Published in final edited form as:

HIV Med. 2018 November ; 19(10): 734–744. doi:10.1111/hiv.12665.

Longitudinal Evaluation of Markers of Inflammation in HIV-Positive and HIV-Negative Rwandan Women

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Keywords

Women; Inflammation; hsCRP; transthyretin; D-dimer

Introduction

Women are disproportionately affected by HIV infection, accounting for over half of HIV infections globally and 59% of HIV infections in eastern and Southern Africa (1). While the number of AIDS related deaths in Sub-Saharan Africa has fallen and the number of people accessing antiretroviral therapy (ART) has risen (1), people living with HIV (PLWH) also face numerous non-AIDS comorbidities including cardiovascular, liver and kidney disease and some cancers (2–6). Inflammation is one factor associated with this excess risk of non-AIDS events; inflammatory markers remain elevated above levels seen in people without HIV despite ART use and viral suppression (7–10). There are few longitudinal evaluations of these systemic inflammatory markers in HIV-infected women, despite known differences by gender in HIV natural history and immunity (11–14). As awareness increases of a double burden of HIV infection and chronic diseases, there is urgent need for research on these associations in African women (15).

In PLWH, high sensitivity C-reactive protein (hsCRP), D-dimer, and transthyretin (prealbumin) have previously been examined as markers of inflammation. hsCRP is elevated in HIV-infected individuals compared to HIV-negatives, and independently predicts HIV mortality, HIV disease progression, and risk for AIDS and non-AIDS events (13, 15–28). Higher D-dimer in HIV infection has been associated with increased all-cause mortality and

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E.M.K, D.R.H, Q.S., and K.A designed the research study. Q.S and D.R.H. performed statistical tests. E.M.K, D.R.H, Q.S., and K.A analyzed the data. E.M.K wrote the paper. E.M.K, D.R.H, Q.S., J.C.D, J.D.S, and K.A reviewed and edited the paper.

All authors have seen and reviewed the final submitted manuscript and have no conflicts of interest to declare. This research represents new data which is not published nor submitted elsewhere.

non-AIDS death (4, 9, 29–34), although results may be inconsistent in women (34–36). Lower transthyretin was associated with higher HIV mortality and a negative acute phase response (18, 37–39). Longitudinal evaluation of these markers has not been well described in African women, and it is unclear how they change over time in HIV-negatives, or in PLWH with or without ART. Current studies are conflicting: hsCRP and D-dimer in PLWH have been observed to increase (4, 10, 19, 40–42), remain unchanged (43–49), or decrease (45, 46, 50–53) after ART and/or over time. Few studies have examined longitudinal changes in transthyretin in HIV (39, 54). Studies have been limited to mostly men, with short follow-up times, and to developed countries (40, 50, 55, 56).

The Rwanda Women's Interassociation Study and Assessment (RWISA) was an observational prospective cohort of HIV-negative and positive women which collected historical, physical exam, laboratory, and HIV treatment data every 6 months beginning in 2005. The study ended in December, 2010. We examined levels of three markers of inflammation, hsCRP, D-dimer, and transthyretin, at baseline and at follow-up of at least 2 years in 185 HIV-negative and 510 HIV-positive Rwandan women, all of whom were ART-naïve at study entry. The goal of the current study is to examine how these markers changed after ART initiation and over time in a population of Rwandan women including HIV-negatives, untreated HIV-positives or HIV-positives who were initially untreated but then initiated ART.

Methods

Parent Study

RWISA was an observational prospective study of 710 ART-naïve HIV-infected and 226 HIV uninfected women enrolled in 2005. The methods of RWISA have been previously described in detail (57). Participants were recruited through grassroots women's organizations and clinical care sites that served PLWH. Eligible participants were 25 years or older, willing to give informed consent and to be tested for HIV infection, and able to return for bi-annual visits. Women were excluded if they had previously received any antiretroviral treatment, with the allowable exception of prior single-dose nevirapine to prevent mother-to-child HIV transmission. Each participant provided written informed consent after watching a video demonstrating the study procedures. RWISA was approved by the Rwanda National Ethics Committee and the Montefiore Medical Center Institutional Review Board (10-05-138E).

At study entry and each subsequent visit, participants underwent a physical examination. Medical and social history was collected, including demographic characteristics and questions regarding the exact date of ART initiation (verified by clinic data) and reported adherence to ART. Blood specimens were taken for measuring CD4 cell count, full blood count and other laboratory studies, and serum stored at -80°C . For this analysis, the baseline visit was defined as study entry for HIV-negative participants and HIV-infected ART-naïve women not initiating ART during follow-up (ART non-initiators), and as the immediate pre-ART visit for women who initiated ART during follow-up (ART initiators).

Sample selection for this study

We included all women in the RWISA parent study with stored serum samples available at baseline (baseline visit) and at the longest follow-up time greater than or equal to 2 years (follow-up visit). We excluded women with a positive urine pregnancy test at baseline or at any follow-up visit.

Laboratory data:

hsCRP, D-dimer, and transthyretin were measured from serum analyzed at the Einstein-Montefiore Institute for Clinical and Translational Research at the Biomarker Analytic Research Core. Specimens from the baseline visit and the follow-up visit were blinded and randomized to testing order prior to analysis. All samples from the same participant were tested on the same laboratory test date.

Outcome and Exposure Variables:

hsCRP, D-dimer, and transthyretin were the outcome variables in each of three separate models. The primary exposure variable was HIV serostatus/CD4 quartile among HIV-positives, with groups stratified as: HIV-negative, HIV-positive with a CD4 count < 185 cells/ μ L (quartile 1, Q1), HIV-positive with a CD4 count of 186 to 288 cells/ μ L (quartile 2, Q2), HIV-positive with a CD4 count of 289 to 415 cells/ μ L (quartile 3, Q3), HIV-positive with a CD4 count > 415 cells/ μ L (quartile 4, Q4). We included this variable measured at both the baseline and follow-up visit and defined quartiles based on the pooled baseline and follow-up measures for HIV-positive women.

We considered ART use in two ways. Those ART-naïve HIV-positive women who had indications for ART use (ART-indicated), were placed on ART after the baseline visit, and were continued on ART at the follow-up visit were compared to HIV-negatives and HIV-positives who were never placed on ART (ART was not indicated). We created a separate ART variable (ARV treatment) to capture the effect of initiating ARV treatment itself on each inflammatory marker. ART was initiated after the baseline visit, and inflammatory markers were again measured at least 2 years after initiation of ART, at the defined follow-up visit.

Additional exposure variables included associations that may have changed from the baseline to follow-up visit. We included the effect of time between the baseline and follow-up visit, calculated as the difference in calendar dates in years between the baseline visit and the follow-up visit for each participant. For each model, we included the following follow-up time variables: follow-up time for HIV-negatives (set as 0 for HIV-positive women); follow-up time for untreated HIV-positives (set as 0 for HIV-negative women and set to the time between baseline and ART initiation for HIV-positive women who initiated ART); and follow-up time for HIV-positives on ART (set as 0 for HIV-negatives and 0 for untreated HIV-positive women).

The models also adjusted for the baseline visit date, the laboratory test date (date samples were run), and participant age at the baseline visit. There was little smoking in this cohort reported at follow-up visit 2 (7%). Reported hormone use from Depo-Provera (Depo) was

low at baseline (1%); however, there were a large number of missing measures. We examined both pre- and post-Depo use at baseline and follow-up; there were inconsistent patterns of association with the missing measures. Thus, smoking and Depo use were not included in our adjustment models.

Statistical Analysis

hsCRP, D-dimer, and transthyretin were examined for normality. D-Dimer and hsCRP were left skewed and were thus $\log_{10}$ transformed for linear regression and other comparative analyses. For D-Dimer and hsCRP, results are presented on the $\log_{10}$ scale. We created three separate linear regression models, one for each of the inflammatory markers, with each model including covariates with associations at baseline, and covariates that changed from the baseline visit to the follow-up visit. Generalized Estimating Equation (GEE) models with independent correlation structure accounted for intra-person correlation of repeat measures. In our initial models, the variable ART-indicated did not remain independently statistically significant after adjustment for the HIV serostatus/CD4 quartile variable, and was thus dropped from the final model. The ARV treatment variable, however, remained independently significant in two of the models.

Results

We included all 695 non-pregnant women who had specimens available at the baseline visit and one follow-up visit at 2 years. The mean follow-up time was 2.89 (± 0.67) years for HIV-negative women, 2.67 (± 0.62) years for the ART non-initiators, and 2.37 years for HIV-positive ART initiators. Among the ART initiators, the mean time from baseline to ART initiation was 0.27 (± 0.32) years with 2.10 (± 0.90) years of follow-up on ART. Baseline and follow-up characteristics are shown in Table 1. At baseline, HIV-negative women were older (43.2 years) than both groups of HIV-positive women (34.4 and 36.0 years in ART non-initiators and ART initiators respectively, $p < 0.0001$). Mean baseline BMI was similar among groups ($p = 0.37$). At follow-up, BMI increased for all women (Table 1). Among HIV-positive women at baseline (when all were ART-naïve) the future ART *non*-initiators had higher CD4 counts than the ART-initiators both at baseline (473 vs. 211 cells/ μ L respectively) and at follow-up (420 vs. 371 cells/ μ L respectively), indicating the more advanced immune suppression in the ART initiators. Mean hsCRP, D-dimer and transthyretin differed between HIV-negatives, HIV-positive ART non-initiators, and HIV-positive ART initiators at baseline (p between groups hsCRP, $p < 0.0001$; D-dimer $p = 0.003$; transthyretin, $p < 0.0001$).

Figures 1a–c show baseline and follow-up mean log hsCRP, log D-dimer, and transthyretin values, with unadjusted p -value for the change. For hsCRP and D-dimer, log hsCRP and log D-dimer were used in the calculations, but the results were exponentiated to the original scale for the figures. Mean hsCRP increased non-significantly from baseline to follow-up in the HIV-negatives ($p = 0.40$) and HIV-positive ART non-initiators ($p = 0.36$), and decreased non-significantly in the ART initiators ($p = 0.20$) (Figure 1a). Mean D-dimer decreased significantly in all groups from baseline to follow-up (HIV-negatives, $p < 0.0001$; HIV-positive ART non-initiators, $p = 0.018$; HIV-positive ART initiators, $p < 0.0001$) (Figure 1b).

Mean transthyretin decreased significantly from baseline to follow-up in HIV-negative women ($p=0.0002$) and HIV-positive ART non-initiators ($p=0.009$), but increased significantly in ART initiators ($p<0.0001$) (Figure 1c).

Table 2 shows the association of covariates with each of the markers of inflammation. Model results for D-dimer and hsCRP are shown on a log scale. Among HIV-infected women, as quartiles of CD4 increased (compared to HIV-negatives), log hsCRP significantly decreased (0.47 mg/L for Q1, $p<0.0001$; 0.32 mg/L for Q2, $p<0.0001$; 0.27 mg/L for Q3 $p<0.0001$; and 0.23 mg/L for Q4, $p=0.0004$). Log D-Dimer also decreased as quartiles of CD4 increased in HIV-positive (compared to HIV-negative) women, which was significant for the first 2 quartiles (0.18 mg/L for Q1, $p<0.0001$; 0.15 mg/L for Q2, $p=0.0001$; 0.08 mg/L for Q3 $p=0.06$; and 0.07 mg/L for Q4, $p=0.08$). Among HIV-infected women, as quartiles of CD4 increased, the difference in transthyretin compared to HIV-negatives narrowed significantly (-6.17 mg/dL for Q1, $p<0.0001$; -4.09 mg/dL for Q2, $p<0.0001$; -2.58 mg/dL for Q3 $p=0.0001$; and -2.55 mg/dL for Q4, $p=0.0001$). In other words, women with more advanced HIV infection and lower CD4 counts (those in lower quartiles) had higher hsCRP, higher D-dimer and lower transthyretin.

A later baseline visit date was associated with lower log D-dimer -0.06 mg/L, $p=0.002$) but not with differences in log hsCRP (-0.06 mg/dL, $p=0.15$) or transthyretin (0.13 mg/dL, $p=0.75$). Age was not significantly associated with any of the markers.

ARV treatment initiation after baseline was not independently associated with change in log hsCRP levels (0.08 mg/L, $p=0.36$), but was independently associated with lower log D-dimer (-0.10 mg/L, $p=0.03$), and higher transthyretin (2.77 mg/dL, $p=0.0008$) at the follow-up visit.

Longer follow-up time among HIV-negative women was significantly associated with lower log D-dimer (-0.06 mg/L per year, $p<0.0001$) and lower transthyretin (-0.28 mg/dL per year $p=0.03$), but not significantly associated with log hsCRP (-0.01 mg/dL per year, $p=0.45$). In untreated HIV-positive women, follow-up time (without ART) was significantly associated with lower log D-dimer (-0.06 mg/L per year, $p=0.0001$) but not with change in log hsCRP levels (-0.009 mg/dL per year, $p=0.72$) or transthyretin (-0.02 mg/dL per year, $p=0.91$). Longer follow-up time among HIV-positive ART initiators was associated with lower log D-dimer (-0.08 mg/L per year, $p=0.0001$) but not significantly with change in log hsCRP (-0.02 mg/dL per year, $p=0.55$) or transthyretin (0.11 mg/dL per year, $p=0.77$).

Discussion

In this cohort of 695 Rwandan women (HIV-negative, HIV-positive ART-naïve who did not initiate ART, and HIV-positive ART-naïve who initiated ART after the baseline visit) we found that HIV infection with more advanced immune suppression was associated with higher inflammation as measured by higher hsCRP and D-dimer, and lower transthyretin, compared to HIV-negatives. ARV treatment, which captures the cumulative effect of ART within the time frame of initiation of ART until 2 years or greater follow-up, was associated with decreased inflammation, indicated by lower D-Dimer and higher transthyretin at

follow-up, but was not associated with changes in hsCRP. Over 2 years or more of follow-up from baseline, we found no significant change in hsCRP from baseline to follow-up in any of the groups; D-Dimer declined significantly in all groups; and transthyretin declined significantly in HIV-negatives and HIV-positives not initiating ART, but increased in the HIV-positives who initiated ART.

Of the inflammatory markers we examined, hsCRP has been the most examined in prior literature. We found that hsCRP was not associated with ART use, and over the 2 years or more of follow-up no group had significant change in hsCRP. Our study is the first large study to investigate hsCRP in a population of African women. These findings are important because hsCRP is an acute phase reactant which can fluctuate with infection, nutrition and inflammation (58), and in this Rwandan population the levels might be elevated at baseline due to other non-HIV related diseases or malnutrition. At baseline and at follow-up however, the mean levels of hsCRP in HIV-negative women remained at average risk according to the Centers for Disease Control and the American Heart Association (59). Interestingly, women in a 2017 study of South Africans with a 22% prevalence of HIV had high average hsCRP at baseline (3.3mg/dL) which was also higher than the male baseline hsCRP (3.1mg/dL) (15). HIV-positive women in our study had higher baseline values compared to HIV-negatives, consistent with other studies (21, 56, 60).

Previous longitudinal studies of hsCRP, mostly done in men, have shown varying results. Most recently, Funderberg et al. compared effects of a Tenofovir disoproxil fumarate regimen and a Tenofovir alafenamide regimen on 194 participant (19% female), hsCRP levels. Mean hsCRP levels at baseline were 1.6 mg/L and did not change statistically in either arm after 48 weeks of treatment (45). hsCRP decreased in a small ACTG study of men over 31 months (53), in a small study of HIV patients on rosiglitazone (52), and in about 30% of each arm of patients randomized to either abacavir/lamivudine or tenofovir/emtricitabine in the HEAT study (41). However later analysis of the HEAT study showed that within the abacavir/lamivudine arm plus efavirenz, hsCRP actually increased out to 96 weeks after treatment initiation (61). Multiple other studies have also observed increasing hsCRP over time with varying ART regimens (19, 62–64) or no change (46–49, 65). The longest of these studies found that hsCRP increased over 12 years, although this study was done in 81 men only (19). In the Strategies for Management of Anti-Retroviral Therapy Study (SMART) study, episodic use of ART guided by CD4 count (drug conservation arm) was compared to continuous ART; in both arms and in a group that had never or not taken ART in the past 6 months, hsCRP levels did not change significantly at 6 months (66) nor at 96 weeks in a similar study (48).

Among women, results have also varied. Palella et al. looked at pre/post exposure to abacavir among 328 women in the Women's Interagency HIV Study and found that after a mean of 4.2 years, hsCRP increased (42). Interestingly, a study by Shakuma et al. found that among HIV-positive individuals who were treated with an efavirenz based ART regimen, hsCRP increased over 96 weeks in women but not men (67). In a study in Thailand in which 62% of the participants were women, Calmy et. al found no change in hsCRP at 12 weeks (49). There may be hormonal bases to these sex-specific differences in inflammatory markers, as other studies in non-HIV infected people have found that associations of

markers such as D-dimer and cardiovascular outcomes vary by sex, and estrogen is known to be pro-thrombotic (68–70).

We found that ART use was associated with decline in D-dimer at follow-up, consistent with some other studies (4, 48, 71–73). A recent study by Freiberg et al. following 249 active duty military members measured D-dimer and other inflammatory markers prior to HIV seroconversion, at least 6 months after seroconversion but before ART initiation, and 6 months after ART. D-dimer increased statistically after seroconversion, decreased statistically after ART, but remained significantly elevated above pre-conversion levels, despite viral suppression with ART (10). Further, the D-dimer elevation was significantly associated with non-AIDS events at a median follow-up of 3.7 years (10). In the SMART study, D-dimer levels rose at 4 weeks in the drug conservation arm (episodic use of ART) compared to those who were continuously suppressed with ART, and in this drug conservation arm there was increased risk of mortality (4).

One unexpected finding was that D-dimer decreased in all groups over time. In general, age is a known risk factor for thrombosis (74) and we might expect a subtle rise, rather than a fall in D-dimer among HIV-negative women. However, in our analysis age was not associated with any of the inflammatory markers. We also controlled for laboratory testing variability by randomizing the samples for testing and testing samples from the same participant in the same batch. This finding of decreased D-dimer in all groups could have also been due to an unmeasured effect of calendar time; however, we adjusted for this using the baseline visit date, laboratory test date, and the follow-up times to account for the effects of normal aging (HIV-negative follow-up time), the effects of HIV disease progression (HIV-positive follow-up time among who did not start ART) and the effects of ART over time (HIV-positive follow-up time among those on ART). These findings need further investigation.

The longitudinal role of transthyretin has not been well investigated in the literature (75). We found that at baseline and follow-up, HIV infection with lower quartiles of CD4 was progressively associated with lower transthyretin. At follow-up, given all else was equal, ART use was associated with higher transthyretin. These associations suggest that advanced HIV infection is inversely related to transthyretin as an inflammatory marker and this association may be reversed by ART use. One small study in 92 HIV-positive and 52 HIV-negative breast-feeding mothers in South Africa also found lower transthyretin in HIV-positive women (not on ART) compared to HIV-negative women at baseline (54). These differences in transthyretin remained even after controlling for other acute phase proteins (alpha-1 acid glycoprotein and hsCRP). Interestingly, transthyretin remained lower in HIV-positive compared to the negative breast-feeding mothers after 6 months of follow-up, which could reflect ongoing inflammation. Again, in our population even after adjusting for ART impact on change in CD4 level, those on ART experienced a significant increase in transthyretin suggesting an additive improvement in inflammation.

The strengths of this study include a long follow-up time of at least 2 years, a study population of all women, treatment naïve status at baseline, and the comparison to an HIV-negative control group in an African population.

There are some limitations to our study. Although self-reported adherence to ART was high, we did not have viral load measurements, which could have aided in evaluation of impact of ART. ARV treatment was also significantly associated with changes in transthyretin and D-dimer within 2 years or greater. However, because the minimum time between baseline and the follow-up visit was 2 years, we could not assess the time course of post-ART initiation changes in the inflammatory markers during these first 2 years. For example, large changes could have occurred nearly immediately (i.e. within the first 30 days) after ART initiation followed by a plateau, or the inflammatory marker levels could have been delayed with a large change occurring later. Finally, laboratory testing for these markers may vary depending on the assay, reagents and samples. We believe this was adequately controlled for as described above, but the possibility of other unmeasured confounders still exists. We did not have data on other potential confounders of systemic inflammation such as AIDS-defining illnesses or other common infections.

Conclusions

In summary, this is the first study to examine multiple markers of inflammation in an African population of HIV-negative and HIV-positive women. Taken together, the findings indicate that HIV infection and more advanced immune suppression were associated with inflammation, measured by higher hsCRP and D-dimer, and lower transthyretin. After at least 2 years of ART initiation and use, independent of its effect on CD4 count, ARV treatment was significantly associated with a decrease in inflammation as measured by lower D-dimer levels and higher transthyretin. In contrast to some other studies, hsCRP did not change post ART use, and we found no change in hsCRP over time in any of the groups.

Acknowledgments

This work was supported by American Heart Association Grant #11CRP5130028 (Elizabeth Kiefer), a Center for AIDS Research Pilot Grant # P30-AI-124414 (Harris Goldstein). The study was also supported in part by the Central Africa International Epidemiological Databases to evaluate AIDS (IeDEA) (5U01-AI-096299) and by a supplement from the National Institute of Allergy and Infectious Diseases to the Bronx/Manhattan Women's Interagency HIV Study (WIHS), which is funded by the National Institute of Allergy and Infectious Diseases (U01-AI-35004). This publication was also supported by Clinical and Translational Science Award grant number 5UL1TR001073 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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Figure 1a. Mean Unadjusted Change in hsCRP (mg/L) from Baseline visit to Follow-up visit, in HIV-negative and HIV-positive women, ART naïve at study entry*
*p value is for the unadjusted change in the mean value of log hsCRP from the baseline visit to follow-up visit. Log hsCRP exponentiated to original scale for figure

Figure 1b. Mean Unadjusted Change in D-dimer (mg/L) from Baseline visit to Follow-Up visit, in HIV-negative and HIV-positive women, ART naïve at study entry*

*p value is for the unadjusted change in the mean value of log D-dimer from the baseline visit to follow-up visit. Log D-dimer exponentiated to original scale for figure

Figure 1c. Mean Unadjusted Change in Transthyretin (mg/dL) from Baseline to Follow-up, in HIV-negative and HIV-positive women, ART naïve at study entry*

*p value is for the unadjusted change in the mean value of transthyretin from the baseline visit to follow-up visit

Table 1.
Mean ($\pm$ Standard Deviation) Baseline and Follow-up Characteristics of 695 Rwanda Women*

Variable	HIV- negative n=185		ART-Naïve HIV+, not initiating ART N=89		ART-Naïve HIV+ at Baseline, initiating ART Before Follow-Up n=421		p [†]
	Baseline	Follow-up	Baseline (ART-naïve)	Follow-up	Baseline (ART-naïve)	Follow-up	
Age, years	43.2 ($\pm$ 10.3)	46.1 ($\pm$ 10.4)	34.4 ($\pm$ 6.7)	37.1 ($\pm$ 6.6)	36.0 ($\pm$ 7.2)	38.4 ($\pm$ 7.1)	<0.0001
BMI, kg/m ²	21.3 ($\pm$ 3.9)	22.2 ($\pm$ 4.4)	21.9 ($\pm$ 4.4)	22.8 ($\pm$ 4.5)	21.5 ($\pm$ 3.8)	22.4 ($\pm$ 3.9)	0.37
CD4 count, cells/ μ L	NA	NA	473 ($\pm$ 171)	420 ($\pm$ 182)	211 ($\pm$ 111)	371 ($\pm$ 166)	
Follow-up time, years	NA	2.89($\pm$ 0.67)	NA	2.67 ($\pm$ 0.62)	NA	2.37 [‡]	
Date of initial visit, year	2005.6($\pm$ 0.20)	2005.6($\pm$ 0.20)	2005.9($\pm$ 0.20)	2005.9($\pm$ 0.20)	2006.1($\pm$ 0.70)	2006.1($\pm$ 0.70)	<0.0001
hsCRP, mg/L							
Non-Transformed Mean	2.06 ($\pm$ 4.07)	2.00 ($\pm$ 3.59)	4.63 ($\pm$ 17.38)	7.21 ($\pm$ 21.61)	7.99 ($\pm$ 19.38)	5.57 ($\pm$ 15.19)	<0.0001
Log-Transformed	-0.07 ($\pm$ 0.55)	-0.09 ($\pm$ 0.58)	0.12 ($\pm$ 0.56)	0.20 ($\pm$ 0.66)	0.31 ($\pm$ 0.69)	0.23 ($\pm$ 0.66)	
D-dimer, mg/L							
Non-Transformed Mean	3.63 ($\pm$ 4.52)	2.12 ($\pm$ 2.39)	3.16 ($\pm$ 2.08)	3.05 ($\pm$ 6.41)	4.33 ($\pm$ 5.26)	1.96 ($\pm$ 2.28)	0.003
Log-Transformed	0.36 ($\pm$ 0.42)	0.18 ($\pm$ 0.36)	0.39 ($\pm$ 0.30)	0.27 ($\pm$ 0.39)	0.47 ($\pm$ 0.36)	0.13 ($\pm$ 0.40)	
transferrin, mg/dL	22.93 ($\pm$ 5.60)	21.68 ($\pm$ 5.42)	21.13 ($\pm$ 5.25)	19.76 ($\pm$ 5.78)	17.88 ($\pm$ 6.69)	22.56 ($\pm$ 6.40)	<0.0001

* normally distributed variables presented as a mean (standard deviation)

[†] p value between groups at baseline

[‡] Among the ART initiators 0.27 ($\pm$ 0.32) years of the follow-up time was prior to ART initiation and 2.10 ($\pm$ 0.90) was the follow-up time on ART

Multivariate Associations of Covariates with Markers of Inflammation in 695 Rwandan Women with visits at Baseline and at 2 Years of Follow-up *

Table 2.

Variable	Log ₁₀ hsCRP			Log ₁₀ D-dimer			Transthyretin		
	Beta coefficient	(95% CI, mg/L	p	Beta coefficient	(95% CI, mg/L	p	Beta coefficient	(95% CI, mg/L	p
HIV+/CD4Q1 vs. HIV-	0.47	(0.34, 0.60)	<0.0001	0.18	(0.10, 0.26)	<0.0001	-6.17	(-7.41, -4.94)	<0.0001
HIV+/CD4Q2 vs. HIV-	0.32	(0.20, 0.44)	<0.0001	0.15	(0.07, 0.23)	0.0001	-4.09	(-5.39, -2.79)	<0.0001
HIV+/CD4Q3 vs. HIV-	0.27	(0.14, 0.40)	<0.0001	0.08	(-0.002, 0.16)	0.06	-2.58	(-3.91, -1.25)	0.0001
HIV+/CD4Q4 vs. HIV-	0.23	(0.10, 0.36)	0.0004	0.07	(-0.01, 0.16)	0.08	-2.55	(-3.85, -1.25)	0.0001
Baseline visit date	-0.06	(-0.14, 0.02)	0.15	-0.06	(-0.10, -0.02)	0.002	0.13	(-0.67, 0.93)	0.75
Age (per 5 years), baseline	-0.004	(-0.03, 0.02)	0.74	0.01	(-0.004, 0.02)	0.17	-0.16	(-0.40, 0.07)	0.16
ARV treatment effect †	0.08	(-0.09, 0.25)	0.36	-0.10	(-0.19, -0.009)	0.03	2.77	(1.16, 4.39)	0.0008
Follow-up time, per year									
HIV- ‡	-0.01	(-0.04, 0.02)	0.45	-0.06	(-0.09, -0.04)	<0.0001	-0.28	(-0.54, -0.03)	0.03
HIV+, untreated §	-0.009	(-0.06, 0.04)	0.72	-0.06	(-0.09, -0.03)	0.0001	-0.02	(-0.44, 0.40)	0.91
HIV+, on ART at follow-up ¶	-0.02	(-0.09, 0.05)	0.55	-0.08	(-0.12, -0.04)	0.0001	0.11	(-0.59, 0.81)	0.77

* model included baseline and follow-up marker of inflammation; model also adjusted for laboratory test date, not shown

† ARV used prior to follow-up visit

‡ time difference between follow-up visit and baseline visit; 0 at baseline and 0 for HIV-positives

§ time difference between follow-up visit not treated with ART and baseline visit; 0 at baseline and 0 for HIV-negatives

¶ time difference between follow-up visit treated with ART and baseline visit; 0 at baseline and 0 for HIV-negatives