.5	15	10.2	
Gender Identity, n (%)[1]							1.000
Male	253	85.8	127	85.8	126	85.7	
Transwomen	41	13.9	20	13.5	21	14.3	
Other	1	0.3	1	0.7	0	0.0	
Sexual Orientation, n (%)							0.004
Gay	198	67.1	112	75.7	86	58.5	
Bisexual	63	21.4	21	14.2	42	28.6	
Other	34	11.5	15	10.1	19	12.9	
BMI (kg/m^2), mean (SD)[4]	26.0 (6.6)	–	25.1 (5.5)	–	26.9 (7.4)	–	0.029
Biomarkers of systemic inflammation,[3] **mean (SD)**							
Unadjusted CRP (mg/L)	6.6 (12.6)	–	5.8 (7.8)	–	7.4 (16.1)	–	0.299
Log-transformed CRP	1.1 (1.3)	–	1.1 (1.3)	–	1.2 (1.3)	–	0.499
TNF-α (pg/mL)	2.7 (2.4)	–	3.2 (2.9)	–	2.0 (0.6)	–	<0.001
IL-6 (pg/mL)	0.6 (0.5)	–	0.5 (0.4)	–	0.6 (0.6)	–	0.424

Abbreviations: SD = standard deviation; BMI = body mass index; CRP = C-reactive protein; IL = interleukin

[1] HIV negative and HIV positive participants were matched 1:1 based on these factors

[2] One duplicate participant was enrolled in the study

[3] Immunologic markers were collected on 148 HIV+ participants; CRP was collected on 147 HIV- participants; TNF-α and IL-6 were collected on 89 HIV- participants

[4] Available on 273 participants