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D-dimer levels and traditional risk factors are associated with incident hypertension among HIV-infected individuals initiating antiretroviral therapy in Uganda

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Abstract

Objectives—We sought to describe blood pressure changes after antiretroviral therapy (ART) initiation and evaluate the association of markers of inflammation with incident hypertension in a cohort of HIV-individuals in Uganda.

Methods—We used mixed effects linear regression to model changes in systolic blood pressure (BP) over time among a cohort of HIV-infected individuals initiating ART in Uganda. After exclusion of participants with pre-existing hypertension, we identified participants with normal BP

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throughout follow-up (controls) and those with elevated BP on ≥3 consecutive visits (cases). Prior to ART initiation, participants had testing for lnterleukin-6, kynurenine/tryptophan ratio, lipopolysaccharide, soluble CD14, soluble CD163, and D-dimer and those with viral suppression at six months during ART had repeat tests. We fit logistic regression models to estimate associations between biomarkers and risk of incident hypertension.

Results—In the entire cohort, systolic BP increased by 9.6 mmHg/year (95% CI 7.3 - 11.8) in the first six months of ART, then plateaued. Traditional factors: male gender (AOR 2.76, 95% CI 1.34-5.68), age (AOR 1.09, 95% CI 1.04-1.13), overweight (AOR 4.48, 95%CI 1.83-10.97), and a CD4 count < 100 cells (AOR 3.08, 95% CI 1.07-8.89) were associated with incident hypertension. After adjusting for these, D-dimer levels at month 6 were inversely associated with incident hypertension (AOR 0.61, 95% CI 0.37-0.99). Although not significant, similar associations were seen with sCD14 and Kynurenine/Tryptophan (K/T) ratio.

Conclusion—Blood pressure increases early after ART initiation in Ugandans. Traditional risk factors, rather than immune activation were associated with incident hypertension in this population.

Keywords

D-dimer; Immune activation; Hypertension; Antiretroviral therapy; Africa

Background

Early HIV infection is characterized by a dramatic depletion of CD4+ T cells in the gut, leading to depletion of the immunity at the gastrointestinal mucosal surface[1]. This heightens translocation of microbial products, particularly lipopolysaccharide (LPS), into the systemic circulation[2-4]. The resultant immune activation escalates monocyte activation [2,5], often measured by the level of circulating soluble CD14 (sCD14) and soluble CD163 (sCD163). Although these inflammatory markers have been associated with an increased risk of hypertension in the general population [6,7], few data are available on associations between ART, inflammation, and hypertension in HIV-infected individuals.

Data on the epidemiology of hypertension among HIV-infected persons in sub-Saharan Africa have demonstrated conflicting findings. While a number of studies have reported high incidence rates [8-12], others suggest that people with HIV are at lower risk of hypertension than matched HIV uninfected counterparts [13-16]. However, these studies are confounded by the inconsistent inclusion of patients with and without AIDS as well as the variable use and duration of ART in the cohorts[17].

It remains unclear whether HIV-mediated systemic inflammation and immune activation increases hypertension risk. If they did, then inflammatory biomarkers may be good candidates for identifying HIV-infected patients at risk of hypertension. Furthermore, a better understanding of these relationships could help identify pathophysiologic mechanisms of cardiovascular disease in this population. We therefore sought to describe blood pressure changes after ART initiation in a cohort of HIV-individuals initiating ART in Uganda, and hypothesized that biomarkers of inflammation (lnterleukin-6 [IL6]), indoleamine 2,3-

dioxygenase-1 (IDO) activity as measured by kynurenine/tryptophan [K/T] ratio), microbial translocation (plasma lipopolysaccharide [LPS]), monocyte activation (soluble CD14, soluble CD163), and altered coagulation (D-dimer), would be associated with incident hypertension.

Methods

Study population

We conducted a closed cohort study nested within the Uganda AIDS Rural Treatment Outcomes (UARTO) cohort, which has been described in detail previously [18]. The UARTO cohort is a population-based prospective cohort study of HIV-infected adults, aged at least 18 years, living within a 60-kilometer radius around the Mbarara Regional Referral Hospital Immune Suppression Syndrome (ISS) clinic. Participants were enrolled just prior to initiation of ART and were observed every 3-4 months to collect biologic and socio-behavioral data. By November 2014, 771 individuals were enrolled in UARTO and 94% initiated ART within four days of enrolment. Enrollment started in 2005, and follow-up for health events was completed in September 2015. For this analysis, study participants were observed from enrollment into the UARTO cohort until the earliest of the date of hypertension diagnosis or their last recorded clinic visit with a blood pressure measurement. Of note, all UARTO participants received biomarker testing prior to ART initiation but only those with HIV viral load suppression (< 400 viral copies/mL) at 6 months of ART had repeat biomarker tests done. Therefore, to describe the mean change in blood pressure, all UARTO cohort data was used. However, only the data of those with pre-ART and on-ART biomarkers data were used to determine the association of biomarker levels with incident hypertension in an unmatched case-control design.

The ethical review boards at Mbarara University of Science & Technology, University of California San Francisco, Partners Healthcare, and Uganda National Council of Science and Technology, approved the conduct of this study. All participants signed written informed consent.

Data collection

Biomarker measurements—At enrollment into UARTO (just prior to ART initiation) and six months later, participants underwent blood draw for CD4+ T cell count and inflammatory biomarker testing. A trained laboratory technician collected about 40-mL of venous blood into sodium heparin-lined vacutainers. All plasma samples were drawn in the morning before 9:30am. Blood samples were centrifuged immediately after blood draw, and derivative plasma aliquots were then preserved at -80°C until shipment for laboratory testing at the University of California San Francisco, California, USA.

Thawed cryopreserved plasma from the pre-ART and 6 months time points were assessed for several biomarkers. Plasma lipopolysaccharide (LPS) levels were measured from Anticoagulant Citrate Dextrose (ACD) - anticoagulated plasma with the Limulus amebocyte assay as described previously[19]. We used liquid chromatography–tandem mass spectrometry to assess kynurenine and tryptophan levels[20]. Cryopreserved plasma was also assessed for

soluble CD14 (sCD14, R&D Systems), soluble CD163 (sCD163, Trillium Diagnostics), interleukin-6 (IL-6, Human IL-6 Ultra-Sensitive Kit, Meso Scale Diagnostics), and D-dimer (Diagnostico Stago). We chose biomarkers based on prior data which observed important relationships between each of these markers and cardiovascular disease outcomes, mortality, or both [2,21-24].

Blood pressure measurements—Separate from the UARTO study visits, participants were seen at the Immune Suppression Syndrome (ISS) Clinic at Mbarara Regional Referral Hospital for routine clinical care every 2 weeks to 3 months, as determined by clinical staff. At the ISS clinic, trained nurses measured blood pressure at each visit using an aneroid sphygmomanometer (Welch Allyn® Tycos 767 Series; Skaneateles Falls, New York, USA), with normal (22–32 cm) cuff sizes. We defined hypertension as occurrence of a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on at least three consecutive clinic visits or prescription of antihypertensive medications after ART initiation.

Weight and height were measured using standardized scales (seca 762, Hanover, USA) and roll-up measuring stadiometers (seca 206, Hanover, USA), respectively. Height was measured to the nearest 0.1 cm after removal of shoes. Weight was measured to the nearest kilogram after the participants had removed their shoes, as well as any heavy clothing. We used height and weights to calculate body mass indexes (BMI) as weight (in kilograms) divided by the square of height (in metres squared) for all participants, and categorized BMI as less than 25, 25 to 29.9, or 30 or greater.

We set implausible values as missing, including systolic blood pressure recorded as >300 or <50, diastolic blood pressure recorded as >200 or <30mmHg and weight <25kg or >200kg. In the ISS clinic, clinical data were collected on paper forms and subsequently entered into an Open Medical Records System electronic database as part of the International Epidemiologic Databases to Evaluate AIDS Project[25].

Statistical analysis

We conducted two principal analyses. In the first, we included all participants in the cohort with biomarker data and at least one blood pressure measurement after ART initiation. We fit mixed effects linear regression models with systolic blood pressure as the dependent variable, duration of ART as a fixed effect variable with spline breakpoints at 6 months, 1 year, and 5 years, and a random effect by participant to estimate changes in mean systolic blood pressure over time from after ART initiation.

We then conducted a nested case-control analysis to estimate associations between inflammatory markers at pre-ART and 6-month on ART time points with incident hypertension. We restricted this analysis to study participants who had three or more consecutive visits with high blood pressure during follow-up (cases) or those who had no visits with high blood pressure during follow-up (controls). We plotted mean levels of biomarkers at pre-ART and months 6 to show change in biomarkers over 6 months. We fit logistic regression models to calculate odds ratios for incident hypertension, including traditional risk factors (age, gender, BMI, smoking history, and pre-treatment CD4 count); and then added each biomarker at the pre-ART and 6 month visit individually into the

model. Models at the pre-ART visit were adjusted for viral load, whereas those at 6 months were not because biomarker testing at 6 months of ART was restricted to participants with a suppressed HIV RNA viral load (< 400 copies/mL). Biomarkers were modeled as changes in each interquartile range (IQR) of the log-transformed value.

Sensitivity analysis

We performed sensitivity analyses to assess the robustness of our findings. First, we altered our definition of the outcome to include either prevalent or incident hypertension (as opposed to incident hypertension alone). Then, we altered our definition of a case to include any participant who was prescribed any anti-hypertensive medication at least once during follow-up. All analyses were performed with STATA® version 13 (College Station, Texas, USA).

Results

As of November 2014, 771 participants had been enrolled into the UARTO cohort study. We excluded 225 who had no biomarker testing available and 10 participants with no blood pressure measurements (Figure 1). Among the remaining 536 participants, females constituted the majority (70%) and the median age at ART initiation was 34 years IQR (29 - 39) (Table 1).

In the total cohort of 536 participants, systolic blood pressure increased significantly at 9.6 mmHg/year (95%CI 7.3 - 11.8) in the first six months after ART initiation (Figure 2). However, blood pressure plateaued thereafter, with total average increase in systolic blood pressure of 2.3 mmHg/year (95%CI 2.1 - 2.5) from years 1 through 5 of observation, and only 0.7 mmHg/year thereafter (95%CI 0.3 - 1.0). We found no difference in mean systolic blood pressure between those with undetectable HIV viremia versus detectable HIV viremia at 6 months (p=0.18). In contrast, increasing weight from ART initiation to 6 months time point was significantly correlated with increasing systolic blood pressure over first 6 months (R^2 = 0.14, p <0.0001).

In the restricted case-control analysis, we excluded 18 participants with prevalent hypertension before ART initiation and 288 participants who had at least one but never 3 consecutive visits with hypertension during follow-up. We identified 73 participants who had ≥3 consecutive high blood pressure visits after ART initiation (cases), and 157 participants who never had elevated blood pressure readings on a minimum 3 consecutive visits after ART initiation (controls) (Table 1).

We found significant associations between traditional risk factors and incident hypertension in multivariable logistic regression models for each year increase in age (AOR 1.09, 95% CI 1.04 - 1.13, p<0.001), male gender (AOR 2.76, 95% CI 1.34 - 5.68, p=0.006), overweight (AOR 4.48, 95%CI 1.83 - 10.97, p=0.001), obesity (AOR 8.36, 95% CI 1.27 - 54.79, p=0.027), and a low pre-ART CD4+ T cell count (< 100 cells) at ART initiation (AOR 3.08, 95% CI 1.07 - 8.89, p=0.037) with incident hypertension (Table 2).

At month 6 of ART-mediated viral suppression, all biomarkers had declined from pre-ART levels. The greatest mean change from pre-ART to 6 months levels were observed in D-dimer, K/T ratio, interleukin-6, and sCD163 (Figure 3). In multivariable logistic regression models adjusted for known cardiovascular risk factors, each unit interquartile range decrease in D-dimer levels at 6 months (while taking ART) was associated with an increased risk of incident hypertension (AOR 0.61, 95% CI 0.37 - 0.99, p=0.049). Although we found no other significant associations between other biomarkers and incident hypertension (Table 2), the estimates indicated that lower levels of IL-6 and sCD14 at 6 months were associated with an increased risk of incident hypertension.

Sensitivity analyses

Anti-hypertensive medications were prescribed at approximately 1% of all observed visits (220/18,698) and were ever prescribed in only 30% (22/74) of patients with three or more consecutive visits with high blood pressure; 21 of these were prescribed antihypertensive medication after ART initiation and were already considered cases. In comparison, 7 participants among controls were ever prescribed antihypertensive medication (3 before starting ART and 4 after starting ART) and an additional 18 participants who had been neither classified as cases nor controls in the main models were prescribed antihypertensive medication at least once after starting ART. After reclassifying these 22 participants as cases, we found no significant differences in estimates between models with or without antihypertensive medication use as part of the definition of incident hypertension.

Discussion

In this study of HIV-infected individuals taking ART in southwestern Uganda, we found that blood pressure increases rapidly in the months immediately following initiation of antiretroviral therapy. We hypothesize that this represents an ART-mediated “return to health” [26], which may in turn unmask other mechanisms of hypertension risk such as increased body mass index and lipid abnormalities. Although our study did not have an HIV-uninfected group for comparison, the elevations we observed in blood pressure are comparable to those described in HIV cohorts [27-29] though greater than what would be expected over the same period in the general population [30]. In support of this ART-mediated “return to health” hypothesis, we observed a positive correlation between weight gain and systolic blood pressure shortly after ART initiation. Alternatively, ART might directly mediate vascular remodeling which has also been demonstrated in other metabolic disorders and is associated with risk of hypertension [31,32].

Although we document increasing blood pressure after ART initiation, our finding should be taken in light of population-based surveys from sub-Saharan Africa, which have suggested that people with HIV appear to be at lower risk of hypertension than matched HIV uninfected counterparts [13-16]. Given that we did not have an HIV-uninfected comparison group in our study, we cannot rule out the possibility that blood pressure remains lower in the HIV-infected population despite the increases we documented. Alternatively, because prior studies tended to assess HIV-infected patients irrespective of ART status, they may not have noted the “return to health” phenomenon we report here.

To the best of our knowledge, ours is the first report from a large cohort demonstrating no statistical association between biomarkers of immune activation and risk of incident hypertension after adjusting for traditional risk factors. Indeed, we found that D-dimers levels at month 6 of ART (IL-6 and sCD14 to a lesser extent) were inversely associated with risk of incident hypertension. These findings contrast those from a Norwegian HIV cohort that showed increased inflammation (LPS and sCD14) predicted hypertension [33]. However, participants in that study had less advanced HIV disease at ART initiation compared to those in our study. Our findings therefore, suggest that – if anything – lower inflammation is associated with higher blood pressure, implying distinct pathophysiologic mechanisms of hypertension in this population. Whereas HIV associated inflammation and immune activation are known to contribute to arterial stiffness [34] and atheroma formation[22,35,36], similar pathways are not known to be primarily responsible for hypertension. In fact, certain immune activation pathways that are increased by microbial products in HIV infection like the kynurenine pathway of tryptophan catabolism may be causally associated with vasodilation [37].

In contrast, our findings of increasing age, male gender, overweight and obesity, lower pre-ART CD4+ T cell counts, are consistent with prior studies [13,38-40]. These data reaffirm that, unlike atherosclerosis, risk factors for hypertension among those with HIV are largely similar to the known risk factors in those without HIV [8,13,41]. We did find a paradoxical association between low pre-ART CD4+ T cell count and hypertension. This suggests that the mechanism by which low pre-ART CD4 is associated with hypertension may not be mediated by chronic immune activation[42,43]. Whereas further data will be required to help elucidate these mechanisms, it could be explained by the possibility that immunodeficiency and immune activation affect hypertension risk through fundamentally distinct pathways [14,44,45].

Our data should be interpreted in the context of the study design. Our results could be biased by both exposure and outcome misclassification. We attempted to minimize this through rigorous laboratory quality assurance protocols and by using strict criteria for our definitions of both cases and controls, respectively. Differential misclassification of inflammatory markers is also unlikely because laboratory testing of biomarkers was performed without knowledge of participant blood pressure results, which further mitigates risk of systematic bias in our results.

Our study was observational without a randomized intervention, and thus our results could be susceptible to both measured and unmeasured confounders. Confounding by other conditions such as diabetes mellitus [39], dyslipidemia, and chronic kidney disease, which were not captured in the database, offers a particularly important challenge in the context of hypertension. These conditions are known to directly or indirectly cause hypertension and may also be associated with immune activation. We attempted to mitigate such confounding by adjusting for surrogates common to the above potentially confounding conditions (e.g. age, sex, and BMI). However, we lacked data on renal function or glucose intolerance and so were unable to assess other putative pathways between inflammation and hypertension risk. The findings described are largely generalizable to those HIV-infected individuals achieving viral suppression within 6 months of ART.

Conclusion

We found significant elevations in blood pressure among HIV-infected persons in the first six months after initiation of ART. This effect might be mediated by an ART-induced "return to health", as evidenced by our observation that the risk of incident hypertension was positively associated with traditional risk factors (age, male gender, and BMI), but not elevated levels of biomarkers of immune activation. In fact, we found evidence that HIV-associated immune activation, inflammation and altered coagulation may be inversely related to risk of incident hypertension, such that lower levels of D-dimer at 6 months after ART initiation were associated with an increased risk of incident hypertension. Taken together, the lack of an association between incident hypertension and inflammatory markers may suggest that traditional cardiovascular risk factors are the main predictors of hypertension in this population. If corroborated, our results support the integration of strategies for hypertension prevention and management into routine HIV care. Focusing attention on traditional cardiovascular risk factors might be the most appropriate method to affect hypertension related morbidity and mortality in HIV-infected individuals in this setting.

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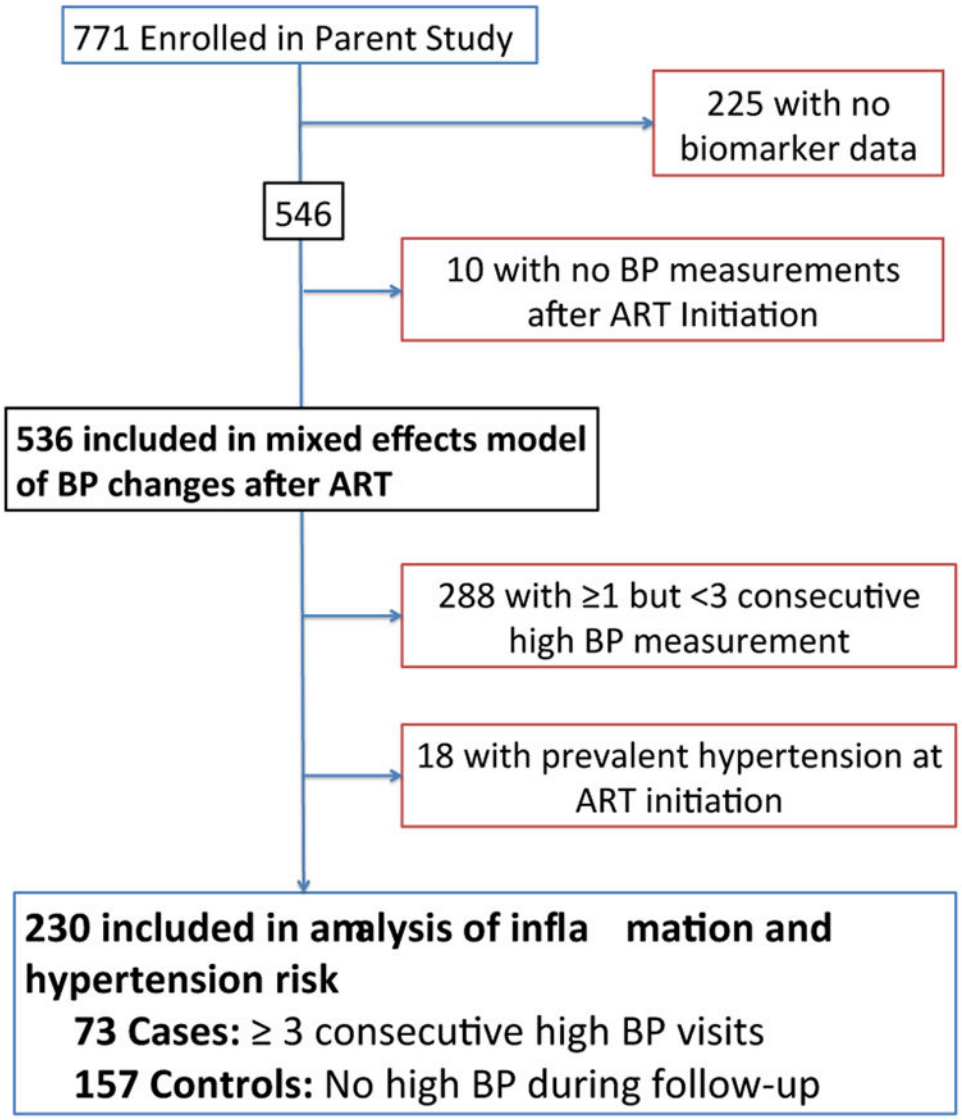

Figures 1. Study profile showing selection of subjects

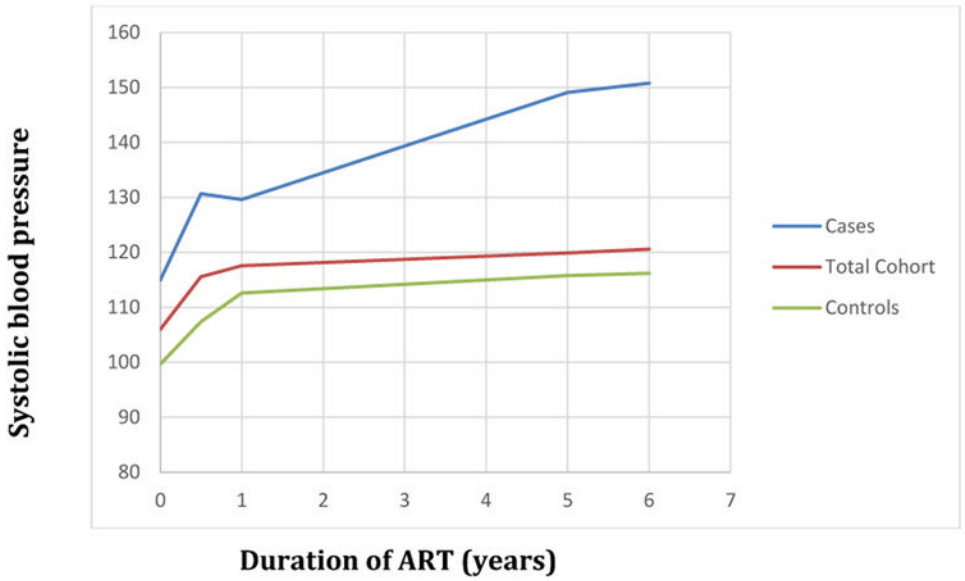

Figure 2. Change in mean systolic blood pressure by ART duration for patients who developed hypertension and those who remained normotensive during follow-up

Mixed effects linear regression model with random effect by participant and fixed effect by hypertension status and ART duration with spline terms at 6months, 1, and 5 years. Total cohort consisted of 536, cases were 73, and controls were 157.

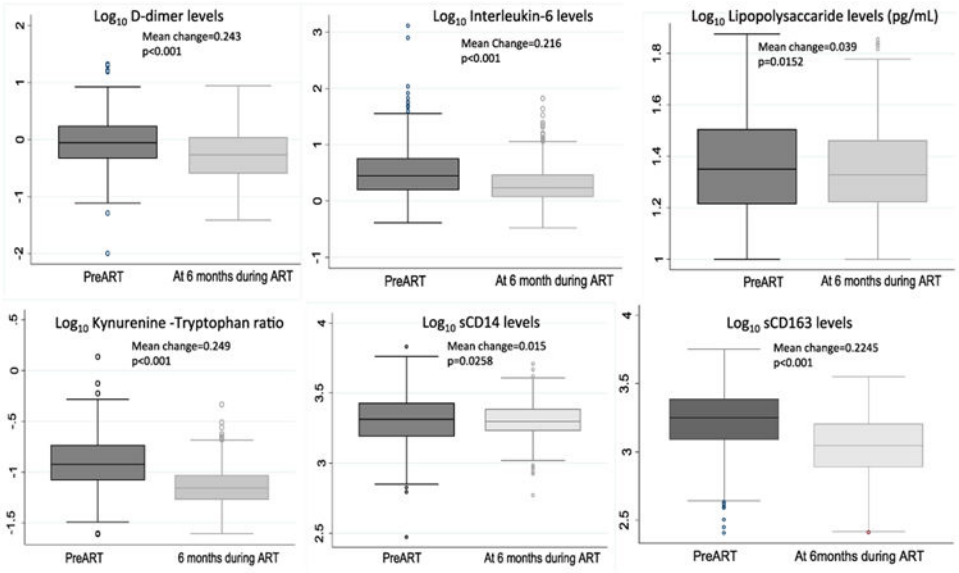

Figure 3. Change in biomarker levels from preART to 6months time point for all participants

Table 1

Baseline characteristics

Characteristic	Cases n=73 (31%)	Controls, n=157 (69%)
Male gender, n (%)	30 (41.10)	40 (25.48)
Age at ART initiation, median (IQR)	36 (32 - 43)	33 (28 - 38)
Smoking Status		
Never	53 (72.60)	119 (75.80)
Past or current	18 (26.14)	36 (22.93)
BMI (Kg/m^2) categories, n (%)		
< 25	50 (68.49)	128 (81.53)
25 - 29.9	15 (20.55)	17 (10.83)
≥ 30	4 (5.48)	2 (1.27)
Missing	4 (5.48)	10 (6.37)
CD4+ T cell counts ($cells/mm^3$) at ART initiation, n (%)		
< 100	29 (39.73)	48 (30.57)
100 – 249	35 (47.95)	82 (52.23)
≥ 250	9 (12.33)	27 (17.20)
Missing	1 (1.37)	4 (2.55)
HIV viral load (Log_{10}/mm^3), median (IQR)	5.09 (4.72 - 5.63)	5.07 (4.60 - 5.50)
Duration of observation until censor (years), median (IQR)	7.29 (6.37 - 7.87)	5.76 (1.59 - 7.14)
Clinic visits with blood pressure measurement during observation, median (IQR)	35 (29 - 38)	27 (13 - 36)

BMI: Body mass index; ART: Antiretroviral therapy; CD4: cluster differentiation cells; IQR: interquartile range

Table 2
Association between traditional risk factors, biomarkers and incident hypertension

Characteristic	Univariable models		Multivariable models	
	*OR (95%CI)	p-Value	*AOR (95%CI)	p-Value
Age (each year)	1.07 (1.04 - 1.11)	<0.001	1.09 (1.04 - 1.13)	<0.001
Male gender	2.04 (1.13 - 3.67)	0.018	2.85 (1.37 - 5.94)	0.005
Ever smoked	1.12 (0.58 - 2.15)	0.728	--	--
Body mass index (kg/m^2) at ART initiation				
<25	REF	--	REF	--
25 - 29.9	2.26 (1.05 - 4.87)	0.037	4.47 (1.82 - 10.96)	0.001
≥ 30	5.12 (0.91 - 28.84)	0.064	8.30 (1.26 - 54.79)	0.028
CD4+ T cell counts (cells/mm^3) at ART Initiation				
≥ 250	REF	--	REF	--
100 - 249	1.23 (0.50 - 3.01)	0.655	1.43 (0.51 - 4.01)	0.500
<100	1.74 (0.69 - 4.39)	0.243	3.42 (1.09 - 10.74)	0.035
Log_{10} pre-ART HIV viralload (each viral copy/mL)	1.12 (0.75 - 1.66)	0.592	0.88 (0.53 - 1.43)	0.624
Log_{10} sCD163				
ART initiation	1.11 (0.78 - 1.59)	0.590	1.01 (0.65 - 1.59)	0.947
6 months post-ART initiation	1.14 (0.73 - 1.79)	0.600	1.07 (0.64 - 1.78)	0.801
Log_{10} sCD14				
ART initiation	1.24 (0.81 - 1.89)	0.312	1.26 (0.72 - 2.20)	0.420
6 months post-ART initiation	0.73 (0.49 - 1.07)	0.105	0.79 (0.50 - 1.27)	0.340
Log_{10} lipopolysaccharide				
ART initiation	0.94 (0.64 - 1.38)	0.767	1.07 (0.69 - 1.66)	0.760
6 months post-ART initiation	1.06 (0.69 - 1.63)	0.707	1.13 (0.69 - 1.86)	0.624
Log_{10} K/T ratio				
ART initiation	0.87 (0.59 - 1.30)	0.509	0.89 (0.54 - 1.46)	0.638
6 months post-ART initiation	0.74 (0.49 - 1.09)	0.129	0.91 (0.58 - 1.42)	0.683
Log_{10} IL6				
ART initiation	1.12 (0.81 - 1.56)	0.483	1.12 (0.73 - 1.74)	0.600
6 months post-ART initiation	1.02 (0.73 - 1.43)	0.916	0.98 (0.66 - 1.47)	0.934
Log_{10} D-dimer				

Characteristic	Univariable models		Multivariable models	
	*OR (95%CI)	p-Value	*AOR (95%CI)	p-Value
ART initiation	0.87 (0.59 - 1.28)	0.491	0.85 (0.54 - 1.32)	0.460
6 months post-ART initiation	0.62 (0.39 - 0.97)	0.038	0.61 (0.37 - 0.99)	0.049

*Odds ratios (OR) or Adjusted Odds ratios (OR) of having the given predictor value compared to the reference value by hypertension status.

Adjusted Odds ratios (AOR) of having the given predictor value compared to the reference value by hypertension status. For biomarkers at ART initiation, models are adjusted for age, gender, BMI, pre-ART CD4+ T cell count, and Log_{10} pre-ART HIV RNA viral load. For biomarkers at 6 months post-ART initiation, models are adjusted for age, gender, BMI, and pre-ART CD4+ T cell count since all participants had viral suppression.