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Biomarkers of inflammation in HIV-infected Peruvian men and women before and during suppressive antiretroviral therapy

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Abstract

Objective—Inflammatory biomarkers associated with cardiovascular disease are elevated in HIV-infected persons. These biomarkers improve with antiretroviral therapy (ART) but do not normalize to values observed in HIV-uninfected adults. Little is known regarding biomarkers of inflammation in HIV-infected Peruvians, in whom an increased burden of infectious diseases may exacerbate inflammation, and women, in whom sex difference may alter inflammation compared with men.

Methods—Peruvians initiating first-line ART were enrolled in a prospective observational study. Individuals with suppression of HIV RNA plasma loads to less than 30 copies/ml when determined quarterly over 24 months of ART, had biomarkers of inflammation and cellular

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All authors contributed to the conception and design of the current study. E.T., M.E.B., J.S., C.M., A.L.R., and L.M.F. conceived the idea for the study. R.W.C., J.L., S.M.S., and C.W. were involved in generating and managing the data and databases, whereas statistical analysis was performed by M.E.B. and K.T. All authors contributed to data analysis and interpretation of the results. M.E.B. wrote the first draft of the manuscript and all authors provided input and have approved the final draft of the manuscript.

Conflicts of interest

All authors have no conflicts of interest to disclose.

activation measured pre-ART and at 24-months of ART, and evaluated for associations with sex and clinical parameters.

Results—Pre-ART high-sensitivity C-reactive protein (hsCRP) values of men were in the high-risk cardiovascular disease category ($>3.0\text{mg/l}$) more frequently compared with women ($P = 0.02$); most women's values were in the low/average-risk categories. At 24 months of suppressive ART, hsCRP concentrations decreased in men ($P = 0.03$), but tended to increase in women, such that the proportion with high-risk hsCRP did not differ by sex. Pre-ART, soluble CD163 concentrations were higher in women compared with men ($P = 0.02$), and remained higher after 24 months of suppressive ART ($P = 0.02$). All other inflammatory biomarkers ($P < 0.03$) decreased across sexes. Biomarker concentrations were not associated with BMI or coinfections.

Conclusion—Elevated inflammatory biomarkers persisted despite 24 months of suppressive ART in a subset of Peruvians, and to a greater extent in women compared with men. These findings suggest that lifestyle or pharmacologic interventions may be required to optimize the health of HIV-infected Peruvians, particularly women.

Keywords

antiretroviral therapy; cardiovascular disease; high-sensitivity C-reactive protein; HIV infected; inflammation; interleukin-6; Peruvian; soluble CD163

Introduction

Biomarkers of inflammation, including high-sensitivity C-reactive protein (hsCRP), domain dimer (D-dimer), tumor necrosis factor, and interleukin-6, are associated with cardiovascular disease (CVD) in HIV-uninfected [1–3] and HIV-infected individuals [4–7]. HIV-infected individuals also have elevated levels of inflammatory cytokines such as interleukin-1, interleukin-10, interleukin-12p40, interferon γ produced protein 10, interferon γ , as well as markers of cellular activation [soluble CD25 (sCD25) [8], soluble CD14 (sCD14), soluble tumor necrosis factor 2 (sTNFR-2), soluble vascular cell adhesion molecule 1 (sVCAM-1), and soluble CD163 (sCD163)] [7,9,10].

Suppression of viral replication by ART decreases, but does not always normalize, inflammatory biomarkers [7,11–16]. Residual production of HIV RNA [17] or proteins [18] by infected lymphocytes is hypothesized to contribute to a cycle of gastrointestinal inflammation, mucosal damage, and microbial translocation, leading to systemic inflammation.

Studies investigating the effects of ART on inflammation in HIV-infected Peruvians or Latin Americans could not be found. Given a relatively higher burden of infectious diseases in Peruvians of lower socioeconomic status [19], we hypothesized that suppression of viral replication by ART would not normalize inflammatory biomarkers, and inflammation in Peruvian women would differ from men, because of hormonal and other sex differences.

Methods

Study design

HIV-infected, ART-naïve Peruvians about to initiate ART based on a CD4⁺ count less than 350 cells/μl or diagnosis of AIDS were offered enrolment in a 24-month observational cohort study. The study was approved by Institutional Review Boards in Lima, Peru, and Seattle, Washington, USA. Study visits occurred every 3 months, and included collection of blood specimens for determination of plasma HIV RNA and documentation of medicines. Markers of inflammation and cellular activation were evaluated in blood collected pre-ART and at 24 months of ART (24-month ART) from individuals whose viral replication was optimally suppressed, defined as all plasma HIV RNA suppressed (<30 copies/ml) during the 24-month study.

BMI

Height and weight were obtained pre-ART by chart review to calculate BMIs. BMI categories were defined according to the Center for Disease Controls and American Heart Association [20] as follows: normal 18.5–24.9, overweight 25–29.9, and obese at least 30 kg/m².

Biomarkers of inflammation

Participants hsCRP concentrations were determined using an immunoturbidimetric assay (Beckman, Brea, California, USA). CVD risk categories were based on hsCRP: low, less than 1.0; average, 1.0–3.0; and high more than 3.0 mg/l [21].

sTNFR-2, sCD14, high-sensitivity interleukin-6, and sCD25 were assayed (Quantikine ELISA kits; R&D Systems, Inc., Minneapolis, Minnesota, USA); sVCAM-1 (Millipore, Billerica, Massachusetts, USA) and sCD163 (Macro163; Trillium Diagnostics, LLC, Brewer, Maine, USA) were quantified in plasma by ELISA according to the manufacturer's instructions. Each individual's specimens were assayed on the same plate.

Statistical analysis

Pre-ART continuous and categorical variables between men and women were compared using Mann–Whitney and Fisher's exact tests, respectively. Correlations between pre-ART demographic and clinical parameters, and between interleukin-6 and hsCRP were assessed by Spearman's rank correlation coefficient, and biomarkers between sexes by Wilcoxon rank sum tests. The proportion of women in the high-risk category was compared pre-ART and post-ART using McNemar's test. Spearman's and McNemar's test were performed using Stata SE V12 (StataCorp, College Station, Texas, USA), and other tests using GraphPad Prism Version 5 (La Jolla, California, USA).

Results

A total of 126 ART-naïve participants enrolled into the study between 2007 and 2011. All received ART composed of zidovudine or stavudine, lamivudine, and nevirapine. Twenty-five participants did not complete the study and were not analyzed. A total of 101

participants ($n = 49$ women and $n = 52$ men) completed the study. Nineteen (19%) participants had virologic failure, defined as confirmed plasma HIV RNA at least 500 copies/ml. Virologic suppression, defined as HIV RNA less than 500 copies/ml, was observed in 82 of 101 (81%), including 35 (35%) with HIV RNA consistently less than 30 copies/ml after starting ART, and 47 (47%) participants who experienced one or more low level viremia (LLV). As individuals with LLV may have had imperfect adherence with low levels of HIV replication inducing inflammatory responses, these participants are excluded from this study. The 35 (18 men and 17 women) who achieved and maintained plasma HIV RNA less than 30 copies/ml had inflammatory biomarkers evaluated prior to ART and after 24 months of ART.

The optimally ART-suppressed participants' ages [females median 37 years, interquartile range (IQR): 29–42; males median 35 years, IQR: 29–38], pre-ART plasma HIV RNA copies/ml (females median 4.97 $\log_{10}$ copies/ml, IQR: 4.52–5.48; males $\log_{10}$ 5.24 copies/ml, IQR: 4.86–5.86), and pre-ART CD4 cell counts (females median 149 cells/ μ l, IQR: 42–226; males 98, 31–210) were similar to those of the larger cohort (data not shown).

Treatment of *Mycobacterium tuberculosis* was ongoing in ten (29%) of the 35 participants. During the 24-month study, no new anti-*M. tuberculosis* therapy was initiated in these 10 or the other 25 participants, and no other new infections were noted. Pre-ART BMI was within the normal range for the majority of participants (15/24; 63%), with relatively few overweight (7/24; 29%) or obese (2/24; 8%) individuals.

The optimally ART-suppressed participants mirrored the larger group (data not shown) in that a greater proportion of men had pre-ART hsCRP values in the high-risk CVD category compared with women: 12 of 18 men (67%; 95% confidence interval: 44–84) vs. four of 17 women (24%; 95% confidence interval: 9–48; $P = 0.02$) (Fig. 1a). Notably, at 24-month ART, the proportion of women in the high-risk CVD category increased from four to nine of 17 women ($P = 0.16$) (Fig. 1a), and the hsCRP concentrations decreased in men ($P = 0.03$), such that the proportion with hsCRP higher than 3.0 mg/l did not differ by sex. The participants' pre-ART and 24-month ART hsCRP did not correlate with BMI. Across sexes, hsCRP correlated with interleukin-6 values, both pre-ART ($r = 0.73$; $P < 0.0001$) and at 24-month ART ($r = 0.55$; $P = 0.0007$). When examined within sexes, this correlation was observed in men both pre-ART ($r = 0.69$; $P = 0.002$) and at 24-month ART ($r = 0.77$; $P = 0.0002$), but in women only pre-ART ($r = 0.70$; $P = 0.002$).

The pre-ART markers of cellular activation (macrophages sCD14, sCD163, and T cells sCD25) and proinflammatory cytokines (interleukin-6, sTNFR-2, sVCAM-1) were similar across sexes, with the exception of sCD163, which was higher in women compared with men ($P = 0.02$). After 24-month ART, all the biomarkers decreased within each sex ($P < 0.03$), with sCD163 remaining significantly higher in women compared with men ($P = 0.02$) (Fig. 1b–1g).

Discussion

This study revealed different patterns of inflammatory biomarkers between HIV-infected, ART-naïve Peruvian men and women. These differences were most pronounced with respect to hsCRP and sCD163. Notably, pre-ART, the majority of men's hsCRP were in the high-risk CVD category. Suppression of HIV replication by ART was associated with decreases in hsCRP among men. In contrast, the pre-ART values of the majority of women were in the low/average-risk CVD category. However, with suppressive ART, the hsCRP values increased, resulting in approximately half of the women shifting to the high-risk CVD category. Last, sCD163 concentrations were higher in women compared with men, both before and after 24 months of suppressive ART.

Although numerous studies have evaluated hsCRP in HIV-infected ART-naïve participants [4,13,22], few studies have directly compared concentrations between sexes before and after suppressive ART [23]. The sex differences observed in HIV-infected antiretroviral-naïve Peruvians is consistent with a comparison of antiretroviral-untreated men in the exclusively male Multicenter AIDS Cohort (MACS) and with untreated women in the all-female Women's HIV Interagency Study (WIHS) [24]. Notably, MACS males demonstrated increased hsCRP relative to WIHS females despite increased CVD risk factors in the latter (i.e. significantly higher BMI, rates of diabetes, and smoking) [24]. The observation of fewer WIHS and Peruvian ART-untreated women in the high-risk hsCRP category compared with men suggests sex-related differences in viral pathogenesis or HIV-associated social factors.

Many of our female participants had a normal BMI. These women were physically active, which we speculate may have contributed to their largely normal pre-ART hsCRP concentrations. Although smoking rates and alcohol intake were not evaluated in our Peruvian cohort, these behaviors are more prevalent among Peruvian men [25,26].

As with hsCRP, the pre-ART concentrations of inflammatory cytokines and markers of cellular activation were relatively higher in Peruvians compared with HIV-infected individuals from the United States and Europe [3,4,6,11,22,27,28], likely because of more advanced HIV disease [29]. Concentrations of sCD163 were higher in women compared with men in our study, and corresponded to the high values reported in ARV-naïve and ART-suppressed US HIV-infected women [7,30]. Soluble CD163 released from monocyte/macrophage activation is an adipokine associated with metabolic syndrome [31,32]. Although the BMI suggested that women in our cohort were largely not obese, the waist circumference, a more accurate marker of CVD, was not assessed. Abdominal obesity occurred in more than 70% of women in a smaller study at our site [25], and along with advanced HIV disease may have contributed to elevated sCD163.

After 24 months of suppressive ART, the hsCRP of more than half of the Peruvian women in our study were in the high-risk category CVD category. Although hsCRP has been found to fluctuate over the menstrual cycle, the described changes were small and all within the low-risk CVD category [33], suggesting that the pre-ART to 24-month ART differences were not likely attributable to cyclical hormones. The Peruvian women, like women in other resource-

limited studies, may have had a prolonged variant of immune reconstitution inflammatory syndrome [3,34,35].

The biomarkers of inflammation decreased across the Peruvians during ART suppression, however, remained elevated relative to most values reported in the US and European studies [3,4,6,11,22,27,28,36]. Specifically, the 24-month ART concentrations of hsCRP, interleukin-6, and sCD163 were increased in our Peruvian cohort relative to concentrations presented in other studies from the United States and Spain [27,30,36–39]. This may be because of the Peruvians having relatively more advanced HIV disease at the time of ART initiation, which may have led to a sustained compromise of their intestinal mucosa facilitating microbial translocation [19], differences in abdominal obesity [25], immune reconstitution inflammatory syndrome, or other factors.

Limitations of this study include the small study population, incomplete information on coinfections, and risk factors for CVD. Assays for sTNFR-2, sCD14, sCD25, and sCD163 do not use international standards, which limits comparisons across studies. In addition, ethnic ‘normal’ values for the inflammatory biomarker concentrations were not available for comparison to the participants’ 24-month ART values.

The observed sex differences in our cohort of HIV-infected ART-naive Peruvians, which paralleled differences observed between the MACS and WIHS cohorts, suggests that sex-related variations in HIV pathogenesis may disproportionately increase inflammation and the risk of CVD for women. ART suppression of HIV replication reduced the concentrations of hsCRP in men, and most biomarkers across sexes. However, the tendency for women’s hsCRP to increase and the persistence of elevated sCD163 compared with men suggests that further research is needed to define sex differences in the immune activation that continues despite effective ART, and determine whether lifestyle and/or pharmacologic interventions could further optimize the health of women.

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Fig. 1. Biomarkers of inflammation in the plasma of antiretroviral therapy-naïve Peruvian women and men prior to and after consistent suppression of HIV RNA to less than 30 copies/ml over 24 months of antiretroviral therapy

Pre-ART, the proportion of men with pre-ART hsCRP values in the high-risk CVD category (panel a; >3.0 mg/l, indicated by dashed line) is significantly greater compared to women ($P=0.02$), with most women in the low/average CVD risk category. After 24 months of suppressive ART, the hsCRP concentrations decreased in men ($P=0.03$), and the proportion of women with hsCRP in the high-risk CVD category tended to increase ($P=0.16$) (lines are drawn between pre and 24-month-ART values that increased into the high-risk CVD category). The pre-ART interleukin-6 concentrations in men tended to be ($P=0.07$) higher compared with women (panel b; dashed line at 3.0 pg/ml indicates the upper limit of values observed in 'healthy' US blood donors [40]). Additional markers of T-cell proliferation/activation (sCD25, panel c), monocyte/macrophage activation (sCD14 and sCD163, panels d and e, respectively), and inflammation (sTNFR-2 and sVCAM-1, panels f and g, respectively) were similar pre-ART between men and women. At 24-month ART, biomarkers of cellular activation and inflammation decreased across both men and women. However, both pre and 24-month-ART sCD163 concentrations were significantly increased in women compared with men (panel e). ART, antiretroviral therapy; CVD, cardiovascular disease; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; sCD25, soluble CD25;

sTNFR-2, soluble tumor necrosis factor 2; sVCAM-1, soluble vascular cell adhesion molecule 1.

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