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Human Immunodeficiency Virus Is Associated With Higher Levels of Systemic Inflammation Among Kenyan Adults Despite Viral Suppression

Sarah J. Masyuko,[1,2] Stephanie T. Page,[2,3] Stephen J. Polyak,[2,4] John Kinuthia,[5] Alfred O. Osoti,[2,6] Fredrick C. Otieno,[7] Joseph M. Kibachio,[1] Jerusha N. Mogaka,[3] Paul M. Macharia,[1] Bhavna H. Chohan,[2] Jessica Wogner,[4] Aidan O'Connor,[4] Tecla M. Temu,[2] Jerry S. Zifodya,[8] Amos Otedo,[1] Damalie Nakanjako,[9] James P. Hughes,[10] and Carey Farquhar[2,3,11]

[1]Ministry of Health, Nairobi, Kenya, [2]Department of Global Health, University of Washington, Seattle, Washington, USA, [3]Department of Medicine, University of Washington, Seattle, Washington, USA, [4]Department of Laboratory Medicine and Pathology, University of Washington, Seattle, Washington, USA, [5]Department of Research and Programs, Kenyatta National Hospital, Nairobi, Kenya, [6]Department of Obstetrics and Gynecology, University of Nairobi, Nairobi, Kenya, [7]Department of Clinical Medicine and Therapeutics, College of Health Sciences, University of Nairobi, Nairobi, Kenya, [8]Department of Medicine, Tulane University, New Orleans, Louisiana, USA, [9]Department of Medicine, School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda, [10]Department of Biostatistics, University of Washington, Seattle, Washington, USA, [11]Department of Epidemiology, University of Washington, Seattle, Washington, USA

Background. Systemic inflammation independently predicts future cardiovascular events and is associated with a 2-fold increase in cardiovascular disease (CVD) risk among persons living with human immunodeficiency virus (PLHIV). We examined the association between inflammatory markers, HIV status, and traditional CVD risk factors.

Methods. We conducted a cross-sectional study of Kenyan adults with and without HIV seeking care at Kisumu County Hospital. Using a multiplex immunoassay, we measured interleukin (IL) 1β, IL-6, tumor necrosis factor α (TNF-α), and high-sensitivity C-reactive protein (hsCRP) concentrations. We compared inflammatory marker concentrations by HIV status using the Wilcoxon rank-sum test. Multivariable linear regression was used to evaluate associations between inflammatory biomarkers and HIV status, adjusting for CVD risk factors.

Results. We enrolled 286 PLHIV and 277 HIV-negative participants. Median duration of antiretroviral therapy for PLHIV was 8 years (interquartile range, 4–10) and 96% were virally suppressed. PLHIV had a 51% higher mean IL-6 concentration ($P < .001$), 39% higher mean IL-1β ($P = .005$), 40% higher mean TNF-α ($P < .001$), and 27% higher mean hsCRP ($P = .008$) compared with HIV-negative participants, independent of CVD risk factors. Male sex, older age, and obesity were associated with higher concentrations of inflammatory markers. Restricting to PLHIV, viral load of ≥1000 copies/mL was associated with higher TNF-α levels ($P = .013$).

Conclusions. We found higher levels of systemic inflammatory biomarkers among PLHIV who were virally suppressed, and this was independent of traditional CVD risk factors. Further longitudinal analyses to determine whether these inflammatory markers predict future CVD events, and are possible therapeutic targets among PLHIV, are warranted.

Keywords. HIV; inflammation; Kenya; cardiovascular disease risk.

Systemic inflammation has been shown to increase cardiovascular disease (CVD) risk and independently predict future cardiovascular events such as myocardial infarction and stroke [1–5]. In addition, increased levels of biomarkers such as interleukin (IL) 6 and tumor necrosis factor α (TNF-α) have been associated with increased risk of mortality among those with pre-existing CVD [6, 7]. IL-1β has been shown to play a role in the atherosclerosis process and is a future therapeutic target to reduce risk of myocardial infarction or cardiac death [8]. There is evidence that CVD risk remains increased even if there are significant reductions in low-density lipoprotein cholesterol (LDL-C) levels, a marker of CVD risk, after use of lipid-lowering statin therapy [9]. The relative contribution of the inflammatory pathway to this residual CVD risk among both people with and without HIV is unclear [10].

In sub-Saharan Africa (SSA), which accounts for 67% of the global human immunodeficiency virus (HIV) burden, there is growing concern about rising CVD morbidity and its related mortality despite decreasing CVD death rates in high-income countries [11]. Evidence from the United States and Europe suggests that CVD risk among persons living with HIV (PLHIV) is double that of the general population [12–16]. Higher levels of inflammatory biomarkers such as C-reactive protein (CRP) and IL-6 are associated with HIV disease progression [17] and these persist at least up to 1 year following initiation of antiretroviral therapy (ART) [18, 19]. Persistent inflammation may contribute to the increased occurrence of subclinical atherosclerosis, myocardial infarction, and stroke and increased CVD-related mortality among PLHIV [18, 20–22]. In SSA there is a paucity of

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Correspondence: S. J. Masyuko, National AIDS and STI Control Program, Ministry of Health, P.O. Box 13131 00202 Nairobi, Kenya (smasyuko@uw.edu).

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data regarding the association between inflammation and CVD risk, especially comparing people with and without HIV.

We therefore sought to determine the association between HIV status and inflammatory markers, specifically high-sensitivity CRP (hsCRP), IL-1β, IL-6, and TNF-α. We measured these biomarkers, traditional CVD risk factors, and HIV-specific characteristics among PLHIV and HIV-negative adults in Kisumu, Kenya. We hypothesized that PLHIV would have higher mean inflammatory biomarker levels when compared with HIV-negative study participants.

METHODS

Study Design and Setting

Between September 2017 and May 2018, we conducted a cross-sectional study among 300 women and men with HIV and 300 women and men without HIV from Kisumu County Hospital, a tertiary, public county referral facility located in Western Kenya where HIV prevalence is high (16.3%) [23].

Study Procedures

Participants were eligible if they were at least 30 years of age and lived within a 50-km radius of the hospital. Persons living with HIV had to be engaged in care at the HIV Comprehensive Care Clinic (CCC) and taking ART for at least 6 months. Persons living with HIV who met the inclusion criteria and provided consent were consecutively enrolled by a study nurse from the CCC while HIV-negative participants were recruited from HIV testing points until the sample size was reached. All participants provided written informed consent prior to any study procedures or data collection. Human subjects approval was obtained from the University of Washington Institutional Review Board and locally from the Kenyatta National Hospital/University of Nairobi Ethical and Scientific Review Committee.

Clinical Procedures

Using tablets, study nurses enrolled and interviewed all participants collecting data on sociodemographics, HIV disease status if HIV-positive, and CVD risk factors using the validated World Health Organization STEPS (STEPwise approach to surveillance) questionnaires modified to fit the Kenyan context [24]. Waist and hip circumference, weight, and height were measured to determine waist to hip ratio and body mass index (BMI). Two blood pressure readings on each arm and pulse were measured and averaged. Participants were asked to return the following day after fasting for 8 hours for a blood draw if not already fasting.

Laboratory Procedures

Blood samples were collected at least 8 hours after fasting for quantification of lipids (total cholesterol, high-density lipoprotein cholesterol [HDL-C], LDL-C, triglycerides), glucose, and inflammatory markers including hsCRP, IL-1β, IL-6, and TNF-α as well as CD4 and viral load for PLHIV. Blood samples were processed to obtain serum and stored at the Kenya Medical Research Institute (KEMRI) laboratory at −80°C. Absolute CD4+ T-cell count and HIV-1 RNA viral load testing were performed at the KEMRI laboratory in Kisumu. HIV RNA viral load values below 50 copies/mL were classified as undetectable. Absolute CD4 cell counts were measured using flow cytometry. Samples for lipids, glucose, and inflammatory markers were batched and shipped for testing to the University of Washington, Seattle. Serum lipids, glucose, and hsCRP tests were performed at the University of Washington Research Testing Services using an automated Beckman Coulter, Inc. Brea, CA AU5812. All samples were tested in duplicate according to the manufacturer's protocols.

Cytokine Assays

Serum samples for IL-1β, IL-6, and TNF-α were analyzed using Mesoscale Discovery, Rockville, MD (MSD) VPlex Proinflammatory Panel 1 (human kit). Samples with a coefficient of variation greater than 30% were rerun and the duplicate with the lower coefficient of variation was averaged for the analyses. If a biomarker level was below the lower limit of detection for the assay, the lower limit was used as the biomarker value. Lower limit of detection concentrations were 0.2 mg/L for hsCRP, 0.01 pg/mL for IL-1β, 0.05 pg/mL for IL-6, and 0.01 pg/mL for TNF-α.

Primary Outcomes and Dependent Variables

The primary outcomes were inflammatory biomarker concentrations: hsCRP, IL-1β, IL-6, and TNF-α. HIV status was the exposure. Multivariable models were adjusted for age, gender, smoking status, blood pressure, BMI, hypertension, diabetes, and lipids determined a priori and supported by the literature. We assessed the presence of effect modification by metabolic syndrome and high atherosclerotic CVD risk (ASCVD) [25]. Metabolic syndrome was defined by the 2009 Consensus Criteria as any 3 of the following: (1) abdominal obesity (waist circumference of >88 cm for women and >94 cm for men), (2) triglycerides 150 mg/dL or greater, (3) HDL-C less than 50 mg/dL for women and less than 40 mg/dL for men, (4) blood pressure greater than 130/85 mmHg, and (5) fasting plasma glucose of 100 mg/dL or greater [26]. For each participant without prior history of myocardial infarction or stroke, we calculated their 10-year ASCVD risk score using the Pooled Cohort Equation as outlined in the 2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease [25, 27].

Statistical Analysis

Continuous variables were summarized using means and standard deviations for normally distributed data and by medians and interquartile range (IQR) for non–normally

distributed variables. We compared people with and without HIV using a *t* test for normally distributed continuous variables, Wilcoxon rank-sum test for non–normally distributed continuous variables, and chi-square test for categorical variables. We restricted our analysis to hsCRP values of 10 mg/L or less as hsCRP values greater than 10 mg/L are most consistent with a transient or acute-phase response as would commonly occur with acute infections common in this setting. Due to the cross-sectional nature of the study, we were unable to repeat measurements after 2 weeks to rule out transient acute inflammation.

We compared inflammatory markers by HIV status using the Wilcoxon rank-sum test. We created separate multivariable linear regression models to evaluate the association between (log-transformed) IL-1β, IL-6, TNF-α, and hsCRP and HIV status and adjusted for CVD risk factors including age, sex, smoking, alcohol use, diet (at least 5 servings of fruits and vegetables per day), physical activity (at least 150 minutes of moderate activity or 75 minutes of vigorous activity per week), BMI, hypertension and diabetes, and lipids. Subgroup analyses for metabolic syndrome and high ASCVD risk (score >7.5%) were carried out to assess whether associations of each biomarker with HIV status were consistent across the subgroups by including an interaction term between HIV status and the subgroup variable. In a separate model including only PLHIV, we included nadir CD4 count, viral suppression, and ART duration as covariates.

We report the exponentiated B-coefficients and their calculated 95% confidence intervals (CIs) representing the fold increase/decrease in biomarker level. We used a significance (α) level of 0.05. All analyses were conducted using Stata version 14.0 (StataCorp, College Station, TX).

RESULTS

Participant Characteristics

Of the 600 eligible participants, complete data were available for 563 participants (94%): 286 PLHIV and 277 HIV-negative participants. The median age was 45 years (IQR, 40–54 years) for PLHIV and 40 years (IQR, 31–54 years) for HIV-negative participants. Persons living with HIV were older ($P < .001$), less educated ($P < .001$), had a lower BMI ($P < .001$), and had consumed less alcohol in the past 12 months ($P = .007$) as compared with HIV-negative participants (Table 1). The prevalences of metabolic syndrome, hypertension, and abdominal obesity were significantly lower among PLHIV as compared with those without HIV (Table 1). There were no significant differences in smoking, diet, physical activity, triglycerides, HDL-C, and fasting glucose levels by HIV status.

Among PLHIV, the current median CD4 count was 512 cells/mm^3 (IQR, 364–666 cells/mm^3) and the median duration on ART was 8 years (IQR, 4–10 years). The majority (86%) of PLHIV were on a first-line regimen (2 nucleoside reverse transcriptase inhibitors [NRTIs] plus 1 non-NRTI) with only 13% on a protease inhibitor (PI)–based regimen (2 NRTIs plus PI). Eighty percent (229/287) of PLHIV had an undetectable HIV RNA level (<50 copies/mL), 16% (46/287) had low-level viremia (HIV RNA, 50–1000 copies/mL) and 4% (12/287) had high-level viremia (HIV RNA concentration ≥1000 copies/mL) (Table 1).

Overall, the median (IQR) IL-1β, IL-6, TNF-α, and hsCRP levels were 0.11 pg/mL (0.05–0.30), 0.94 pg/mL (0.50–1.83), 2.78 pg/mL (1.96–4.02), and 1.4 mg/L (0.6– 2.8), respectively. Median IL-1β, IL-6, TNF-α, and hsCRP levels were higher among PLHIV compared with HIV-negative participants (Figure 1). Persons living with HIV had a significantly higher median IL-1β (0.14 pg/mL vs 0.10 pg/mL, $P = .019$), IL-6 (1.15 pg/mL vs 0.80 pg/mL, $P < .001$), TNF-α (3.06 pg/mL vs 2.61 pg/mL, $P < .001$), and hsCRP (1.5 mg/L vs 1.2 mg/L, $P = .052$) level compared with HIV-negative participants (Figure 1).

IL-6 showed the greatest mean difference among the biomarkers examined comparing PLHIV and HIV-negative participants. After adjusting for age, sex, smoking, alcohol use, diet, physical activity, BMI, hypertension, diabetes, and lipids, PLHIV had a 51% higher mean IL-6 level ($P < .001$), a 39% higher mean IL-1β level ($P = .005$), a 40% higher mean TNF-α level ($P < .001$), and a 27% higher mean hsCRP level ($P = .008$) compared with HIV-negative participants (Table 2).

Stratification by Metabolic Syndrome and High Atherosclerotic Cardiovascular Disease Risk

We previously reported that the prevalence of metabolic syndrome and calculated ASCVD risk among these study participants was lower among PLHIV compared with HIV-negative participants [25]. However, in this analysis, the differences in biomarker levels between those with and without metabolic syndrome/high ASCVD risk in PLHIV were not significantly different from similar differences in those without HIV. We therefore observed no significant interaction between HIV status and metabolic syndrome or ASCVD and the inflammatory markers.

Factors Associated With IL-1β, IL-6, TNF-α, and hsCRP

The demographic and CVD risk factors found to be independently associated with higher IL-1β levels were male sex and obesity (BMI >30 kg/m^2) (Table 3). A significantly higher IL-6 level was associated with older age (>50 years), male sex, and lower HDL-C (Table 4). While a significantly higher TNF-α was associated with older age (>60 years) and male sex, TNF-α levels were significantly lower among participants with diabetes (Table 5). Older age (>50 years) and being overweight or obese and a current smoker were associated with higher hsCRP (Table 6).

Table 1. Characteristics of 598 Study Participants Stratified by HIV Status

Variable	Total (N = 564)	HIV-Positive (n = 287)	HIV-Negative (n = 277)	*P*
1. Sociodemographic characteristics				
Age categories, n (%)				<.001
<40 years	201 (35.6)	68 (23.7)	133 (48.0)	
40–49 years	162 (28.7)	106 (36.9)	56 (20.2)	
50–59 years	128 (22.7)	83 (28.9)	45 (16.2)	
≥60 years	73 (12.9)	30 (10.5)	43 (15.5)	
Sex (female)	299 (50.0)	144 (50.2)	138 (49.8)	.93
Marital status, n (%)				.002
Single	38 (6.4)	15 (5.2)	23 (8.3)	
Currently married	414 (73.4)	205 (68.3)	235 (78.9)	
Separated/widowed/divorced	112 (19.8)	80 (26.7)	40 (13.4)	
Education, n (%)				<.001
Less than primary school completed	78 (13.8)	39 (13.6)	39 (14.1)	
Primary school completed	211 (37.4)	124 (43.2)	87 (31.4)	
Secondary school completed	183 (32.4)	95 (33.1)	88 (31.8)	
More than secondary school completed	92 (16.3)	29 (10.1)	63 (22.7)	
2. Characteristics of persons living with HIV				
Nadir CD4 count,[a] cells/mm^3	…	365 (213 571)	…	
Time since diagnosis, years	…	9 (5, 11)	…	
Regimen, n (%)				
First-line regimen (non-PI)	…	248 (86.4)	…	
Second-line regimen (PI)	…	38 (13.2)	…	
Third-line regimen (PI)	…	1 (0.3)	…	
ART duration, years	…	8 (4, 10)	…	
Current CD4 count,[c] cells/mm^3	…	512 (364, 666)	…	
Viral load[c] (copies/mL), n (%)				
Undetectable (<50)	…	229 (79.8)	…	
Low-level viremia (50–1000)	…	46 (16.0)	…	
Viremic (>1000)	…	13 (4.2)	…	
3. Traditional risk factors				
BMI categories (kg/m^2), n (%)				<.001
Underweight (<18.5)	51 (9.0)	32 (11.1)	19 (6.9)	
Normal weight (18.5–24.9)	319 (56.6)	177 (61.7)	142 (51.3)	
Overweight (25–29.9)	119 (21.1)	54 (18.8)	65 (23.5)	
Obese (>30)	75 (13.3)	24 (8.4)	51 (18.4)	
Smoking, n (%)				.17
Never smoked	494 (87.6)	249 (88.4)	245 (88.4)	
Ever smoked but stopped	43 (7.6)	27 (9.4)	16 (5.8)	
Current smoker	27 (4.8)	11 (3.8)	16 (5.8)	
Alcohol use in past 12 months	105 (18.6)	41 (14.3)	64 (23.1)	.007
Recommended healthy diet	31 (5.5)	12 (4.2)	19 (6.9)	.16
Recommended physical activity	134 (95)	79 (95.0)	55 (95)	.92
Waist circumference, mean (SD), cm				
Female	84.6 (13.0)	82.3 (12.6)	87.0 (13.1)	<.002
Male	82.0 (11.0)	81.2 (9.8)	82.9 (12.2)	.22
4. Components of metabolic syndrome criteria,[d] n (%)				
Elevated blood pressure (≥135/85 mmHg)	161 (28.5)	63 (22.0)	98 (35.4)	<.001
Abdominal obesity (waist circumference >88 cm for women and >94 cm for men)	130 (23.0)	54 (18.8)	76 (27.4)	.01
Low HDL-C (<50 mg/dL for women and <40 mg/dL for men)	167 (29.6)	75 (26.1)	92 (33.2)	.06
Elevated triglycerides (≥150 mg/dL)	48 (8.5)	30 (10.5)	18 (6.5)	.09
Elevated fasting plasma glucose (≥100 mg/dL)	28 (5.0)	10 (3.5)	18 (6.5)	.09
Metabolic syndrome	50 (9.0)	18 (6.3)	32 (11.6)	.027

Data are presented as n (%) or median (IQR) unless otherwise indicated.

Abbreviations: BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HIV, human immunodeficiency virus; IQR, interquartile range; PI, protease inhibitor.

[a]Eighteen participants were missing nadir CD4 count data.

[c]Two participants were missing CD4 results and viral load result.

[d]Excludes 34 participants without blood sample data.

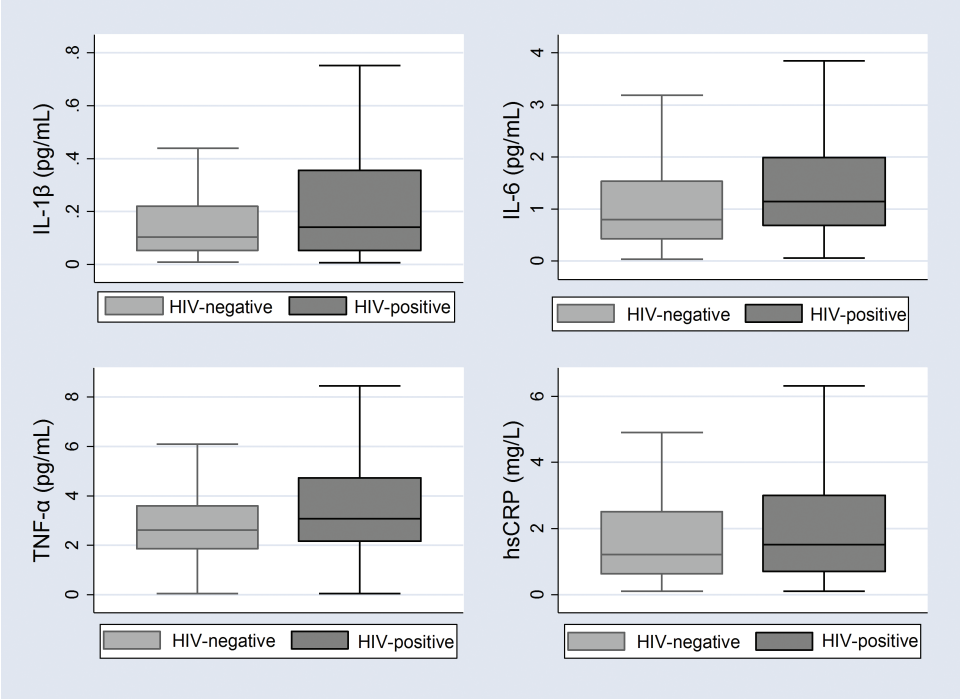

Figure 1. Boxplots of median and interquartile ranges of serum biomarker levels comparing HIV-positive and HIV-negative participants. Abbreviations: HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; IL-1β, interleukin 1 beta; IL-6, interleukin 6; TNF-α, tumor necrosis factor α.

In a model restricting the analysis to participants who are PLHIV, we added HIV-specific factors, including ART regimen, nadir CD4 count, current CD4 count, viral load, and duration of ART use in addition to the CVD risk factors. Persons living with HIV who had a viral load of 1000 or more copies/mL had a 114% higher TNF-α level as compared with those who had an undetectable viral load (P = .013). Apart from TNF-α, there was no association between the HIV-specific risk factors and the other biomarkers.

DISCUSSION

In this study, we found a higher level of inflammatory markers (IL-1β, IL-6, TNF-α, and hsCRP) among PLHIV, the majority of whom were virally suppressed, compared with HIV-negative participants. These higher concentrations among PLHIV persisted even after adjusting for traditional risk factors for CVD, including dyslipidemia, obesity, diabetes, and smoking. Our findings are among the first to examine the relationships between inflammation, HIV, and CVD risk factors in SSA and are consistent with some but not all of the literature from Europe, North America, and SSA [18, 28–32]. In addition, we demonstrated that TNF-α concentrations were even greater among PLHIV who were not virally suppressed relative to PLHIV with optimal viral suppression. Those PLHIV not achieving viral suppression (HIV RNA concentrations ≥1000 copies/mL) had twice the concentration of TNF-α compared with those PLHIV with an undetectable viral load. Higher levels of biomarkers among those not virally suppressed may indicate residual inflammation

Table 2. Exponentiated B-Coefficient Estimates and Confidence Intervals for the Association Between Biomarkers and HIV Status

	Unadjusted			Adjusted[a]		
Variable	Exponentiated β-Coefficient	95% CI	*P*	Exponentiated β-Coefficient	95% CI	*P*
IL-1β (pg/mL)	1.38	1.06, 1.59	.010	1.39	1.10, 1.73	.005
IL-6 (pg/mL)	1.46	1.21, 1.75	<.001	1.51	1.23, 1.84	<.001
TNF-α (pg/mL)	1.45	1.22, 1.70	<.001	1.40	1.16, 1.67	<.001
hsCRP (mg/L)	1.22	1.02, 1.45	.027	1.27	1.06, 1.52	.008

Exponentiated B-coefficients represent the fold increase in mean level of the inflammatory biomarkers comparing HIV-positive and HIV-negative participants. For example, 1.39 is interpreted as PLHIV having a 39% higher mean IL-1 level as compared with HIV-negative participants (P = .005).
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; PLHIV, persons living with HIV; TNF-α, tumor necrosis factor α.

[a]Adjusted for age, sex, smoking, alcohol use, diet, physical activity, body mass index, hypertension and diabetes, and lipids.

Table 3. Unadjusted and Adjusted Multivariable Linear Regression of Factors Associated With IL-1β

	Unadjusted		Adjusted	
	β-Coefficient (95% CI)	*P*	β-Coefficient (95% CI)	*P*
HIV status	.27 (.06, .47)	.010	.30 (.07, .52)	.011
Age (years)				
30–39	Reference		Reference	
40–49	.24 (−.11, .49)	.061	.10 (−.17, .37)	.473
50–59	.03 (−.25, .31)	.837	−.11 (−.42, .20)	.487
≥60	.04 (−.29, .38)	.796	−.06 (−.42, .30)	.746
Sex				
Female	Reference		Reference	
Male	.32 (.13, .53)	.002	.37 (.13, .60)	.002
BMI (kg/m^2)				
Normal (18–24)	Reference		Reference	
Underweight (<18)	−.16 (−.52, .20)	.379	−.26 (−.61, .11)	.175
Overweight (25–29)	−.27 (−.53, −.01)	.039	−.10 (−.37, .17)	.469
Obese (≥30)	.12 (−.18, .42)	.429	.36 (.04, .69)	.030
Current smoker	.18 (−.18, .42)	.459	.08 (−.41, .57)	.741
Alcohol use in past 12 months	.13 (−.13, .39)	.322	.01 (−.28, .28)	.984
Hypertension	−.13 (−.38, .12)	.306	.11 (−.14, .38)	.373
Diabetes	.01 (−.46, .48)	.964	.03 (−.44, .51)	.887
LDL cholesterol >130 mg/dL	−.34 (−.64, −.05)	.024	−.42 (−.96, .11)	.120
HDL cholesterol <50 mg/dL for males and <40 mg/dL for females	−.15 (−.37, .71)	.183	−.08 (−.32, .16)	.526
Total cholesterol >200 mg/dL	−.21 (−.48, .07)	.139	.04 (−.46, .54)	.871
Triglycerides >150 mg/dL	−.01 (−.38, .36)	.969	−.13 (−.52, .27)	.524

Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IL-1β, interleukin 1β; LDL, low-density lipoprotein.

as a result of persistent viremia or a low pretreatment CD4 count [33]. This is consistent with other studies that have shown that high viral load concentrations are correlated with high levels of inflammation and increased CVD risk [33].

Studies examining the relationships between HIV, inflammation, and ART in SSA are limited and have reported heterogeneous results. A multicountry study including sites in Kenya, Nigeria, South Africa, Uganda, and Zambia reported higher levels of CRP but no differences in IL-6 levels comparing PLHIV on ART with individuals without HIV [30]. A study in South Africa comparing individuals without and with HIV who were ART naive and those on ART found that mean TNF-α levels were significantly increased pre-ART among those with opportunistic infections and TNF-α remained elevated 1 year post-ART. However, IL-6 levels were comparable in treated patients without opportunistic coinfection compared with those without HIV [31]. The Monitoring of Early Treatment Adherence Study recruited participants from Uganda and South Africa who were starting ART in late-stage disease and found that individuals starting ART had higher levels of IL-6 pretreatment but found no difference in levels of biomarkers comparing those initiating treatment with earlier- or late-stage disease 1 year after treatment initiation [32]. In summary, ART appears to lower inflammatory markers, but whether low-grade inflammation persists compared with HIV-negative individuals remains a question. In our cross-sectional study in Kenya, low-grade inflammation appears to persist despite ART. The heterogeneity of results across studies may reflect context-specific differences as well as different underlying pathophysiology for each biomarker, as suggested by Siedner et al [32].

Consistent with previously published literature, we found an increase in hsCRP, IL-6, and TNF-α levels with increasing age, especially above the age of 50 years. This is thought to occur due to natural aging resulting in a persistent low-grade inflammation, a process termed "inflammaging" [34]. Males in our study had higher mean IL-1β, IL-6, and TNF-α concentrations compared with females. This has been reported in previous studies and may be explained by the downregulation of these inflammatory marker genes by estrogen [35, 36]. We also report that higher IL-6 levels were associated with lower HDL-C, and higher levels of hsCRP and IL-1β were noted among obese individuals. Obesity has been linked to low-grade inflammation as adipose tissue releases cytokines that trigger the production of CRP [37]. In addition, current smoking was associated with increased levels of TNF-α. Smoking cessation and obesity interventions have been shown to decrease CRP levels, and thus may provide an opportunity for reducing inflammation and CVD risk in both persons with and without HIV [38].

Contrary to our expectation, there was no significant interaction between HIV and metabolic syndrome. Higher levels of inflammation have been seen in cardiometabolic conditions such as metabolic syndrome and hypertension [39], but the data have

Table 4. Unadjusted and Adjusted Multivariable Linear Regression of Factors Associated With IL-6

	Unadjusted		Adjusted	
	β-Coefficient (95% CI)	*P*	β-Coefficient (95% CI)	*P*
HIV status	.38 (.19, .56)	<.001	.41 (.21, .61)	<.001
Age (years)				
30–39	Reference		Reference	
40–49	.33 (.10, .56)	.005	.17 (−.06, .42)	.163
50–59	.48 (.23, .73)	<.001	.28 (−.01, .55)	.051
≥60	.71 (.41, 1.01)	<.001	.59 (.27, .92)	<.001
Sex				
Female	Reference		Reference	
Male	.36 (.18, .55)	<.001	.34 (.13, .55)	.001
BMI (kg/m^2)				
Normal (18–24)	Reference		Reference	
Underweight (<18)	−.16 (−.50, .18)	.355	−.22 (−.55, .10)	.183
Overweight (25–29)	−.24 (−.50, −.18)	.048	−.10 (.35, .14)	.406
Obese (≥30)	.10 (−.19, .38)	.505	.27 (−.04, .58)	.083
Current smoker	.35 (−.09, .79)	.117	.19 (−.26, .63)	.410
Alcohol use in past 12 months	.17 (−.07, .42)	.162	.17 (−.87, .42)	.198
Hypertension	−.15 (−.07, .38)	.194	.08 (−.15, .31)	.501
Diabetes	−.31 (−.74, .12)	.158	−.33 (−.75, .10)	.129
LDL cholesterol >130 mg/dL	−.13 (−.15, −.41)	.355	−.01 (−.49, .46)	.962
HDL cholesterol <50 mg/dL for males and <40 mg/dL for females	−.05 (−.16, .25)	.660	.24 (−.02, .45)	.031
Total cholesterol >200 mg/dL	.16 (−.08, .42)	.191	.08 (−.36, .52)	.729
Triglycerides >150 mg/dL	.21 (−.13, .55)	.225	−.01 (−.36, .34)	.973

Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IL-6, interleukin 6; LDL, low-density lipoprotein.

Table 5. Unadjusted and Adjusted Multivariable Linear Regression of Factors Associated With TNF-α

	Unadjusted		Adjusted	
	β-Coefficient (95% CI)	*P*	β-Coefficient (95% CI)	*P*
HIV status	.37 (.20, .53)	<.001	.34 (.16, .52)	<.001
Age (years)				
30–39	Reference		Reference	
40–49	.33 (.12, .54)	.002	.22 (−.01, .45)	.052
50–59	.38 (.15, .60)	.001	.23 (−.02, .48)	.073
≥60	.50 (−.23, .77)	<.001	.42 (.13, .71)	.005
Sex				
Female	Reference		Reference	
Male	.31 (.14, .48)	<.001	.27 (.08, −.46)	.005
BMI (kg/m^2)				
Normal (18–24)	Reference		Reference	
Underweight (<18)	−.19 (−.50, .11)	.210	−.26 (−.55, .04)	.088
Overweight (25–29)	−.18 (−.39, .04)	.119	−.05 (−.27, .17)	.671
Obese (≥30)	−.19 (−.45, .07)	.144	−.06 (−.34, .22)	.646
Current smoker	.13 (−.26, .52)	.506	−.02 (−.42, .39)	.927
Alcohol use in past 12 months	.12 (−.10, .33)	.289	.12 (−.11, .35)	.306
Hypertension	.03 (−.17, .24)	.745	.10 (−.11, .31)	.873
Diabetes	−.37 (−.76, .02)	.063	−.43 (−.84, −.03)	.045
LDL cholesterol >130 mg/dL	.02 (−.23, .27)	.894	−.20 (−.63, .23)	.359
HDL cholesterol <50 mg/dL for males and <40 mg/dL for females	.01 (−.18, .19)	.938	.16 (−.04, .35)	.110
Total cholesterol >200 mg/dL	.11 (−.11, .34)	.326	.20 (−.20, .60)	.319
Triglycerides >150 mg/dL	.15 (−.15, .45)	.336	−.02 (−.34, .30)	.893

Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; TNF-α, tumor necrosis factor α.

Table 6. Unadjusted and Adjusted Multivariable Linear Regression of Factors Associated With hsCRP

	Unadjusted		Adjusted	
	β-Coefficient (95% CI)	*P*	β-Coefficient (95% CI)	*P*
HIV status	.20 (.02, .37)	.027	.24 (.06, .42)	.008
Age (years)				
30–39	Reference		Reference	
40–49	.28 (.07, .49)	.010	.15 (−.06, .37)	.161
50–59	.54 (.32, .77)	<.001	.42 (.18, .67)	.001
≥60	.57 (.28, .85)	<.001	.59 (.30, .88)	<.001
Sex				
Female	Reference		Reference	
Male	−.21 (−.38, −.03)		−.06 (−.25, −.13)	.523
BMI (kg/m^2)				
Normal (18–24)	Reference		Reference	
Underweight (<18)	−.14 (−.44, .16)	.361	−.19 (−.48, .11)	.221
Overweight (25–29)	.46 (.25, .67)	<.001	.43 (.21, .64)	<.001
Obese (≥30)	.84 (.58, 1.11)	<.001	.83 (.56, 1.11)	<.001
Current smoker	.02 (−.19, .60)	.318	.39 (.01, .78)	.050
Alcohol use in past 12 months	−.28 (−.50, −.58)	.014	−.17 (−.39, .05)	.131
Hypertension	.29 (.07, .50)	.009	−.02 (−.22, .18)	.857
Diabetes	.08 (−.33, .48)	.713	−.04 (−.41, .34)	.843
LDL cholesterol >130 mg/dL	.28 (.02, .53)	.034	−.07 (−.48, .34)	.733
HDL cholesterol <50 mg/dL for males and <40 mg/dL for females	.28 (.08, .47)	.005	.17 (−.03, .37)	.089
Total cholesterol >200 mg/dL	.22 (−.01, .45)	.057	.06 (−.30, .44)	.727
Triglycerides >150 mg/dL	.46 (.12, .30)	.003	.19 (−.12, .50)	.228

Abbreviations: BMI, body mass index; CI, confidence interval; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

not been consistent. This may be explained by genetic factors or the fact that participants in our study were relatively healthy PLHIV but would need further investigation.

The strengths of this study are that we included participants both with and without HIV. The participants with HIV were on highly active ART, the majority having achieved viral suppression, and are thus representative of the current ART program in Kenya [40]. We also measured several inflammatory markers. The limitations of this study include the cross-sectional design, which limits inferences of causality. While we found significant differences in age, BMI, and components of metabolic syndrome comparing participants with and without HIV, we did adjust for these variables in our analysis. We did not measure the inflammatory markers over time to observe their trajectory. In addition, we lack data regarding CVD endpoints such as myocardial infarction or stroke to test how these biomarkers predict these events. Further longitudinal studies in SSA prospectively measuring and following inflammatory markers and CVD events will further our understanding of the relationship between inflammation and CVD risk in PLHIV and could justify intervention studies targeting inflammation for CVD risk reduction.

Conclusions

Greater systemic inflammation was seen among PLHIV compared with HIV-negative individuals, independent of traditional CVD risk factors. Persistent inflammation among PLHIV, even those with optimal viral suppression, is a potential mechanism contributing to increased CVD risk among PLHIV. Periodic measurement of inflammatory markers may be useful for risk stratification and predicting CVD events over time, ultimately helping to identify those PLHIV at highest risk for CVD morbidity and mortality. Research is also needed to determine whether interventions that target both the metabolic and inflammatory pathways reduce CVD risk in PLHIV in SSA.

Notes

Author contributions. C. F., S. T. P., and S. J. M. developed and implemented the CVD study protocol. S. J. M., J. P. H., S. T. P., and C. F. designed this analysis. S. J. P., J. W., A. O., P. M. M., and S. J. M. coordinated data collection. S. J. M. and S. J. P. analyzed the data, and S. J. M. drafted the manuscript. All authors contributed to editing of the manuscript and approved submission of the final draft for publication.

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