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Reduced heart rate variability is associated with altered clinical laboratory profile in people living with HIV

Yunqiu Zhang [a,1], Lei Han [b,1], Luqian Shi [a], Meiyang Gao [a], Jun Chen [c,**], Yingying Ding [a,*]

[a] Department of Epidemiology, School of Public Health, And Key Laboratory of Public Health Safety of Ministry of Education, Fudan University, Shanghai, China
[b] Jing'an District Center for Disease Control and Prevention, Shanghai, China
[c] Department of Infectious Diseases and Immunology, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China

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ABSTRACT

Background: We compared heart rate variability (HRV) indices between people living with HIV (PLWH) and HIV-negative individuals to ascertain the independent association between HIV infection and reduced HRV, and further investigated whether distinct clinical laboratory profiles exist between PLWH with and without reduced HRV.

Methods: This cross-sectional analysis included 304 PLWH and 147 HIV-negative individuals with comparable age and sex. Thirty-two routine clinical laboratory indices (including hematology and biochemistry) closest to the survey were extracted from the Electronic Medical Record System. HRV indices were divided into two categories: low (lowest quartile, Q1) and moderate-to-high (combined, Q2–Q4).

Results: The time domain indices, ln(SDNN), ln(RMSSD), and ln(PNN50), as well as the frequency domain indices, ln(HF), ln(LF), and ln(VLF), were all significantly reduced in PLWH versus HIV-negative individuals (all $p < 0.05$). These associations remained for ln(SDNN), ln(PNN50), ln(HF) and ln(LF) even after adjusting for potential confounders in multivariable models. PLWH with low HRV indices exhibited distinct clinical laboratory profiles that were characterized by an elevation in fasting plasma glucose, white blood cell count, neutrophil count, neutrophil%, and a reduction in albumin, total protein, urine creatinine, lymphocyte%, red blood cell count (RBC) and nadir CD4 count. The final stepwise logistic regression models for low SDNN included older age, decreased total cholesterol levels, elevated neutrophil count, and the use of antidiabetic medications, whereas the final model for low LF included older age, reduced RBC and the use of antidiabetic medications.

Conclusion: PLWH exhibit impaired parasympathetic activity, as evidenced by reduced SDNN, PNN50, LF and HF. Furthermore, PLWH who have reduced HRV indices exhibits distinct clinical laboratory profiles that are related to systematic inflammatory response and diabetes.

1. Introduction

With the widespread availability of antiretroviral therapy (ART), people living with HIV (PLWH) are experiencing an increasing disease burden from age-related comorbidities, particularly cardiovascular diseases (CVD) (Moyo-Chilufya et al., 2023). Emerging data indicates that PLWH experience an earlier onset and greater risk of CVD than the general population, which is not explained by conventional risk factors (Ntsekhe and Baker, 2023). Cardiovascular system is regulated by autonomic nervous system (ANS) function, in which sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) balance are important for cardiovascular health (Carnevale, 2022).

ANS dysfunction is commonly observed in PLWH, even among those achieved viral suppression, but the underlying mechanism is not fully understood (Robinson-Papp and Sharma, 2013; Schrock, 2024). In addition to conventional risk factors such as older age, psychological stress, and diabetes (Schrock, 2024; Askgaard et al., 2011), direct engagement of HIV infection in the central nervous system specifically targeting areas such as the hippocampus, basal ganglia and hypothalamus (Shao and Li, 2023), HIV-associated autonomic neuropathy is thought to be another main cause for ANS dysfunction in PLWH

* Corresponding author. Department of Epidemiology, School of Public Health, Fudan University, P. O. Box 289, 138 Yi Xue Yuan Road, Shanghai, 200032, China.
** Corresponding author. Department of Infectious Diseases and Immunology, Shanghai Public Health Clinical Center, Fudan University, 2901 Caolang Road, Shanghai, 201508, China.
E-mail addresses: qtchenjun@163.com (J. Chen), dingyy@fudan.edu.cn (Y. Ding).
[1] Both authors contributed equally to this manuscript.

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List of abbreviation

Alanine aminotransferase ALT
Aspartate aminotransferase AST
Antiretroviral therapy ART
Autonomic nervous system ANS
Body mass index BMI
Comprehensive Response Information Management System CRIMS
Cardiovascular disease CVD
Diastolic blood pressure DBP
Fasting plasma glucose FPG
Hematocrit HCT
Heart rate variability HRV
High-density cholesterol HDL-C
High-frequency power HF
Low-density cholesterol LDL-C
Low-frequency power LF
Mean erythrocyte hemoglobin concentration MCHC
Mean corpuscular volume MCV
Mean platelet volume MPV
Platelet count PLT
People living with HIV PLWH
Parasympathetic nervous system PNS
Percentage of RR intervals greater than 50 ms different from its predecessor pNN50
Red blood cell RBC
Red cell distribution width-coefficient of variation RDWCV
Root of the mean squares of successive RR differences RMSSD
Serum total protein STP
Sympathetic nervous system SNS
Standard deviation of the normal RR intervals SDNN
Systolic blood pressure SBP
Urine creatinine Ucr
Very low-frequency power VLF
White blood cell WBC
Waist-to-hip ratio WHR

(Robinson-Papp and Sharma, 2013). Recent cross-sectional observations demonstrated a positive relationship between ANS dysfunction and inflammatory biomarkers in PLWH (Robinson-Papp et al., 2020; Heravi et al., 2020; Lawrence et al., 2023). This may provide insight into the links between inflammation, accelerated aging and increased risk of CVD in PLWH (Ntsekhe and Baker, 2023; Schrock, 2024; Kwon et al., 2023).

Heart rate variability (HRV) – the physiologic fluctuation between adjacent normal heart beats –is a well-established marker of cardiac autonomic function. Reduced HRV is indicative of increased SNS or PNS activity, and is strongly associated with poor cardiovascular outcomes in healthy and diseased populations (Kwon et al., 2023; Jarczok et al., 2022; Godijk et al., 2020). In the post-ART era, studies comparing HRV indices showed equivocal findings, limited by the very small number of participants and the non-comparable control group (McIntosh, 2016).

In clinical care, PLWH receive routine laboratory evaluations of blood and urine. In China, treated PLWH received hematology and biochemistry tests every 3 months to assess their overall health and oversee the side effects of antiretroviral drugs (Ma et al., 2010). A new concept of Clinlabomics has been proposed recently (Wen et al., 2022), pointing out the importance of analyzing laboratory test data with statistics and machine learning to uncover more hidden information. Such data could contribute to a deeper understanding of the physiological alterations related to diseases and uncover previously unknown clinical implications of standard laboratory testing. HRV indices have been correlated with biochemical and hematologic indices such as blood glucose and cholesterol in PLWH (Askgaard et al., 2011) as well as leukocytes in the general population (Williams et al., 2019). Nevertheless, researchers usually analyzed laboratory indices individually. Studies that evaluated the relationship between clinical laboratory test data and HRV indices among PLWH have been lacking.

Here, we compared HRV indices between PLWH and HIV-negative individuals with comparable age and sex to ascertain the independent associations between HIV infection and various HRV indices. We further explored whether distinct clinical laboratory profiles existed between PLWH with and without reduced HRV using unsupervised hierarchical clustering method.

2. Methods

2.1. Study participants

This cross-sectional study was conducted in Shanghai, China. Between January and December 2023, PLWH were recruited by health care providers in the nine community hospitals in Jingan District and a non-governmental organization (NGO). PLWH should meet the following criteria: ≥18 years old; permanent resident of Shanghai; received treatment in the Shanghai Public Health Clinical Center if being on ART at enrollment. During the same period, HIV-negative individuals with similar age and sex were recruited similarly to the PLWH from community hospitals and NGO if met the following criteria: ≥18 years old; permanent resident of Shanghai; test negative for HIV.

In total, 304 PLWH and 170 HIV-negative individuals were recruited. We randomly selected HIV-negative individuals from the entire sample using Proc Survey Select in SAS software, based on age categories (per 5 years) and sex, to achieve an approximate 2:1 frequency matching with PLWH. Ultimately, 304 PLWH and 147 HIV-negative individuals were included for analysis.

2.2. Data collection and measurements

All participants completed standardized questionnaires to collect information on demographics, lifestyles, insomnia symptoms, comorbidities, and medication use. Participants also underwent anthropomorphic (height, weight, waist circumference, etc.) and blood pressure measurements. Regular alcohol use was defined as often or always drinking alcohol in the past month. Regular exercise was defined as one or more times exercise every week. Insomnia symptoms were assessed by asking participants four sleep-related questions based on Jenkins Sleep Problems Scale, and was used in our prior work (Li et al., 2023). We calculated the body mass index (BMI) by dividing the body weight by the squared height (kg/m^2). The cut-off values for waist-to-hip ratio (WHR) for abdominal obesity were 0.90 cm for men and 0.85 cm for women. Hypertension was defined as consecutive systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, a self-reported history of hypertension, or use of antihypertensive medication. Diabetes was defined as fasting plasma glucose (FPG) ≥ 7.0 mmol/L, or documented history of diabetes, or use of antidiabetic medication.

2.3. HIV-related variables and laboratory measurements

In China, immediate and free ART initiation has been recommended for PLWH regardless of CD4 count since 2016. Routine clinical follow-up visits were done at 0.5, 1, 2, 3 months, and every 3 months thereafter; CD4 count test was provided every 6 months, and viral load test was provided every 12 months (Ma et al., 2010). We extracted HIV-related variables, such as CD4 cell counts, date of HIV diagnosis, date of ART

initiation, antiretroviral regimens, and HIV viral load, from the HIV/AIDS Comprehensive Response Information Management System (CRIMS) (Ma et al., 2010). Nadir CD4 count was defined as the lowest CD4 cell count recorded.

Treated PLWH received routine clinical laboratory tests, such as hematology and biochemistry tests, performed every 3 months in the Shanghai Public Health Clinical Center, China. Laboratory test indices closest to the survey were extracted from the Electronic Medical Record System from this hospital. Among all PLWH, 283 had available laboratory measurements within the 3 months. These measurements included: liver function (albumin; alanine aminotransferase, ALT; aspartate aminotransferase, AST; serum total protein, STP; renal function (creatinine; microalbuminuria; uric acid; urine creatinine, Ucr), fasting plasma glucose (FPG), lipids (high-density cholesterol, HDL-C; low-density cholesterol, LDL-C; total cholesterol; triglyceride); erythrocyte count (red blood cells, RBC) and counts of its main subtypes (hematocrit, HCT; hemoglobin; mean erythrocyte hemoglobin concentration, MCHC; mean corpuscular volume, MCV; red cell distribution width-coefficient of variation, RDWCV), leukocyte count (white blood cells, WBC) and counts of its main subtypes (basophils; eosinophils; lymphocytes; monocytes; neutrophils) and percentages (basophil%; eosinophil%; lymphocyte%; monocyte%; neutrophil%), and thrombocyte count (mean platelet volume, MPV; platelet count, PLT). The study included a total of 32 laboratory indices.

2.4. Processing and analysis of HRV data

After a 10-min resting period, participants maintained calm breathing. HRV was measured in a sitting position with the upper body for 20 min using a 12-lead computer-based ECG sampling box (LePu Medical Equipment Co., Ltd., Beijing). Then, transferred the electrocardiographic signal to a computer for further processing and analysis to obtain HRV indices. The electrocardiograph complementary software - LePu Health Management Data Software, was used for HRV data processing through linear statistical analysis.

HRV measures are commonly divided into time- and frequency-domain measurements. Time-domain indices, which are based on simple statistical measures of variability, address the magnitude of variability and give information about the vagal (parasympathetic) modulation of the heart. Generally, higher variability means more PNS modulation. It included the standard deviation of the normal RR intervals (SDNN), the root of the mean squares of successive RR differences (RMSSD), and the percentage of RR intervals greater than 50 ms different from its predecessor (pNN50). SDNN reflects SNS and PNS modulation, whereas RMSSD and PNN50 reflect PNS modulation. Frequency-domain measures are calculated from spectral imaging of the ECG recording. It included low-frequency power (LF; 0.04–0.15 Hz) which represents the general ANS, especially SNS activity, and high-frequency power (HF; 0.15–0.40 Hz) which reflects PNS modulation. Very low-frequency power (VLF) is thought to reflect activity of the renin-angiotensin system and thermoregulation in response to ambient temperatures. The LF/HF power ratio estimates the balance between SNS and PNS activity. SDNN is considered to be the most representative parameter of HRV (Pham et al., 2021). HRV indices were categorized into low (lowest quartile, Q1) and moderate-to-high (upper three quartiles combined, Q2−Q4). For example, low SDNN was defined as the lowest quartile (Q1) of the HRV indices.

2.5. Statistical analysis

All analysis was performed using R (version 4.3.3) or SAS 9.4 statistical software. Differences in characteristics and HRV indices were compared between the two groups using t-tests, χ^2 tests, or Wilcoxon tests, where appropriate. Linear regression models were used to assess the independent association between HIV infection and lower natural-log transformed HRV indices while adjusting for potential confounders. We utilized unsupervised hierarchical clustering analysis on 32 z-score standardized (mean = 0, SD = 1) laboratory indices as well as CD4 and CD8 cell counts to investigate whether PLWH in different quartiles of HRV indices (i.e., Q1 to Q4) had distinct clinical laboratory profiles. It was performed using the "Average" method and the "Euclidean" distance. Heatmaps were drawn using the R package Pheatmap. Then, we used backward stepwise logistic regression models to identify the factors that were associated with low SDNN and low LF (both as categorical variables), separately.

3. Results

3.1. Participant characteristics

In total, 304 PLWH (age 44.9 ± 14.0 years, 93.8% male) and 147 HIV-negative individuals (age 45.1 ± 14.3 years, 95.2% male) were included. Compared to HIV negative individuals, PLWH had a significantly lower BMI but were more likely to report regular alcohol use and have diabetes ($p < 0.05$). Among PLWH, 290 (95.4%) were receiving ART, and 66 (21.7%) had received ART for ≥5 years. About 59.7% had a current CD4 count >500 cells/μL. 285 PLWH had available data on current HIV viral load, and 277 (97.2%) had a current HIV RNA <200 copies/mL (Table 1).

3.2. Association between HIV infection and HRV indices

As shown in Table 2, except for resting heart rate (RHR) and ln(LF/HF), the time domain indices including ln(SDNN), ln(RMSSD), and ln(PNN50), and the frequency domain indices including ln(HF), ln(LF) and ln(VLF) were all significantly lower in PLWH versus HIV-negative individuals (all $p < 0.05$, Table 2). In multivariable linear models adjusting for age and sex, BMI, WHR, hypertension, and diabetes, such associations remained significant for ln(SDNN), ln(PNN50), LN(HF) and ln(LF) (all $p < 0.05$, Table 2).

3.3. Distinct clinical laboratory profiles across the HRV quartiles in PLWH

First, unsupervised HCA was performed to see whether distinct laboratory test profiles exist across quartiles (Q1 to Q4) of two HRV indices (ie, SDNN and LF) in PLWH (Fig. 1). In general, PLWH in Q1 of SDNN and Q1 of LF exhibited distinct laboratory profiles compared to those in Q2 to Q4 of SDNN and LF, respectively (Fig. 1). A similar pattern was observed for RMSSD, HF, and LF/HF (Supplementary Fig. 1).

Then, we focused on the clusters of laboratory indices that were either increased in Q1 versus Q2 to Q4 (up-cluster) or decreased in Q1 versus Q2 to Q4 (down-cluster) among PLWH. For low SDNN, the up-cluster mainly contained FPG, AST, leukocyte count (WBC) and its subtypes (monocyte count, neutrophil count, neutrophil%), whereas the down-cluster mainly contained lipids (HDL-C, LDL-C, total cholesterol), albumin, STP, uric acid, urine creatinine, erythrocytes (RBC, hemoglobin, HCT), lymphocyte%, and nadir CD4 count (Fig. 1A). For low LF, the up-cluster mainly contained FPG, AST, leukocyte count (WBC) and its subtypes (eosinophil count, neutrophil count, neutrophil%, lymphocyte count), erythrocyte subtypes (MCHC, MCV, RDWCV), whereas the down-cluster mainly contained HDL-C, albumin, STP, uric acid, urine creatinine, erythrocytes (RBC) and its subtypes (hemoglobin, MPV, HCT), lymphocyte%, and current and nadir CD4 count (Fig. 1B).

Overall, PLWH with low SDNN and LF exhibited distinct clinical laboratory profiles that were characterized by an elevation in FPG, WBC, neutrophil count, neutrophil%, and a reduction in HDL-C, albumin, STP, uric acid, urine creatinine, RBC and lymphocyte% nadir CD4 count. However, such changes in AST, HDL-C, and uric acid were not consistently observed for RMSSD, HF, PNN50, or LF/HF (Supplementary Fig. 1).

Table 1
Characteristics of PLWH and HIV-negative individuals.

Characteristics	PLWH (n = 304)	HIV-negative individuals (n = 147)	p value[a]
Age	44.9 ± 14.0	45.1 ± 14.3	0.889
Male	285 (93.8)	140 (95.2)	0.525
Education			
Junior middle school or below	54 (17.8)	32 (21.8)	0.250
Senior middle school	112 (36.8)	43 (29.2)	
College or above	138 (45.4)	72 (49.0)	
BMI, mean ± SD	23.3 ± 3.8	24.3 ± 3.3	**0.007**
< 18.5	19 (6.2)	4 (2.7)	0.991
18.5–<24.0	158 (52.0)	67 (45.6)	
≥ 24	127 (41.8)	76 (51.7)	
Abdominal obesity	157 (51.6)	76 (51.7)	0.991
Smoking	79 (26.0)	38 (25.8)	0.975
Regular alcohol use	196 (64.5)	76 (51.7)	**0.010**
Regular exercise	234 (77.0)	106 (72.1)	0.261
Comorbidities and medication use			
Insomnia symptoms	95(31.2)	44(29.9)	0.776
Hypertension	95 (31.2)	56 (38.1)	0.149
Use of antihypertensive medications	45 (14.8)	31 (21.1)	0.095
Self-reported diabetes	48 (15.8)	9 (6.1)	**0.004**
Use of antidiabetic medications	23 (7.6)	8 (5.4)	0.403
HIV-related variables			
Time since HIV diagnosis >5 years	85 (28.0)		
Duration on ART, years			
≤ 5 years	224 73.7)		
> 5 years	66 (21.7)		
Naïve	14 (4.6)		
Current CD4 count (n = 297), cells/μL			
< 200	12 (4.1)		
200–<500	108 (36.2)		
≥ 500	178 (59.7)		
Current CD8 count (n = 297), cells/μL			
< 1250	260 (87.5)		
≥ 1250	37 (12.5)		
Current CD4/CD8 ratio <0.5 (n = 297)			
< 0.5	84 (28.3)		
0.5–<1.4	187 (63.0)		
1.4–<2.0	15 (5.0)		
≥ 2.0	11 (3.7)		
Nadir CD4 count (n = 285), cells/μL			
< 200	81 (28.4)		
200–<500	146 (51.2)		
≥ 500	58 (20.4)		
Current HIV RNA (n = 285), copies/mL			
< 200	277 (97.2)		
≥ 200	8 (2.8)		

Data are n (%) or mean ± SD. [a] By the student's t-test, χ^2 or Wilcoxon test, as appropriate.

3.4. Relationship among clinical laboratory indices, and low HRV indices in PLWH

Given that SDNN and LF are considered to be the representative parameters of general HRV, we further conducted backward stepwise logistic regression models to examine the traditional and laboratory indices associated with low SDNN and low LF (as categorical variables), separately. The final model for low SDNN included age (odds ratio [OR] 1.04; 95% confidence interval [CL] 1.02, 1.06), total cholesterol (OR 0.70; 95% CI 0.50, 0.96)), neutrophil count (OR 1.29; 95% CI 1.03, 1.62), and use of antidiabetic medications (OR 5.76; 95% CI 2.14, 15.45), whereas the final model for low LF included age (OR 1.04; 95% CI 1.02, 1.06), RBC (OR 0.57; 95% CI 0.34, 0.95)) and use of antidiabetic medications (OR 6.68; 95% CI 2.41, 18.50) (Table 3).

4. Discussion

The present study represents the first investigation assessing the clinical laboratory profiles of PLWH with and without reduced HRV. The main findings are as follows: first, HRV indices such as SDNN, PNN50, HF, and LF were significantly lower in PLWH compared to HIV-negative individuals. Second, PLWH with low HRV indices display distinct clinical laboratory profiles that are characterized by an elevation in FPG, WBC, neutrophil count, neutrophil%, and a reduction in albumin, STP, urine creatinine, lymphocyte%, RBC, and nadir CD4 count. The final regression models for low SDNN included older age, decreased total cholesterol levels, elevated neutrophil count, and the use of antidiabetic medications, whereas the final model for low LF included older age, reduced RBC and the use of antidiabetic medications.

ANS dysfunction resulting from HIV infection is commonly marked by impairment of both the PNS (i.e., vagal) and SNS (Shao and Li, 2023; McIntosh, 2016; Bellinger and Lorton, 2022). Studies conducted in the post-ART era have shown inconclusive findings when comparing PLWH to HIV-negative controls using HRV indices (McIntosh, 2016). However, most studies show that HRV indices decreased in PLWH, primarily due to a decrease in parasympathetic or vagal activity, which is reflected in lower SDNN, PNN50, and HF when compared to controls (McIntosh, 2016). A recent study indicated that nocturnal HRV in PLWH neither worsened nor improved after ART initiation (Kavishe et al., 2023). Consistent with previous findings, we observed that HIV infection was independently associated with lower SDNN, PNN50 and HF. Beyond these, our data showed, substantial reductions in LF was observed among PLWH, but no significant difference in LF/HF was observed between the two groups. The initial hypothesis that the SNS generates LF power and that a high LF/HF ratio suggests sympathetic dominance and a low LF/HF ratio indicates parasympathetic dominance has been challenged recently. Research has shown that the SNS to LF power varies profoundly with test conditions (Shaffer and Ginsberg, 2017). For example, when LF is calculated while sitting upright during resting

Table 2
Associations between HIV serostatus and HRV indices using univariable and multivariable linear regressions.

HRV indices	PLWH	HIV-negative individuals	p value	Univariable model		Multivariable model[a]	
				β (95% CI)	p value	β (95% CI)	p value
RHR (bpm)	84.0 (76.0, 92.0)	82.0 (75.0, 92.0)	0.495	0.91 (−1.71, 3.54)	0.495	0.76 (−1.85, 3.36)	0.568
Time-domain indices							
ln(SDNN)	3.8 (3.4, 4.1)	3.9 (3.7, 4.1)	**0.005**	−0.14 (−0.24, −0.04)	**0.009**	−0.14 (−0.24, −0.04)	**0.007**
ln(RMSSD)	3.1 (2.6, 3.4)	3.2 (2.8, 3.6)	**0.016**	−0.13 (−0.28, 0.01)	**0.077**	−0.14 (−0.30,0.01)	**0.065**
ln(PNN50)	0.7 (−0.9, 1.8)	1.1 (0.2, 2.0)	**0.003**	−0.56 (−0.89, −0.23)	**0.001**	−0.59 (−0.92, −0.27)	**<0.001**
Frequency-domain indices							
ln(HF)	5.0 (4.3, 5.9)	5.3 (4.5, 6.2)	**0.017**	−0.31 (−0.62, 0.01)	**0.056**	−0.32 (−0.64, −0.01)	**0.046**
ln(LF)	6.1 (5.2, 6.9)	6.4 (5.7, 7.1)	**0.003**	−0.40 (−0.75, −0.06)	**0.022**	−0.41 (−0.74, −0.07)	**0.020**
ln(VLF)	6.9 (6.2, 7.4)	7.1 (6.5, 7.5)	**0.015**	−0.22 (−0.50, 0.06)	0.127	−0.26 (−0.54, 0.03)	**0.078**
ln(LF/HF)	0.9 (0.5, 1.4)	1.1 (0.5, 1.5)	0.112	−0.10 (−0.23, 0.03)	0.150	−0.08 (−0.21, 0.05)	0.208

Data are median (interquartile). CI, confidence interval.
[a] Adjust for age, sex, BMI, WHR, hypertension and diabetes.

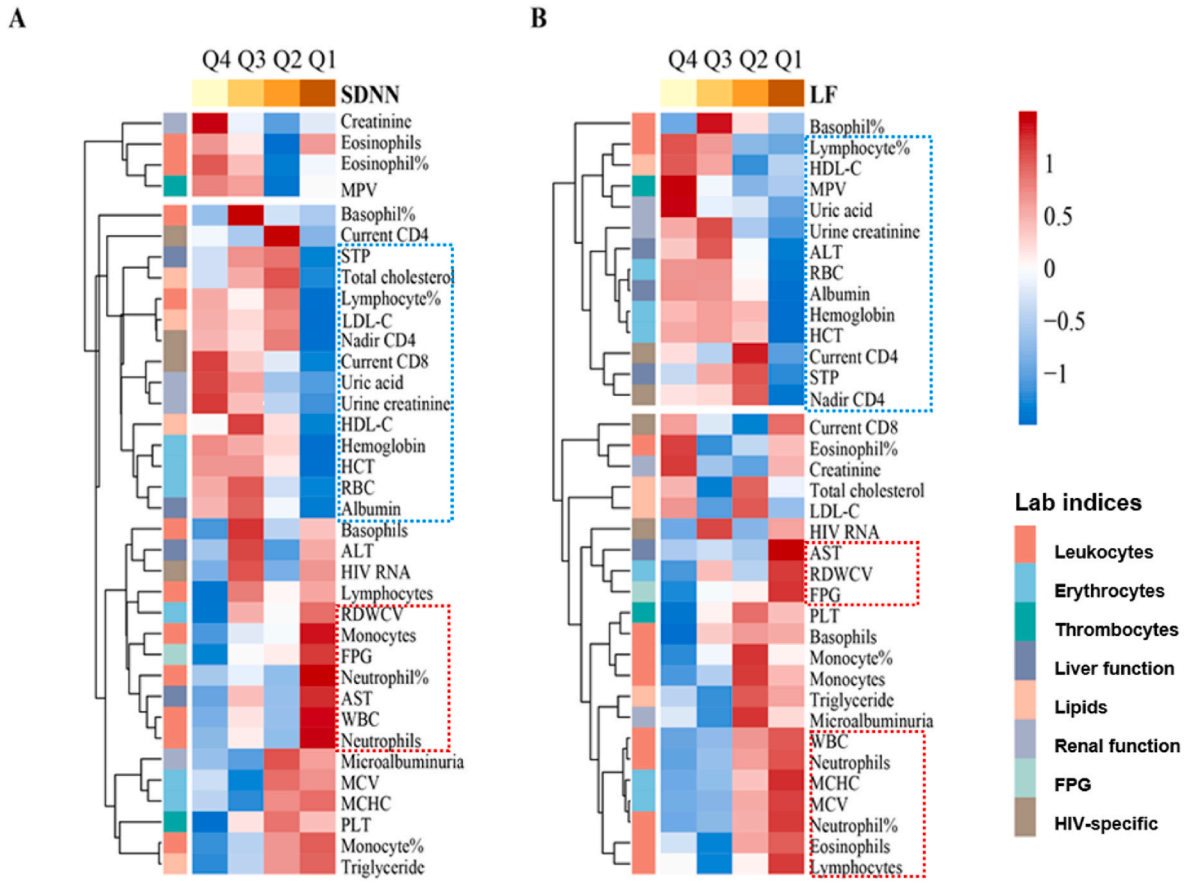

Fig. 1. Unsupervised hierarchical clustering analysis of the 32 standardized (z-score) clinical laboratory indices and 4 HIV-specific indices across the quartiles of HRV indices. A, SDNN; B, LF. Red is increasing, and blue is decreasing across each row. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Backward stepwise Logistic regression of factors associated with low SDNN and LF among PLWH, respectively ($n = 283$).

	aOR (95% *CI*)	*p* value
Q1 of SDNN		
Age	1.04 (1.02, 1.06)	<0.001
Total cholesterol	0.70 (0.50, 0.96)	0.030
Neutrophils	1.29 (1.03, 1.62)	0.027
Antidiabetic medications	5.76 (2.14, 15.45)	<0.001
Q1 of LF		
Age	1.04 (1.02, 1.06)	<0.001
RBC	0.57 (0.34, 0.95)	0.034
Antidiabetic medications	6.68 (2.41, 18.50)	<0.001

aOR, adjusted odds ratio; CI, confidence interval.

conditions, as conducted in our study, the primary contributors are PNS and baroreflex activity—not SNS activity. Therefore, HRV is not a reliable tool for evaluating SNS activity in PLWH, other tools should be used (Robinson-Papp et al., 2020; Zygmunt and Stanczyk, 2010). Nevertheless, our data support the idea that parasympathetic or vagal activity is impaired in PLWH even when on ART and viral suppressed, emphasizing the potential of neuromodulation therapeutic strategies that aim to improve PNS and counteract CVD in PLWH. These interventions have recently gained increasing attention in many disease states and have yielded encouraging results (Bazoukis et al., 2023; Mohanta et al., 2022).

The ANS and the immune system are deeply interrelated. HRV has been robustly associated with WBC in prior large-scale investigations (Williams et al., 2019). Our investigation revealed that PLWH with low HRV indices showed noticeable differences in clinical laboratory profiles compared to those with moderate to high HRV indices, which were primarily characterized by elevated WBC, neutrophil count, and neutrophil%, and decreased albumin, lymphocyte% and nadir CD4 count that are closely related to inflammatory response. The relationship between decreased RBC and low HRV indices especially low LF may reflect the pathophysiological links between red blood cell disorders and cardiovascular diseases (Mozos, 2015). A meta-analysis has found negative correlations between WBC and various HRV indices (Williams et al., 2019). During the systemic inflammatory response, elevated neutrophils and decreased lymphocytes are frequently observed, are believed to be regulators of cardiovascular inflammation, and have been associated with adverse cardiovascular events (Núñez et al., 2011; Silvestre-Roig et al., 2020; Welsh et al., 2018). Our subsequent stepwise logistic regression models revealed a positive correlation between neutrophil count and low SDNN. Our data suggest that reduced HRV is related to inflammatory response in PLWH, as our data also showed that lower CD4 count was observed in PLWH with low HRV indices. Decreased HRV may be one of the mechanisms by which chronic inflammation contributes to heightened cardiovascular risk in PLWH (Carnevale, 2022; Godijk et al., 2020), which requires additional investigation.

Notably, our data showed that older age and antidiabetic medication were strongly associated with low HRV indices. A negative association between age and HRV was commonly observed in the general population (Choi et al., 2020). Given these, differentiating between HIV infection and natural aging as causes of reduced HRV in older PLWH may be difficult. Cardiovascular autonomic neuropathy is a common chronic complication of diabetes, which encompasses damage to the

autonomic nerve fibers that innervate the heart and blood vessels, resulting in impaired ANS function and subsequently increased risk of CVD (Duque et al., 2021). The exact mechanisms driving cardiovascular autonomic neuropathy are still unclear. However, it is well established that hyperglycemia plays a crucial role in activating biochemical pathways related to the metabolic and/or redox state of the cell, along with impaired nerve perfusion, cause autonomic neuropathy (Pop-Busui, 2010). A number of studies have revealed significant negative associations between HRV indices and diabetes in the general population (Benichou et al., 2018), however these associations have been rarely reported in PLWH. Notably, the disease burden of diabetes is exacerbated in PLWH, with a higher risk of developing diabetes compared to HIV-negative individuals (Spieler et al., 2022). These findings indicate that ANS dysfunction is a health concern that needs more attention in PLWH.

Several limitations should be acknowledged. Firstly, the cross-sectional design precluded the determination of the temporal relationship between HRV indices and clinical laboratory analysis. Second, clinical laboratory test indices may vary depending on health status, and one single visit of laboratory test results may not accurately reflect their health status over a longer period; despite the fact that HRV measurements and laboratory samples (urine and blood) were not taken at the same time, our data consistently aligned with existing evidence, thereby not severely affected the findings. Third, laboratory test indices from HIV-negative individuals were not assessed, which hinders the ability to ascertain the mediating role of specific laboratory indices in the relationship between HIV infection and reduced HRV. In addition, our analyses of the associations between clinical laboratory profiles and HRV in PLWH were exploratory and that future studies are needed to verify these patterns.

PLWH exhibit reduced parasympathetic activity, as evidenced by the independent association between HIV infection and lower SDNN and LF. In addition, our data indicates that PLWH who have low HRV indices have distinct clinical laboratory profiles, primarily involving leukocytes and their main subtypes, as well as FPG and RBC. Our findings suggest that reduced HRV is closely related to systematic inflammatory response and diabetes, and emphasize the potential of neuromodulation therapeutic strategies to improve ANS balance and further prevent CVD in PLWH. The interplay between ANS and chronic inflammation and their role in the pathogenesis of cardiovascular diseases among PLWH merits future investigations.

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Data and materials availability

All the data in the paper or in the supplementary materials are free to obtain. Raw data that support the findings of this study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Yunqiu Zhang: Writing – original draft, Investigation, Formal analysis. **Lei Han:** Writing – review & editing, Project administration, Investigation. **Luqian Shi:** Writing – review & editing, Investigation. **Meiyang Gao:** Writing – review & editing, Investigation. **Jun Chen:** Writing – review & editing, Resources, Investigation. **Yingying Ding:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

None.

Declaration of competing interest

None.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100858.

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