Published in final edited form as:

Antivir Ther. 2009 ; 14(6): 763–769. doi:10.3851/1290.

Oxidant Stress in HIV-Infected Women from the Women's Interagency HIV Study

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Abstract

Background—Oxidant stress contributes to the pathogenesis of multiple conditions and can be assessed by measuring plasma F₂-isoprostane concentrations. We hypothesized that oxidant stress is associated with plasma homocysteine concentration and risk factors for atherosclerosis in HIV-infected women.

Methods—We measured plasma F₂-isoprostane concentrations in a cross-sectional study of 249 HIV-infected women attending the Bronx site of the Women's Interagency HIV Study and assessed associations with plasma homocysteine concentration and other metabolic parameters by linear regression.

Results—In multivariate analysis, HCV viremia, waist circumference, homocysteine concentration, and serum aspartate transaminase level were positively associated with log F₂-isoprostane concentration (all $P < 0.005$). There was a trend for an inverse association between log F₂-isoprostane and CD4% ($P = 0.06$). Among women with HCV infection, the FIB-4 index, an indirect marker of liver fibrosis derived from routine laboratory tests, was positively associated with log F₂-isoprostane concentration.

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Conflicts of Interest: The authors have no commercial or other associations that might pose a conflict of interest.

Conclusion—In this cross-sectional study of HIV-infected women, plasma F₂-isoprostane concentration was positively associated with homocysteine concentration, as well as HCV infection, abdominal obesity, and aspartate transaminase level.

Keywords

Oxidant stress; oxidative stress; F₂-isoprostanes; homocysteine; HIV; HCV

Introduction

Oxidant stress, characterized by release of free radicals that damage tissue, is thought to contribute to the aging process and the pathogenesis of many diseases, including atherosclerosis, cancer, diabetes, and neurodegenerative disorders [1–5]. Measurement of plasma F₂-isoprostanes, which are prostaglandin-like substances produced by free radical-catalyzed peroxidation of arachidonic acid, has emerged as an accurate and reproducible way to assess oxidant stress in vivo [6].

The relationship of oxidant stress to complications of HIV disease and antiretroviral therapy, including mitochondrial toxicities and metabolic complications, is uncertain. McComsey and Morrow found that plasma F₂-isoprostane levels were higher in HIV-infected subjects who had clinically apparent lipoatrophy compared with those without lipoatrophy [7]. In addition, all four subjects in their study with symptomatic hyperlactatemia/lactic acidosis had elevated F₂-isoprostane levels relative to those with asymptomatic sustained hyperlactatemia, who did not differ from subjects with normal lactates [7]. In contrast, Hulgán et al found no association between F₂-isoprostane levels and nucleoside reverse transcriptase inhibitor (NRTI)-associated peripheral neuropathy [8]. While F₂-isoprostanes have been shown to correlate with subclinical atherosclerosis in young healthy individuals [9], data on the relationship between oxidant stress and factors associated with atherosclerotic risk in HIV-infected subjects are lacking.

We hypothesized that greater oxidant stress would be associated with higher levels of homocysteine. The rationale for this hypothesis is that homocysteine, a thiol-containing amino acid, generates free radicals when it is oxidized, primarily via auto-oxidation [10,11]. This relationship of homocysteine to oxidant stress is one potential mechanism by which homocysteine elevations may contribute to atherosclerosis [1,12,12]. Specifically, homocysteine may contribute to oxidation of low density lipoprotein (LDL) and to lipid peroxidation, the latter which may be assessed by assaying circulating F₂-isoprostanes. To study this, we measured plasma F₂-isoprostanes and homocysteine cross-sectionally in the Bronx, New York site of the Women's Interagency HIV Study and assessed their relationships to other metabolic parameters.

Methods

The Women's Interagency HIV Study (WIHS) is a prospective cohort study that has enrolled 3,772 primarily minority women with or at high risk of HIV infection at six urban sites in the United States [13]. The Bronx, New York site enrolled 537 women beginning in 1994 with an additional 233 women enrolled in 2001. At baseline and at each follow-up visit, detailed information is collected on demographics, HIV-related risk behavior, antiretroviral therapy, anthropometric data, co-morbidities, and lifestyle and medication history. Women are asked specifically whether they have taken any complementary or alternative medications, including nutritional supplements, vitamins, or minerals since their last study visit, and the names of any such products are recorded. For this study, antioxidant vitamin or mineral use was defined dichotomously (yes/no) as self-reported use of a multivitamin/mineral, zinc, vitamins A, C, or

E, and/or beta-carotene since last study visit. Informed consent was obtained from all subjects and human experimentation guidelines of the US Department of Health and Human Services and those of the authors' institutions were followed in the conduct of this research.

We conducted a cross-sectional study at a recent follow-up visit (visit 24, April-September 2006) in the Bronx WIHS site. Currently enrolled HIV-infected women who were still under active follow-up were included in the present study. The only exclusion criterion was acute illness at the time of the visit as determined by the interviewer at the WIHS site. Blood samples collected in tubes containing EDTA anticoagulant were immediately placed on ice and plasma was separated within one hour and stored at -70 degrees Celsius.

Plasma levels of 15-F₂t-isoprostane (8-iso-prostaglandin F₂ α) were assayed by gas chromatography/negative ion chemical ionization mass spectrophotometry [6]. The intraday variability of this assay is $< 10\%$, and the mean level of F₂-isoprostanes in healthy volunteers is 35 pg/ml (standard deviation 6 pg/ml)[6]. The upper limit of normal of plasma F₂-isoprostanes in healthy adults is considered to be 41 pg/ml. Homocysteine was assayed by fluorescence polarization immunoassay (Quest Diagnostics, Baltimore, MD). The interassay coefficient of variation for this assay is 8.8%. In order to remove skewness, we used natural log F₂-isoprostane in most analyses. High sensitivity C-reactive protein (hsCRP) was measured at visits 19 or 20 (about 2–2.5 years prior to the time of F₂-isoprostane measurement) and 20 or 21 (about 1.5–2 years prior to the time of F₂-isoprostane measurement). The mean of both measurements (which were natural log transformed first to remove skewness) was used.

Homeostasis model-insulin resistance (HOMA-IR) [14] was calculated from fasting insulin and glucose values tested within one year of the F₂-isoprostane blood collection using the formula: Fasting serum insulin (μ U/mL) x fasting plasma glucose (mg/dL)/405. Hepatitis C viremia at entry into the WIHS cohort was assessed by either the COBAS Amplicor Monitor 2.0 or the COBAS Taqman assays (both from Roche Diagnostics, Branchburg, New Jersey, USA) as previously described [15]. FIB-4, a noninvasive marker of hepatic fibrosis developed for HCV/HIV co-infected subjects [16], was calculated in our HCV/HIV co-infected women as: $\text{FIB-4} = [\text{Age (years)} \times \text{AST}]/[\text{Platelet Count (10}^9/\text{L)} \times \text{ALT}^{1/2}]$

Statistical Analysis

Data were descriptively analyzed using plots, histograms, means, medians, standard deviations, skewness and kurtosis to identify erroneous values, outliers and optimal transformations. Due to large skewness in the original variables, F₂-isoprostane, hsCRP, fasting glucose concentrations and HOMA-IR were natural log transformed. Continuous variables are summarized in this paper by means $\pm$ standard deviations. Due to the presence of three extreme outliers, serum creatinine values > 2.0 mg/dL were set to missing. Associations between log F₂-isoprostane concentration as a continuous variable and other variables of interest were assessed by univariate and multivariate linear regression modeling, the latter using forward stepwise selection of covariates with a P-value of < 0.10 to enter or leave the model. Only covariates with P-values of < 0.10 in univariate analyses were considered in multivariate analyses. Regression results and 95% confidence limits are expressed as relative (percent) change in F₂-isoprostane concentration associated with a given change in the predictor, calculated as $100 \times (\exp^{\beta} - 1)$ where β is the regression coefficient from the model with log F₂-isoprostane concentration as the outcome. Statistical analysis was performed using SAS version 9.1 software (SAS Institute Inc. Cary, NC, USA).

Results

Table 1 summarizes the demographic and clinical characteristics of the 249 HIV- infected women enrolled in this study at the time of the F₂-isoprostane blood draw. The majority of women had a prior clinical diagnosis of AIDS, although the mean current CD4 cell count was 485 ± 326 cells/mm³ and 53% had HIV RNA levels below the level of quantification (< 80 copies/ml). The prevalence of diabetes was 20%, and 28% of women were actively infected with HCV based on circulating HCV RNA.

The mean log plasma F₂-isoprostane level was 4.11 ± 0.53 log pg/ml, and 195 (78.3%) women had levels of 3.71 log pg/ml (41 pg/ml) or greater (one SD above the mean level reported in healthy volunteers). Plasma F₂-isoprostane concentration correlated with plasma homocysteine concentration (Figure; $r = 0.30$, $P < 0.0001$).

In univariate linear regression with log transformed F₂-isoprostane concentrations as the outcome (Table 2), the strongest associations (all at $P < 0.0001$) were observed with waist circumference, presence of HCV viremia, and plasma homocysteine concentration. For example, on a logarithmic scale, a woman who had HCV viremia had 40.4% higher F₂-isoprostane concentrations than did a woman without HCV viremia. F₂-isoprostane was also positively associated with older age, current smoking, and higher weight, body mass index, systolic blood pressure, diastolic blood pressure, log insulin level, AST, and ALT. Log F₂-isoprostane concentrations were inversely associated with use of antioxidant vitamins or minerals. There were trends for positive associations between log F₂-isoprostane concentration and log HOMA-IR, and negative associations between log F₂-isoprostane concentration and CD4% and any use of nevirapine. Log F₂-isoprostane concentrations were not associated with the log hsCRP measurements obtained approximately two years previously.

In the final forward stepwise multivariate linear regression model (Table 2), HCV viremia, waist circumference, homocysteine concentration, and serum AST level were all positively associated with log F₂-isoprostane concentration, while CD4% was inversely associated in this multivariate model. We also constructed a separate model that included both these covariates selected by forward stepwise regression and also current smoking and age (forced into the model). In this model, age and current smoking were not statistically significant ($P = 0.37$ and 0.22 , respectively), and adjusting for them had minimal impact on the magnitude of the beta coefficients and statistical significance of the other covariates (data not shown).

To explore the association between HCV infection and F₂-isoprostane concentrations further, we assessed the association between degree of hepatic fibrosis estimated by FIB-4 and plasma F₂-isoprostanes among the 68 of the 70 women with HCV viremia for whom FIB-4 could be calculated. Their mean FIB-4 value was 2.13 ± 1.64 . In a univariate linear regression model, F₂-isoprostane concentrations increased by 9.05% for each unit increase in FIB-4 score ($P = 0.049$).

Discussion

In this cross-sectional study, we found that plasma F₂-isoprostane concentrations, an in vivo marker of oxidant stress, were positively associated with plasma homocysteine concentrations, in accordance with our primary hypothesis. We also found positive associations between this measure of oxidant stress and several metabolic and body composition parameters, including waist circumference, body mass index, and HOMA-IR, as well as transaminase levels and HCV viremia. F₂-isoprostane levels were inversely associated with use of antioxidant vitamins or minerals and % CD4 cells. In multivariate analysis, however, only homocysteine level, waist circumference, HCV viremia, and AST level remained significantly associated with this measure of oxidant stress.

In a cross-sectional study of 120 patients in an HIV clinic, Hulgan et al found that 23% of patients had F₂-isoprostane levels above what they considered to be the upper limit of normal (41 pg/ml) [17]. Using the same assay and criterion, 78% of the women in our study had elevated levels. This discrepancy is likely related in part to well-established sex differences in this marker of oxidative stress; in the general population, women have significantly higher plasma levels of F₂-isoprostanes than men [18]. Only 13% of the patients in Hulgan's initial study were women. Preliminary results of a larger follow-up cross-sectional study by the same group found that female sex was associated with higher levels of F₂-isoprostanes [19]. The clinical implications of these apparent sex-related differences are uncertain.

In their initial report, Hulgan et al found that F₂-isoprostane concentrations were lower in patients using efavirenz and inversely associated with HIV RNA level [17]. In their follow-up study, use of a non-nucleoside reverse transcriptase inhibitor (in particular nevirapine) was associated with lower F₂-isoprostane concentrations [19]. Other factors associated with oxidant stress in the second study were female sex, greater BMI, and heavy smoking. In the present study, we extend their findings by inclusion of additional metabolic, body composition, and liver-related covariates, some of which were positively associated with log F₂-isoprostane concentration.

The positive association between homocysteine level and oxidant stress, assessed by F₂-isoprostane concentrations, is consistent with data from the general population [11]. While homocysteine has been considered to be an independent risk factor for coronary heart disease, lowering of homocysteine through folate supplementation has not had an effect on secondary prevention of myocardial infarction [20,21]. Whether lowering of homocysteine through folate supplementation could reduce oxidant stress and consequently the incidence of other conditions associated with increased oxidant stress is speculative at this time. Similarly, while our finding of an inverse relationship between antioxidant vitamin or mineral use and oxidative stress is intriguing, it is not clear if use of these supplements is of clinical benefit.

The presence of both HCV viremia and AST level were independently positively associated with oxidant stress in this study. Given the high prevalence of obesity in our study population, AST level may be a marker of non-alcoholic fatty liver disease. Oxidant stress has been postulated to play a role in the pathogenesis of non-alcoholic fatty liver disease, making the association between AST and F₂-isoprostane levels biologically plausible [22]. It is also conceivable that oxidant stress may contribute to the pathogenesis of HCV-related liver disease. Since liver biopsy data were not available, we were unable to assess definitively whether stage of liver disease was associated with oxidant stress. Among women with HCV infection, however, FIB-4, a validated noninvasive marker of hepatic fibrosis [16] was associated positively with F₂-isoprostane concentration, suggesting that more advanced fibrosis was associated with greater oxidant stress. Given recent associations between HCV infection and atherosclerotic burden [23], further studies are warranted to determine if oxidant stress may be mediating this relationship.

Our study has several noteworthy strengths and limitations. This is the largest study of F₂-isoprostanes in HIV-infected subjects and focuses on an underrepresented population of women of predominantly African-American and Latino backgrounds. In the general population, African-American men and women have lower circulating F₂-isoprostanes relative to whites and other races [18]. While we did not find a statistically significant association between race/ethnicity and F₂-isoprostanes in this study, we could not rule out the presence of modestly lower levels in blacks. The metabolic and anthropometric data collected in this study enabled us to explore novel associations. Due to the cross-sectional design, however, we are unable to assess the temporal and potentially causal relationships between oxidant stress and the covariates under study. In addition, the high prevalence of both obesity and diabetes in our

study may limit the generalizability to other populations of HIV-infected women. The lack of data on HIV- uninfected controls makes it impossible to determine if plasma F₂-isoprostane concentrations were elevated in HIV-infected women relative to HIV-uninfected women.

In summary, in this cross-sectional study of HIV-infected women, oxidant stress assessed by plasma F₂-isoprostane concentration was positively associated with waist circumference, HCV viremia, homocysteine level, and AST level. The clinical significance of an elevated marker of in vivo oxidant stress is uncertain and requires further study.

Acknowledgments

Data in this manuscript were collected by the Bronx/Manhattan Consortium of the Women's Interagency HIV Study (WIHS) (U01-AI35004.) The study is co- funded by the National Cancer Institute, the National Institute on Drug Abuse, and the National Institute on Deafness and Other Communication Disorders. This work was also supported in part by the Center for AIDS Research at the Albert Einstein College of Medicine and Montefiore Medical Center funded by the National Institutes of Health (NIH AI51519), the National Institute of Diabetes and Digestive and Kidney Disease (DK54615 and RO1 DK48831), the National Heart Lung and Blood Institute (R01 HL083760), the National Institute of General Medical Sciences (P50 GM15430), the National Institute of Environmental Health Sciences (P01 ES13125), and the National Institute of Allergy and Infectious Diseases (K24 AI 78884).

The authors thank the study participants and staff of the Bronx WIHS site, especially Esther Robison, PhD and Tania Williams, and William Meyer, PhD and Larry Hirsch of Quest Diagnostics for their assistance. The authors dedicate this paper to the memory of their colleague Dr. Jason Morrow.

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Figure 1. Scatterplot of plasma F₂-isoprostane concentration by plasma homocysteine concentration. The grey line represents the regression line ($R^2 = 0.089$, adjusted $R^2 = 0.086$, $P < 0.0001$) and the black line represents the loess (smoothed) line.

Table 1

Characteristics of Study Participants

Variable	Value ^a
No. of women	249
Clinical variables	
Age (yr)	45 ± 7.3
Race/ethnicity	
African American	124 (50%)
Hispanic	109 (44%)
White	10 (4%)
Other	6 (2%)
HIV risk group	
Injection drug use	65 (26%)
Heterosexual	115 (46%)
Blood transfusion	1 (<1%)
None	67 (27%)
Clinical AIDS at or before visit	137 (55%)
Diabetes at or before visit	51 (20%)
Body mass index (kg/m ²)	29.0 ± 6.9
Waist circumference (cm)	89.4 ± 14.5
Use of antioxidant vitamin/mineral	53 (21%)
Current smoker	147 (59%)
Current use of NRTI	190 (76%)
Current use of stavudine	16 (6%)
Current use of PI	122 (49%)
Current use of NNRTI	66 (27%)
Current use of nevirapine	18 (7%)
Current use of efavirenz	47 (19%)
Current use of statin	29 (12%)
Current use of fibrate	7 (3%)
Biochemical variables	
CD4 count (/mm ³)	485 ± 326
CD4%	26.5 ± 11.3
HIV viral load (log copies/mm ³)	2.69 ± 1.11
Detectable viral load	116 (47%)
Fasting glucose (mg/dL)	98 ± 30
Fasting insulin (μU/ml)	17.0 ± 16.2
HOMA-IR index	4.42 ± 5.27
HCV RNA positive, n (%)	70 (28%)
Hepatitis B surface Ag positive, n (%)	5 (2%)
Homocysteine (μmol/L)	7.36 ± 2.62
Log (F ₂ -Isoprostane) (pg/ml)	4.11 ± 0.53

Variable	Value ^a
F ₂ -Isoprostane > 3.71 log pg/ml (41 pg/ml)	195 (78%)
FIB-4 ^b	2.13 ± 1.64
Platelet Count (× 10 ⁹ /L)	233.0 ± 75.1
Serum ALT (IU/L)	28.1 ± 23.9
Serum AST (IU/L)	33.5 ± 25.8
Log hsCRP ^c (mg/L)	0.31 ± 0.56

^aContinuous variables are expressed as mean ± standard deviation and categorical values as n (%)

^bFIB-4 [16] was calculated for the 68 of 70 women with HCV viremia who had available data.

^cAvailable on 224 women.

Abbreviations: BMI, body mass index; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; HOMA-IR, homeostasis model assessment-insulin resistance; hsCRP, high sensitivity C-reactive protein.

Table 2

Associations with Percent Change in Plasma F₂-Isoprostane Concentrations in HIV-infected Women from Univariate and Multivariate Linear Regression of Log F₂-Isoprostane

Variable	Unadjusted model			Multivariate model ^b		
	Percent Change ^a	95% Confidence Interval	P- value	Percent Change ^a	95% Confidence Interval	P- value
Age (per 10 years)	10.27%	0.87% to 20.5%	0.032			
Race			0.25			
Black	0%	-----				
White	-9.79%	-24.37% to 7.59				
Hispanic/Other	12.86%	-2.31% to 30.39				
Current smoking	14.66%	0.47% to 30.86%	0.044			
Diabetes mellitus	2.66%	-12.73% to 20.74%	0.75			
Weight (per 10 kg)	6.47%	3.00% to 10.06%	0.0003			
BMI (per 5 kg/m ²)	9.57%	4.67% to 14.81%	0.0002			
Waist circumference (per 10 cm)	10.80%	6.01% to 15.81%	<0.0001	11.63%	6.92% to 16.55%	<0.0001
Systolic blood pressure (per 10 mmHg)	4.65%	0.96% to 8.47%	0.014			
Diastolic blood pressure (per 10 mmHg)	7.61%	0.93% to 14.74%	0.026			
cART since last visit	6.75%	-8.64% to 24.75%	0.41			
Any PI use	8.27%	-5.00% to 23.38%	0.23			
Any NNRTI use	-5.35%	-18.40% to 9.78%	0.47			

Variable	Unadjusted model			Multivariate model ^b		
	Percent Change ^a	95% Confidence Interval	P- value	Percent Change ^a	95% Confidence Interval	P- value
Any NRTI use	9.93%	-5.73% to 28.19%	0.23			
Any stavudine use	13.33%	-13.21% to 47.97%	0.36			
Any nevirapine use	-19.86%	-37.68% to 3.06%	0.086			
Any efavirenz use	3.49%	-12.46% to 22.35%	0.69			
Use of any lipid- lowering drug	-9.13%	-23.82% to 8.38%	0.29			
Statin use	0.67%	-17.93% to 23.49%	0.95			
Antioxidant vitamin or mineral use	-15.54%	-27.94% to -1.02%	0.038			
Serum creatinine (mg/dl)	30.15%	-11.15% to 90.66%	0.18			
CD4 Number (per 100 cells/mm ³)	0.38%	-1.62% to 2.42%	0.71			
CD4 percent (per 5%)	-2.53%	-5.31% to 0.34%	0.085	-2.64%	-5.28% to 0.06%	0.06
Detectable HIV RNA	-6.26%	-17.78% to 6.87%	0.3345			
HCV RNA positive	40.31%	22.04% to 61.31%	<0.0001	26.87%	9.21% to 47.39%	0.002
HBV sAg positive	-7.09%	-41.76% to 48.21%	0.76			
Log fasting glucose (mg/dL)	-10.77%	-34.39% to 21.34%	0.47			
Log Fasting Insulin (μU/ml)	10.88%	1.44% to 21.18%	0.024			

Variable	Unadjusted model			Multivariate model ^b		
	Percent Change ^a	95% Confidence Interval	P- value	Percent Change ^a	95% Confidence Interval	P- value
LogHOMA-IR	7.47%	-0.62% to 16.22%	0.073			
Total cholesterol (per 10 mg/dL)	0.33%	-1.16% to 1.84%	0.66			
Platelets (per 100/mm ³)	-4.29%	-12.39% to 4.56%	0.33			
AST (per 10 IU/ml)	4.65%	2.08% to 7.28%	0.0004	3.72%	1.19% to 6.31%	0.004
ALT (per 10 IU/ml)	4.24%	1.47% to 7.09%	0.0028			
Homocysteine (μmol/L)	6.05%	3.54% to 8.62%	<0.0001	4.39%	1.82% to 7.04%	0.0009
FIB-4 ^c	9.05%	0.19% to 18.7%	0.049			
Log hsCRP	0.92%	-4.44% to 6.58%	0.74			

^a Reflects the percentage change on a multiplicative scale, obtained as $100(\exp\beta - 1)$ where β is the regression coefficient (or corresponding lower or upper confidence limit for this coefficient) using log-transformed F₂-isoprostane as the outcome

^b From stepwise multiple regression model of all variables in this table (except for FIB-4) that had unadjusted P values < 0.10

^c FIB-4 [16] was calculated on 68 of 70 women with HCV viremia and was not evaluated in multivariate analyses.

Abbreviations: BMI, body mass index; cART, combination antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; HOMA-IR, homeostasis model assessment-insulin resistance; AST, aspartate transaminase; ALT, alanine transaminase; hsCRP, high sensitivity C-reactive protein.