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Relationship between inflammatory and coagulation biomarkers and cardiac autonomic function in HIV-infected individuals

Lari C Young¹, Mollie P Roediger², Greg Grandits², Jason Baker³, Charurut Somboonwit⁴, Ian Williams⁵, Jens D Lundgren⁶, James D Neaton², and Elsayed Z Soliman^{7,*}

¹Center for Integrative Medicine, Wake Forest Baptist Health, Winston Salem, NC, USA

²Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN, USA

³Division of Infectious Diseases, University of Minnesota, Minneapolis, MN, USA

⁴Division of Infectious Disease & International Medicine, University of south Florida, Tampa, FL, USA

⁵Infection & Population Health, University College London, London, UK

⁶HIV Programme, University of Copenhagen, Denmark

⁷Epidemiological Cardiology Research Center (EPICARE), Department of Epidemiology & Prevention & Department of Internal Medicine–Cardiology, Wake Forest School of Medicine, Winston Salem, NC, USA

Abstract

Aim—To examine the relationship between inflammatory and coagulation biomarkers and cardiac autonomic function (CAF) as measured by heart rate variability in persons with HIV.

Materials & methods—This analysis included 4073 HIV-infected persons from the Strategies for Management of Antiretroviral Therapy study. We examined the association between IL-6, high-sensitivity C-reactive protein (hsCRP) and D-dimer with heart rate variability measures (SDNN and rMSSD), both cross-sectionally and longitudinally.

Results—Cross-sectional analysis revealed significant inverse associations between IL-6, hsCRP and D-dimer with SDNN and rMSSD ($p < 0.01$ for all comparisons). However, longitudinal analysis failed to show a significant association between baseline IL-6, hsCRP and D-dimer with change in CAF over time.

Conclusion—Cross-sectionally, higher levels of inflammatory and coagulation biomarkers were associated with lower levels of CAF in the Strategies for Management of Antiretroviral Therapy trial. Although deterioration in CAF was observed during followup, baseline levels of inflammatory and coagulation markers were not predictive of the decline in CAF over time.

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*Author for correspondence: Tel.: +1 336 716 8632 Fax: +1 336 716 0834 esoliman@wakehealth.edu.

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Keywords

biomarkers; cardiac autonomic function; coagulation; D-dimer; heart rate variability; high-sensitivity C-reactive protein; HIV; inflammation; IL-6

For individuals infected with HIV, the role of antiretroviral therapy (ART) in reducing AIDS-related morbidity and mortality is well established [1–3]. However, compared with the general population, individuals with HIV including those on ART have higher rates of inflammatory non-AIDS conditions such as cardiovascular, liver, renal and bone diseases as well as non-AIDS-related cancers [4–7], leading to an elevated risk of non-AIDS-related death. In a study by Lau and colleagues, the risk of non-AIDS-related mortality for individuals with CD4 counts above 200 mm³, was reported to exceed the risk of death from AIDS itself [8].

Many studies highlight the role of chronic activation of inflammatory and coagulation pathways in the pathogenesis of these non-AIDS conditions including cardiovascular disease (CVD) [9–12]. When compared with the general population, inflammatory and coagulation biomarkers such as high-sensitivity C-reactive protein (hsCRP), IL-6 and D-dimer have been reported to be higher in HIV individuals, even after viral suppression with ART. In addition, higher levels are associated with increased risk of all-cause mortality, CVD and non-AIDS cancer [9,12–14].

In the general population there is a growing evidence that cardiac autonomic function (CAF), as assessed by heart rate variability (HRV), is closely linked to chronic inflammation. Recent studies confirm the inhibitory role the parasympathetic system plays in controlling pro-inflammatory cytokine production [10,14–17]. An inverse relationship between HRV and levels of inflammatory markers has been found in apparently healthy persons [10] as well as in those with known or suspected CVD, metabolic syndrome and glucose intolerance [15,18,19]. Data, however, are sparse regarding the relationship between CAF and inflammation in the HIV population.

Given the important role that acetylcholine plays in controlling inflammation, it is plausible that derangements in autonomic signaling between peripheral tissues and hypothalamic centers may contribute to the development of non-AIDS-related morbidity. However, whether CAF is related to increased inflammation in individuals with HIV is not currently known.

The present analysis examines the relationship between inflammatory and coagulation biomarkers with CAF as measured by HRV in HIV-infected individuals enrolled in the Strategies for Management of Antiretroviral Therapy (SMART) trial. We hypothesized that higher levels of inflammatory and coagulation markers would be associated with lower levels of HRV at baseline and during follow up.

Methods

Strategies for management of ART study

The SMART trial was a randomized clinical trial comparing [6] viral suppression strategy (VS group) as suggested by the current guidelines [20] with drug conservation strategy (DC group) which includes the use of ART if CD4⁺ count decreases to less than 250 cells/mm³. The study was stopped on 10 January 2006 because of a safety concern in the DC group and all patients were advised to receive continuous ART and were followed up for another 1.5 years [6].

Study population

All SMART participants (n = 5472) were considered eligible for the present analysis, except for those missing all baseline inflammatory and coagulation biomarkers, (IL-6, hsCRP and D-dimer) or baseline ECG data or those without baseline HRV data due to ECG conditions that prohibited HRV measurement such as presence of ectopic beats or nonsinus rhythm. After these exclusions, 4073 participants remained and were included in this analysis (Figure 1).

Data collection & follow-up

Before randomization, antiretroviral and medical histories were obtained and CD4⁺ cell count and HIV-RNA levels were measured. Consent for storing blood was obtained prior to randomization for participants in the USA and at the time of randomization for all remaining participants. Follow-up visits were scheduled monthly for the first 2 months, every 2 months for the first year and every 4 months thereafter. At each visit a history and examination was performed and CD4⁺ count and HIV-RNA levels were measured. At the baseline visit and each annual visit, a 12-lead ECG was obtained.

ECG methods

Identical ECG (GE MAC 1200 models; GE, WI, USA) were used in all SMART clinics and standard 12-lead ECGs were recorded in all participants by strictly standardized procedures. The electronic ECGs were transmitted regularly over analog telephone lines to the SMART central ECG Reading Center located at the Epidemiological Cardiology Research Center (EPICARE), Wake Forest School of Medicine, Winston-Salem, NC, USA. All ECGs were automatically processed, after visual inspection for technical errors and inadequate quality, using the 2001 version of the GE Marquette 12-SL program (GE). Two-time domain measures (standard deviation of all normal RR intervals [SDNN] and root mean square of successive differences in normal RR intervals [rMSSD]) were automatically calculated from the individual durations between normal RR intervals. SDNN represents the overall parasympathetic and sympathetic autonomic function, while rMSSD is more geared towards the parasympathetic component. Both measures, however, are complimentary and typically used in other similar studies. In this analysis, ECG data from baseline, 12, 24, 36, 48 and 60 months were utilized.

Biomarker methods

Inflammatory and coagulation biomarkers (hsCRP, IL-6 and D-dimer) were measured by the Laboratory for Clinical Biochemistry Research at the University of Vermont, from specimens stored at baseline. Plasma specimens were collected using EDTA (lavender top) blood collection tubes and were shipped frozen to a central repository [9]. The three biomarkers utilized in this analysis were selected because they were strongly correlated with all-cause mortality and CVD clinical endpoints in the SMART study. IL-6 was measured using the chemiluminescent sandwich enzyme-linked immunosorbent assay (R&D Systems, MN, USA); hsCRP using the NM II nephelometer, N Antiserum to Human CRP (Siemens Diagnostics, IL, USA); and D-dimer levels using immunoturbidometric methods on the Sta-R analyzer, Liatest D-DI (DiagnosticaStago, NJ, USA) [21,22].

Statistical methods

Descriptive statistics are presented as mean (SD) or median (interquartile ranges) as appropriate. Since there is no universally accepted normal range for SDNN and rMSSD, differences in demographics, clinical characteristics, HIV/ART status and inflammatory and coagulation biomarkers are displayed by tertile of SDNN and rMSSD. Multivariate analyses were performed without stratification by treatment arms after evaluation of the potential interaction between treatment arm and biomarker levels was found to be nonsignificant. Adjustment for treatment arm was ultimately performed by entering it as a covariate in the multivariate models. Given the strong relationship between age, SDNN/rMSSD and biomarkers at baseline, separate age stratified analyses were performed to assess whether the relationship between SDNN/rMSSD and biomarkers was similar across different age groups.

Linear regression analysis was used to investigate baseline cross-sectional associations between each of the log₁₀ transformed biomarkers separately, and CAF as measured by HRV (SDNN and rMSSD). Differences (expressed as β -coefficients) were calculated on a continuous scale as a 1 SD increase in the log-transformed D-dimer, hsCRP and IL-6, separately. Four sequential models were considered for each biomarker: model 1, unadjusted model; model 2, adjusted for demographic characteristics (age, gender and ethnicity); model 3, adjusted for model 2 plus clinical variables (smoking status, total cholesterol/HDL ratio, BMI, history of baseline CVD, diabetes, use of blood pressure or lipid lowering drugs); model 4, adjusted for model 3 plus baseline duration of ART use, type of ART use, baseline CD4 and HIV-RNA level and hepatitis B or C co-infection. In order to examine potential overlap among the inflammatory variables, we repeated this same approach once again, this time with simultaneous inclusion of all three biomarkers in the regression analyses (results presented in Supplementary Table 1; see online at <http://www.futuremedicine.com/doi/full/10.2217/BMM.14.27>).

Due to differential planned follow up and varied numbers of annual ECG assessments, longitudinal associations between biomarker level and HRV parameters, SDNN and rMSSD, were assessed using random effects regression methods. Sequential models relating log-transformed biomarkers levels to SDNN and rMSSD during follow up were created with the same baseline covariates utilized in the cross-sectional analyses but with addition of treatment arm and baseline values of SDNN and rMSSD to model 1. In addition to models

utilizing both treatment groups (VS and DC), we also ran similar models using VS group only, which represents the current standard of HIV treatment (results presented in Supplementary Tables 2 & 3).

All reported p-values are two sided and $p < 0.05$ was considered statistically significant. SAS software version 9.2 was used in all the analyses.

Results

Characteristics of study population

Baseline median (interquartile ranges) of SDNN and rMSSD values were 20.0 ms (12.5–31.9 ms) and 20.6 ms (12.4–33.8 ms), respectively. Baseline characteristics of the study population by tertiles of SDNN and rMSSD are presented in Table 1. Participants in the lowest tertile were older, more likely to be male and less likely to be Caucasian. Participants in the lowest tertile were also more likely to have diabetes, hypertension and hyperlipidemia. On average, participants in the lowest two tertiles reported longer duration of HIV as compared with participants in the highest tertile while ART use was highest only in participants in the lowest tertile. No significant differences were noted between tertiles of SDNN and rMSSD between SMART treatment groups, baseline CD4⁺ count HIV RNA or use of ART at baseline. Inflammatory and coagulation biomarkers did vary between tertiles and were inversely related to CAF.

Cross-sectional associations between biomarkers & SDNN/rMSSD

In separate unadjusted models, hsCRP, IL-6 and D-dimer were inversely associated with both SDNN and rMSSD ($p < 0.001$ for all three biomarkers). As shown in Table 2, these significant associations persisted in each of the three models even after incremental adjustment for demographics, CV risk factors and HIV/ART status ($p < 0.01$ for all three biomarkers). However, as shown in Supplementary Table 1, when all three inflammatory biomarkers were considered simultaneously in the model, only hsCRP and IL-6 remained significantly associated with SDNN and rMSSD. Age-stratified analyses revealed no significant interaction of age on the relationship between SDNN/rMSSD and biomarkers with findings that were consistent across all age groups.

Longitudinal associations between baseline biomarker & SDNN/rMSSD during follow up

There was a significant decline in CAF over the 60-month follow-up period ($p < 0.001$ for trend for both SDNN and rMSSD). However, IL-6 initially was the only biomarker that remained significantly associated with CAF during follow up (Table 3).

However, in the multivariable models IL-6 failed to remain significantly associated with changes in SDNN and rMSSD over time (Table 4).

Similar findings of a significant decline in CAF during followup were obtained when the analysis was repeated for only the VS group (Supplementary Table 3). Likewise, IL-6 remained the only significant biomarker associated with CAF but failed to remain significantly associated with changes in SDNN and rMSSD after multivariable adjustment (Supplementary Table 2).

Discussion

Our study examined the cross-sectional and longitudinal associations between markers of inflammation and coagulation (IL-6, hsCRP and D-dimer) and CAF as measured by two-time domain HRV parameters (SDNN and rMSSD) in HIV-infected individuals participating in the SMART trial. Univariate analysis revealed that all three biomarkers were inversely related to both SDNN and rMSSD. In cross-sectional multivariate analyses, when considered separately, higher baseline levels of IL-6, hsCRP and D-dimer remained inversely associated with SDNN and rMSSD. However, when considered simultaneously, only IL-6 and hsCRP levels remained inversely associated with SDNN and rMSSD.

In longitudinal analyses, we observed a significant deterioration in both SDNN and rMSSD over the 5-year follow-up period. Yet, in the multivariate analyses, baseline biomarker levels were not significantly associated with longitudinal changes in SDNN and rMSSD. It is possible that over time some unmeasured factors masked the effect of baseline inflammation on the progression of cardiac autonomic dysfunction. Examining temporal relationship between progressive changes in inflammatory coagulation markers (not at one single point as in our study) with changes in CAF over time in individuals with HIV warrants investigation in future studies.

The inverse relationship we found between baseline biomarker levels and CAF in individuals infected with HIV extends previously reported findings in the general population including young healthy adults in the Coronary Artery Risk Development in Young Adults (CARDIA) study and elderly participants (65 years and older) in the Cardiovascular Health Study (CHS) as well as in patients with congestive heart failure, metabolic syndrome, coronary artery disease and prior myocardial infarction [10,23–31]. While all these studies reported a significant association between inflammatory markers and traditional HRV indices of sympathetic function (SDNN, SDANN, total power, low frequency [LF] and very low frequency), most of them failed to demonstrate a significant association between inflammatory markers and the HRV index for parasympathetic function (rMSSD in time domain and high frequency [HF] power in frequency domain). However, Sloan *et al.* [10] did find that HF power was decreased in a subgroup of patients with high CRP levels, a finding that was supported by the time-domain equivalent in our study. To our knowledge, our report is the first to demonstrate an inverse relationship between inflammatory markers and HRV indices of both sympathetic and parasympathetic function in a large cohort of HIV-infected individuals, which lend support to the cholinergic anti-inflammatory pathway model in the counter-regulation of inflammation [14].

SDNN, a global index of HRV reflecting long-term components and circadian rhythms responsible for variability, was closely linked to inflammation in our study. It is generally considered, within the frequency domain analysis of HRV, to reflect activity in the LF range. Controversy exists, however, over the physiological significance of LF power. Currently a growing body of evidence suggests that LF power reflects principally, parasympathetic input, with sympathetic input varying according to several factors, including position. As such, it is possible that the decrease in SDNN that we observed in our study was due primarily to diminished activity of the parasympathetic nervous system (PNS)

rather than over-activity of the sympathetic nervous system. However, in both circumstances, HIV may be considered to play an important role in alteration of sympathovagal balance [32].

Sympathovagal tone may be disturbed in HIV infection in several possible ways, although precise mechanisms remain elusive. In the CNS, HIV tends to localize in hypothalamic regions of the brain involved in autonomic regulation and HIV infiltration of the hypothalamic suprachiasmatic nucleus has been associated with increased sympathetic tone [32–35]. In the PNS, HIV causes inflammatory changes and nerve cell degeneration in the sympathetic ganglia [1,36]. Additionally, HIV peripheral neuropathy may compromise the local anti-inflammatory effects of vagal efferent pathways. Further studies on the pathogenesis of autonomic dysregulation in HIV are needed and may be useful in guiding future therapeutic interventions. Given the significant findings of an inverse association between inflammatory and coagulation biomarkers and CAF in this study, it is possible that therapies aimed at reducing chronic inflammation in HIV infected individuals may also have beneficial effects in preserving sympathovagal balance and associated non-AIDS conditions.

Our study has some limitations. It is difficult to conclude whether inflammation precedes reduced HRV or whether reduced HRV is a product of inflammation (causality issue), especially in our cross-sectional analyses which showed these significant associations. However, given HIV invades regions in both the CNS and PNS involved in autonomic control, it is possible that cardiac autonomic dysfunction may actually be antecedent to inflammation in this clinical group.

The possibility of confounding by unmeasured factors cannot be overlooked. It is therefore possible that our results were confounded by a factor we did not consider or was not measured. However, we adjusted for several factors (demographics, cardiovascular risk factors and HIV characteristics) which should minimize the concerns of residual confounding.

Despite these limitations, our study has many strengths that deserve highlighting. This is the first study to examine the relationship between inflammation and coagulation biomarkers with CAF in a large, well-defined, diverse cohort of individuals with HIV. Also, biomarker data and ECGs were collected in a consistent fashion and were processed by dedicated core laboratories with trained research staff.

Conclusion

In conclusion, baseline elevations in IL-6, hsCRP and D-dimer were associated with reduced CAF as measured by HRV in the SMART trial. However, although deterioration in CAF was observed during follow-up, baseline levels of inflammatory and coagulation markers were not predictive of changes in CAF over time. Further investigation is needed to understand the potential causal relationships between CAF, inflammation and risk for non-HIV inflammatory diseases.

Future perspective

Further investigation of the interplay between inflammation and coagulation biomarkers with CAF could shed light on the pathophysiological process involved in the progression of CVD in individuals with HIV. Better understating of this interplay is likely to help in developing tools to identify individuals at higher risk of developing CVD. Whether interventions aimed to manage inflammation and abnormal coagulation could be of value in preventing cardiac autonomic dysfunction is currently unclear, but it is something worth further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Executive summary

Background

- HIV-infected individuals have higher rates of inflammatory non-AIDS conditions when compared with the general population.
- In the general population emerging evidence supports an inverse relationship between inflammatory and coagulation biomarkers and cardiac autonomic function (CAF) as assessed by HRV.
- Whether HRV is related to inflammation and coagulation in HIV-infected individuals is currently unknown.

Methods

- This study examined the relationship between inflammation and coagulation biomarkers and HRV in 4073 patients enrolled in the Strategies for Management of Antiretroviral Therapy (SMART) trial.
- Baseline cross-sectional associations between three inflammatory and coagulation biomarkers, IL-6, hsCRP and D-dimer, with SDNN and rMSSD were examined using linear regression.
- Longitudinal association between three baseline inflammatory and coagulation biomarkers and changes in SDNN and rMSSD were examined using random effects regression.

Results

- Cross-sectional analysis revealed a significant association between IL-6, hsCRP and D-dimer with SDNN and rMSSD that persisted after incremental adjustment for clinical factors ($p < 0.01$ for all comparisons).
- Significant deterioration in CAF was observed over the 5-year follow-up period.
- The study failed to show a longitudinal association between baseline biomarkers and change in CAF over time.

Conclusions

- Cross-sectionally, higher levels of inflammatory and coagulation biomarkers were associated with lower levels of CAF in the SMART trial. Although deterioration in CAF was observed during followup, baseline levels of inflammatory and coagulation markers were not predictive of decline in CAF over time.
- Further investigation is needed to understand the potential causal relationships between CAF, inflammation and risk for non-HIV inflammatory diseases.

Figure 1. Study entry criteria

rMSSD: Root mean square of successive differences in normal RR intervals; SDNN: Standard deviation of all normal RR intervals.

Table 1

Baseline characteristics.

	SDNN				rMSSD			
	Tertile 1 1.00–14.90 n = 1357	Tertile 2 14.92–26.62 n = 1358	Tertile 3 26.73–186.7 n = 1358	p-value	Tertile 1 1.26–14.82 n = 1360	Tertile 2 14.85–28.18 n = 1355	Tertile 3 28.20–276.6 n = 1358	p-value
Demographics								
Age (in years) (median)	47	43	41	<0.001	47	44	40	<0.001
Gender (% female)	22.4	29.7	30.3	<0.001	19.8	29.2	33.6	<0.001
Race (%):				0.01				<0.001
– White	55.8	56.3	56.0		59.5	58.0	50.6	
– Black	30.1	28.1	31.6		27.3	26.9	35.6	
– Asian	1.1	2.7	1.5		1.3	2.1	1.9	
– Other	13.0	13.0	10.9		12.0	13.0	11.9	
Risk factors								
BMI (kg/m ²)	25.5	25.1	24.8	<0.001	25.5	24.9	25.0	<0.001
Smoking status (%):				0.11				0.02
– Current smoker	42.2	39.8	41.2		42.5	41.2	39.5	
– Past smoker	26.8	26.3	23.6		27.4	24.7	24.6	
– Never smoker	31.0	33.9	35.1		30.1	34.1	35.9	
Total cholesterol (mg/dl)	191	193	186	<0.001	193	191	185	<0.001
LDL-cholesterol (mg/dl)	110	113	109	0.01	112	112	108	0.004
HDL-cholesterol (mg/dl)	39	41	42	<0.001	38	41	42	<0.001
Total cholesterol/HDL	4.9	4.7	4.4	<0.001	5.0	4.6	4.2	<0.001
Diabetes (%)	12.2	5.6	3.4	<0.001	12.1	5.1	3.9	<0.001

	SDNN				rMSSD			
	Tertile 1 1.00–14.90	Tertile 2 14.92–26.62	Tertile 3 26.73–186.7	p-value	Tertile 1 1.26–14.82	Tertile 2 14.85–28.18	Tertile 3 28.20–276.6	p-value
Prior CVD (%)	5.2	3.8	2.9	0.006	5.1	3.4	3.4	0.03
Blood pressure-lowering drugs (%)	27.2	17.7	13.6	<0.001	26.0	17.8	14.7	<0.001
Lipid-lowering drugs (%)	22.0	16.3	41.2	<0.001	22.2	16.8	10.4	<0.001
Hepatitis B or C (%)	18.8	17.3	23.6	0.60	18.4	16.8	19.2	0.24
HIV/ART status[†]								
CD4 ⁺ count (cells/mm ³)	594	601	607	0.52	605	591	609	0.41
HIV RNA (% 400 copies/ml)	70.2	70.6	70.6	0.97	69.1	71.8	70.6	0.32
Antiretroviral therapy (%)	83.9	84.1	82.6	0.54	84.2	84.7	81.7	0.07
SMART treatment group	0.68							
Viral suppression (%)	48.9	50.5	49.9		49.0	49.6	50.7	
Drug conservation (%)	51.1	49.5	50.1		51.0	50.4	49.3	
Duration of ART use (years)	7	6	6	<0.001	7	6	6	<0.001
Duration of HIV (years)	8	8	7	<0.001	9	8	7	<0.001
PI use at baseline (%)	44.7	44.6	44.0	0.94	44.3	45.2	43.8	0.80
NNRTI use at baseline (%)	49.8	51.4	48.6	0.40	50.3	50.3	49.2	0.85
No prior ART use (%)	4.0	4.8	5.1	0.37	3.7	3.9	6.3	0.002
Inflammatory biomarkers								
IL-6 (pg/ml)	2.15	1.79	1.54	<0.001	2.18	1.73	1.56	<0.001
hsCRP (µg/ml)	2.19	1.69	1.40	<0.001	2.27	1.64	1.39	<0.001

	SDNN			rMSSD		
	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
	1.00–14.90	14.92–26.62	26.73–186.7	1.26–14.82	14.85–28.18	28.20–276.6
			p-value			p-value
D-dimer (µg/ml)	0.22	0.22	0.20	0.22	0.22	0.20
			<0.001			<0.001

[†] HIV/ART status including CD4 and HIV RNA were evaluated at study baseline.

ART: Antiretroviral therapy; CVD: Cardiovascular disease; HDL: High-density lipoprotein; hsCRP: High-sensitivity C-reactive protein; LDL: Low-density lipoprotein; NNRTI: Non-nucleoside reverse-transcriptase inhibitor; rMSSD: Root mean square of successive differences in normal RR intervals; SDNN: Standard deviation of all normal RR intervals.

Table 2
Baseline cross-sectional associations between inflammatory and coagulation markers with heart rate variability measures.

Measure	Model 1: unadjusted		Model 2: adjusted for model 1 plus age, gender and race		Model 3: adjusted for model 2 plus smoking status, total cholesterol/HDL ratio, BMI, history of CVD events at baseline, diabetes, blood pressure lowering drugs and lipid		Model 4: adjusted for model 3 plus baseline duration of ART use, type of ART use, baseline CD4 and HIV-RNA and hepatitis B or C co-infection	
	Coef. (95% CI)	p-value	Coef. (95% CI)	p-value	Coef. (95% CI)	p-value	Coef. (95% CI)	p-value
SDNN (log₁₀ms)								
hsCRP (log ₁₀ µg/ml)	-0.09 (-0.10 to -0.07)	<0.001	-0.07 (-0.08 to -0.05)	<0.001	-0.05 (-0.06 to -0.03)	<0.001	-0.05 (-0.07 to -0.03)	<0.001
IL-6 (log ₁₀ pg/ml)	-0.17 (-0.20 to -0.14)	<0.001	-0.11 (-0.14 to -0.09)	<0.001	-0.09 (-0.12 to -0.06)	<0.001	-0.09 (-0.12 to -0.06)	<0.001
D-dimer (log ₁₀ µg/ml)	-0.06 (-0.08 to -0.04)	<0.001	-0.04 (-0.06 to -0.02)	<0.001	-0.03 (-0.06 to -0.01)	0.004	-0.03 (-0.05 to -0.01)	0.01
rMSSD (log₁₀ms)								
hsCRP (log ₁₀ µg/ml)	-0.09 (-0.11 to -0.08)	<0.001	-0.08 (-0.09 to -0.06)	<0.001	-0.05 (-0.07 to -0.04)	<0.001	-0.05 (-0.07 to -0.04)	<0.001
IL-6 (log ₁₀ pg/ml)	-0.18 (-0.21 to -0.15)	<0.001	-0.13 (-0.16 to -0.10)	<0.001	-0.10 (-0.13 to -0.07)	<0.001	-0.10 (-0.13 to -0.07)	<0.001
D-dimer (log ₁₀ µg/ml)	-0.05 (-0.07 to -0.02)	<0.001	-0.04 (-0.07 to -0.02)	<0.001	-0.03 (-0.06 to -0.01)	0.004	-0.03 (-0.06 to -0.01)	0.01

ART: Antiretroviral therapy; CAF: Cardiac autonomic function; Coef.: Coefficient; CVD: Cardiovascular disease; hsCRP: High-sensitivity C-reactive protein; rMSSD: Root mean square of successive differences in normal RR intervals; SDNN: Standard deviation of all normal RR intervals.

Table 3
Longitudinal associations between inflammatory and coagulation biomarkers and heart rate variability measures.

Measure	Model 1: adjusted for treatment group and baseline CAF value		Model 2: adjusted for model 1 plus age, gender and race		Model 3: adjusted for model 2 plus smoking status, total cholesterol/HDL ratio, BMI, history of CVD events at baseline, diabetes, blood pressure-lowering drugs and lipid-lowering drugs		Model 4: adjusted for model 3 plus baseline duration of ART use, type of ART use, baseline CD4 and HIV-RNA and hepatitis B or C co-infection	
	Coef. (95% CI)	p-value	Coef. (95% CI)	p-value	Coef. (95% CI)	p-value	Coef. (95% CI)	p-value
SDNN (log₁₀ms)								
hsCRP (log ₁₀ µg/ml)	-0.01 (-0.03-0.00)	0.14	0.00 (-0.01-0.02)	0.89	0.01 (-0.01-0.03)	0.20	0.00 (-0.01-0.02)	0.58
IL-6 (log ₁₀ pg/ml)	-0.06 (-0.08 to -0.03)	<0.001	-0.02 (-0.05-0.00)	0.08	-0.01 (-0.03-0.02)	0.62	0.00 (-0.03-0.03)	>0.99
D-dimer (log ₁₀ µg/ml)	-0.01 (-0.0-0.01)	0.29	0.00 (-0.02-0.02)	0.76	0.01 (-0.01-0.03)	0.45	0.02 (0.00-0.04)	0.12
rMSSD (log₁₀ms)								
hsCRP (log ₁₀ µg/ml)	0.00 (-0.01-0.02)	0.87	0.01 (-0.01-0.02)	0.26	0.02 (0.00-0.03)	0.04	0.01 (-0.01-0.03)	0.19
IL-6 (log ₁₀ pg/ml)	-0.03 (-0.06 to -0.01)	0.009	-0.01 (-0.04-0.02)	0.43	0.00 (-0.02-0.03)	0.78	0.01 (-0.01-0.04)	0.37
D-dimer (log ₁₀ µg/ml)	0.00 (-0.02-0.02)	0.77	0.00 (-0.02-0.02)	0.88	0.01 (-0.01-0.03)	0.57	0.01 (-0.01-0.04)	0.16

ART: Antiretroviral therapy; CAF: Cardiac autonomic function; Coef.: Coefficient; CVD: Cardiovascular disease; hsCRP: High-sensitivity C-reactive protein; rMSSD: Root mean square of successive differences in normal RR intervals; SDNN: Standard deviation of all normal RR intervals.

Table 4

Changes in cardiac autonomic function during 5-year follow-up.

Visit	SDNN (log ₁₀ ms)			rMSSD (log ₁₀ ms)		
	Number	Mean (SE)	Change mean (SE)	Number	Mean (SE)	Change mean (SE)
Baseline	3428	1.29 (0.01)	0.00 (0.00)	3428	1.31 (0.01)	0.00 (0.00)
Month 12	3025	1.27 (0.01)	-0.02 (0.01)	3025	1.28 (0.01)	-0.03 (0.01)
Month 24	2079	1.26 (0.01)	-0.03 (0.01)	2079	1.26 (0.01)	-0.04 (0.01)
Month 36	1136	1.24 (0.01)	-0.04 (0.01)	1136	1.24 (0.01)	-0.05 (0.01)
Month 48	580	1.24 (0.01)	-0.04 (0.02)	580	1.24 (0.01)	-0.05 (0.02)
Month 60	272	1.18 (0.02)	-0.07 (0.02)	272	1.20 (0.02)	-0.07 (0.02)
All follow-up	3428	1.26 (0.00)	-0.03 (0.01)	3428	1.27 (0.01)	-0.04 (0.01)