

Long-term subclinical cardiac damage in people living with human immunodeficiency virus

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ABSTRACT

Introduction: Human immunodeficiency virus (HIV) infection remains a major global health challenge. People living with HIV are twice as likely to develop cardiovascular disease. Myocardial work is a novel echocardiographic technique that assesses global work index and global work efficiency of the left ventricle, enabling earlier detection of subclinical myocardial dysfunction.

Material and methods: We conducted a cross-sectional study of patients with long-standing HIV infection without previous cardiovascular disease, aiming to evaluate the prevalence of subclinical cardiac dysfunction determined by an impaired global myocardial work efficiency, and studied its predictors by linear regression.

Results: 110 HIV patients (78.2% men) were included, median age 53.3 years and median time since diagnosis of 20.5 years. Echocardiographic measurements were compared with matched control participants. HIV patients showed significantly lower values of global longitudinal strain of the left ventricle, right ventricle free wall and left atrial reservoir, although absolute values remained within normal limits. HIV group had consistently reduced global work efficiency values ($\leq 93\%$) which was associated with by age, diabetes, SCORE2, time from diagnosis, long corrected QT interval, QRS Interval duration, CD4 count nadir, initial and maximum viral load and exposure to didanosine by univariate analysis. After adjustment by SCORE2 and QRS duration, global work efficiency reduction depended on maximum viral load.

Conclusions: Subclinical myocardial dysfunction is present in long-standing HIV infection. Global work efficiency may represent a sensitive marker of subclinical myocardial dysfunction, even in patients with preserved left ventricular ejection fraction, and it was associated with maximum viral load in our patients.

1. Introduction

Human immunodeficiency virus (HIV) infection remains a major

global health challenge [1]. Infectious and immunosuppression related complications have decreased over time, and cardiovascular disease has emerged as a leading cause of mortality, along with neoplastic disease

Abbreviations: HIV, Human immunodeficiency virus; ART, Antiretroviral therapy; LVEF, Left ventricular ejection fraction; LV, Left ventricle; GLS, Global longitudinal strain; RV-FW GLS, right ventricle free wall global longitudinal strain; GWI, Global myocardial work index of left ventricle; GWE, Global myocardial work efficiency of left ventricle; GCW, Global myocardial constructive work of left ventricle; GWW, Global myocardial wasted work of left ventricle; TAPSE, Tricuspid annular plane systolic excursion.

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[2,3].

People living with HIV are twice as likely to suffer from cardiovascular disease, including a wide range of conditions such as coronary artery disease, myopericarditis, heart failure, and arrhythmias, even on those receiving targeted ART and undetectable viral load [2–4].

Pathogenesis is multifactorial, involving an increased prevalence of classic cardiovascular risk factors, along with chronic inflammation, immune activation and infection-related toxicity, as well as the impact of ART [3–6]. Despite their young age, a large percentage of patients exhibit abnormal lipid profiles: hypertriglyceridemia, reduced HDL cholesterol and increased total and LDL cholesterol, especially those receiving protease inhibitors [4–6].

Growing evidence suggests that low-grade chronic inflammation and immune-related mechanisms play a major role in the development of cardiovascular events [3,5,7]: elevated inflammatory markers such as high-sensitivity C-reactive protein, interleukin-6, D-dimer, soluble CD14 and soluble CD163 promote a prothrombotic state involving endothelial dysfunction and coagulation disorders, with increased progression of atherosclerosis [7–10].

The most common form of presentation nowadays is coronary artery disease, with a rate of acute myocardial infarction around 50% higher in HIV patients compared to general population with younger age debut. Ischemic stroke and peripheral artery disease are also common [4,5,9].

Several studies have also reported approximately twice the risk of developing heart failure. Currently, the predominant profile features asymptomatic patients with preserved left ventricular ejection fraction (LVEF), with diastolic dysfunction and altered subclinical dysfunction parameters^{4,7}.

Cardiac magnetic resonance imaging studies and autopsies consistently show higher rates of myocardial fibrosis, steatosis and impaired inflammatory parameters such as increased native T1 values, extracellular volume and late gadolinium enhancement [3,11]. These findings have been associated with adverse cardiovascular outcomes including heart failure, arrhythmias and sudden cardiac death regardless of traditional risk factors [12–14].

Currently, the most common finding in echocardiography studies is diastolic dysfunction, which has been linked to lower nadir CD4 counts and chronic inflammation¹⁶. Modern strain-based techniques have also identified pathological values in left atrial strain and global longitudinal strain (GLS) of the left ventricle (LV) in patients with preserved LVEF [15].

Myocardial work echocardiography is a novel technique that quantifies left ventricular performance by integrating myocardial deformation based on global longitudinal strain (GLS) with a noninvasive estimate of left ventricular filling pressure, thus taking afterload into account [16,17]. It measures the global work index (GWI) and global work efficiency (GWE) which have demonstrated superior sensitivity compared to GLS for detecting subclinical myocardial dysfunction especially in populations at risk of myocardial dysfunction but with preserved LVEF [16–19].

The aim of the study is to assess the presence of subclinical myocardial damage in this population using advanced echocardiography techniques.

2. Methods

We conducted an observational, cross-sectional single-centre study of patients with long-standing HIV infection and no previous cardiovascular disease in order to evaluate the prevalence of subclinical cardiac dysfunction determined by an impaired GWE ($\leq 93\%$) and studied determinants of GWE by linear regression. The study was approved by the hospital Ethical Board, respecting health authorities' regulations.

A group of 113 patients with HIV infection and no history of previous cardiovascular disease who attended scheduled appointments at the Infectious Diseases Unit of Severo Ochoa University Hospital between November 2022 and November 2023 were consecutively recruited.

Three patients were excluded from the study due to meeting at least one of the exclusion criteria, leaving a total of 110 patients for analysis.

Simultaneously, a control group of 50 consecutive individuals without cardiovascular pathology, were selected after a first cardiology appointment if they had no evidence of cardiovascular disease, none of the exclusion criteria were met, and age, and cardiovascular risk SCORE2 scale was within range of HIV patient's media ± 1 SD, and gender frequency was $\pm 2.5\%$.

Participants in both groups signed an informed consent form prior to their inclusion in the study.

Demographic variables (age and gender) and anthropometric variables (height, body mass index, blood pressure and heart rate) were registered in both groups. Classic cardiovascular risk factors such as smoking, high blood pressure, dyslipidemia and diabetes mellitus were analyzed, and overall cardiovascular risk was estimated using the SCORE2 scale [20].

Each participant underwent an electrocardiogram and a complete blood count analysis, including coagulation profile and complete metabolic panel with kidney and liver function tests, as well as lipid profile, thyroid function, glycated hemoglobin and cardiac biomarkers (high-sensitivity troponin I and NT-proBNP).

Other variables related to HIV infection were also documented: time since diagnosis, viral load, disease stage, CD4 and CD8 counts at diagnosis, CD4 and CD8 nadir, logarithmic maximum (the highest value recorded during follow-up), initial and current viral load, as well as the type of ART received and its duration.

We performed a complete transthoracic echocardiogram on both groups, following current statements [19,21]. GLS of the LV, left atrium and right ventricle free wall longitudinal strain (RV-FW GLS), as well as the GWI and GWE of the LV were assessed. The Myocardial Performance Index (aka Tei-Doppler Index), an index of combined systolic and diastolic function, was obtained from tissue doppler velocities at lateral mitral and tricuspid annuli, by dividing the sum of isovolumetric contraction and relaxation time by ejection time.

Myocardial work assessment was performed with a vendor-specific algorithm (GE Healthcare, Pewaukee, WI) in a Vivid E-95 machine [17]. The 3 standard apical views are acquired at a frame rate of >40 frames/s with image quality adequate to visualize myocardial borders. Speckle tracking echocardiography is used for GLS analysis with a generated pressure curve from the duration of the isovolumic and ejection phases, as measured by the timing of aortic valve closure. Valvular event times were assessed automatically by machine and adjusted manually through visual assessment from the apical long-axis view when necessary. These outlines can also be adjusted manually to conform to the myocardium. From this analysis, the bull's-eye GLS plot is generated, and GLS values are calculated and displayed.

Noninvasive measurement of systolic blood pressure in the arm using a sphygmomanometer at the time of image acquisition was obtained. Peak LV systolic pressure is estimated to be noninvasive systolic cuff pressure. This pressure is then inputted into the echocardiography machine for myocardial work analysis.

Myocardial work corrects automated functional imaging with dynamic LV pressures. Once blood pressure is inputted into the software, a myocardial work bull's-eye plot is created, similar to GLS. Four values are calculated: global work index (GWI) (Average myocardial work based on the pressure-strain loop), global constructive work (GCW) (Positive work performed by a segment in systole and negative work (segment lengthening) during isovolumic relaxation), global wasted work (GWW) (Negative work (segment lengthening) during systole and positive work (segment shortening) during isovolumic relaxation), and global work efficiency ($GWE = GCW/(GCW + GWW)$) [17,19].

Due to normal distribution of echocardiographic parameters, Student's *t*-test was used in order to identify significant differences between the two groups, and Fisher's Test for qualitative parameters. Predictors of GWE were studied by linear regression in the HIV group, and multivariate analysis include variables with a $p < 0.2$ in the univariate

analysis, considering a p significant value of <0.05 , or a change in $B > 10\%$ for entering the final model. As smoking was not significant, cardiovascular risk factors were summarized in the SCORE2 index. An IBM-SPSS 27 software package was used for analysis.

3. Results

Baseline characteristics of subjects with HIV infection and control participants were comparable in terms of age and gender, as summarized in Table 1. Most patients had long-standing HIV infection, with a median time since from diagnosis of 20.8 (IQR =14) years.

Regarding cardiovascular risk profile, groups were also similar, with no significant differences in mean systolic blood pressure, body mass index, prevalence of hypertension, diabetes, dyslipidemia or obesity.

Active smoking was significantly more common among people with HIV (68.2% vs 50.0%; $p = 0.028$), showing an odds ratio of 1.67 (95% CI 1.06–2.62) but cardiovascular risk estimated by SCORE2 scale was similar in both groups ($p = 0.197$).

Echocardiographic findings are summarized in Table 2. No differences were found in chambers size, LV mass index, nor LVEF.

Some data were found to support diastolic function impairment in HIV patients: E/Ea mitral and global Ea velocity were both significantly lower (Table 2). Left atrial reservoir strain values were but this difference did not reach statistical significance (mean difference 2.54, 95% CI –0.12 to 5.20; $p = 0.061$). LV myocardial performance index was higher.

No differences were found in right ventricular size or tricuspid annular plane systolic excursion (TAPSE). However, RV-FW GLS was significantly reduced in the HIV group (mean difference 1.91; 95% CI 0.53 to 3.30; $p = 0.007$).

Although LVEF was normal and similar in both groups, HIV patients presented evidence of subclinical myocardial dysfunction with reduced LV GLS and myocardial work indices. LV GLS was significantly lower in HIV, mean difference 1.62 (95% CI 0.99–2.24), $p < 0.001$. Additionally, GWI was 171.02 mmHg% lower in HIV group, $p = 0.001$. GWE was also a 3% lower in HIV group (92.49, 95% CI 91.45–93.53) versus controls (94.98, 95% CI 94.46–95.50); mean difference 3.02 (95% CI 1.89–4.15),

$p < 0.001$ (Fig. 1).

Taking a GWE $< 93\%$ as lowest threshold for myocardial work impairment, a linear uni- and multivariate regression analysis was performed to identify its predictors (Table 3).

By univariate analysis, factors significantly associated with GWE were age, diabetes, SCORE2 risk, time from HIV diagnosis, long QTc interval, QRS Interval duration, CD4 count nadir, initial and maximum viral load, and exposure to didanosine treatment. NT-proBNP (median in HIV patients 42 pg/ml, IQR: 23–82.5), was normal and not predictive ($\beta = -0.012$ (95% CI: -0.025–0.002; $p = 0.102$). Troponin was not determined. After adjustment by cardiovascular risk assessed by SCORE2 and QRS duration, GWE was associated with maximum viral load (Table 3), with a ROC area of 0.674 (95% CI: 0.556–0.791; $p = 0.008$) for a GWE $\leq 92\%$, and a modest R^2 of 0.22 for the linear regression model. There was no collinearity (variance inflation factors were 1.2, 1.01 and 1.2 respectively).

4. Discussion

Our study shows that, in our group, myocardial performance is significantly lower in people living with HIV despite normal LVEF and adequate ART with suppressed viral load. Advanced imaging techniques showed lower LV-GLS and RV-FWGLS strain values in HIV group compared to healthy controls that could not be explained by risk factors and comorbidities. Both groups were comparable in terms of age, sex, and cardiovascular risk factors, except for active smoking, which was more common in the group of patients with HIV infection, but non-significant in adjusted regression multivariate analysis. Nevertheless, this difference should be taken in consideration. Although coronary CT scan was not performed, none of the patients exhibited symptoms suggestive of coronary artery disease or regional findings in contractility or GLS suggesting ischemia, although occult coronary disease could have influence strain values. Despite differences between both groups, no clear cut-off value was found in HIV patients compared to normal threshold values (–18%) described in the literature [22–25], as the highest 95%CI GLS value found was –19%. Prevalence of hypertension was the same, without LV hypertrophy, and no difference in systolic blood pressure measured at time of LV apical chamber acquisition.

LVEF has been used as the gold standard parameter to evaluate global LV function, although it often remains preserved despite myocardial injury until advanced stages. One can argue that LVEF is not the best measure of of systolic dysfunction [26]. Recently new strain-based techniques with higher sensitivity have emerged [11,15,27]. In our cohort, patients with HIV infection exhibited reduced myocardial work indices, specifically GWI and GWE were significantly reduced. Myocardial work combines myocardial deformation with left ventricular pressure (afterload), offering a load-adjusted assessment of myocardial performance. Furthermore, GWE reflects myocardial energetic inefficiency, providing superior sensitivity for subclinical myocardial dysfunction detection than LVEF and GLS [16–18]. Among our HIV patients, the parameter that was most consistently reduced compared to reference values accepted as normal was GWE: 93% is consistently the lowest normal threshold in different studies [18]. GWE includes constructive and wasted work, and its variability is lower than GWI (affected by age and sex), allowing a cut-off definition.

Diastolic parameters and LV myocardial performance index (a Doppler parameter involving both diastolic and systolic function) were also significantly worse in HIV patients, reinforcing the existence of cardiac dysfunction.

In our study, impaired myocardial efficiency after multiparametric adjustment was associated with maximum viral load. This finding highlights the significance of prior viral load and suggests that even in patients with adequate viral control, prior exposure to uncontrolled viremia may have long-lasting detrimental effects on myocardial energy metabolism, and the role of direct viral myocardial damage. The modest R^2 suggests the implication of factors other than cardiovascular risk,

Table 1-
Baseline characteristics of patients with HIV infection and control group.

Variable	HIV Group (n = 110)	Control Group (n = 50)	OR/Mean difference* (95% CI)	P
Gender (male)	86 (78.2%)	40 (80.0%)	0.97 (95% CI 0.75–1.24)	0.485
Age (years)	53.3 (11.0)	53.7 (9.8)	–0.39 (95% CI –3.96 to +3.19)	0.831
Systolic BP (mmHg)	131.1 (17.4)	129.2 (12.7)	1.9 (95% CI –3.5 to +7.3)	0.488
BMI (kg/m ²)	26.8 (4.8)	27.5 (4.6)	–0.70 (95% CI –2.31 to +0.91)	0.395
SCORE2 risk index %	4.90 (2.74)	5.52 (2.8)	–0.63 (95% CI –1.58 to +0.33)	0.197
Smoking history	75 (68.2%)	25 (50.0%)	1.67 (95% CI 1.06–2.62)	0.022
Hypertension	31 (28.2%)	16 (32.0%)	1.06 (95% CI 0.84–1.35)	0.377
Diabetes	4 (3.6%)	2 (4.0%)	1.03 (95% CI 0.58–1.84)	0.610
Dyslipidaemia	49 (44.5%)	21 (42.0%)	0.97 (95% CI 0.79–1.19)	0.450
Obesity	27 (24.8%)	14 (28.0%)	1.06 (95% CI 0.82–1.36)	0.666
Overweight/ Obesity	68 (62.4%)	35 (70.0%)	1.11 (95% CI 0.90–1.37)	0.351

Mean (SD) for quantitative measurements. n(%) for categorical variables. BP: blood pressure. BMI: body mass index. *Odds Ratio (OR) for qualitative parameters (p by Fisher's Test). Mean difference for quantitative measurements (p by Student's t -test).

Table 2-
Echocardiographic characteristics in patients with HIV infection and control group.

Echocardiographic parameters	HIV group	Control group	Mean difference	p
LVED index (mm/m ²)	16.9 (16.2–17.7)	15.9 (15.2–16.6)	0.69 (–0.24–1.63)	0.085
LV mass index (g/m ²)	87.04 (81.9–91.0)	83.93 (78.2–90.0)	3.1 (–3.9–10)	0.383
LVEF (%)	61.96 (60.58–63.35)	62.78 (61.75–63.81)	1.15 (–0.43–2.74)	0.154
LV GLS (%)	–19.57 (–20.1– –19.1)	–21.11 (–21.57– –20.65)	1.62 (0.99–2.24)	<0.001
GWI (mmHg%)	1861.8(1769.1–1954.4)	2003.8(1940.6–2066.9)	171.02(71.2–270.9)	0.001
GWE(mmHg%)	92.49 (91.5–93.55)	94.98 (94.5–95.5)	3.02 (1.89–4.15)	<0.001
LV MPI	0.42 (0.39–0.45)	0.48 (0.45–0.52)	0.07 (0.03–0.10)	0.001
E/Ea mitral	7.39 (6.82–7.96)	6.42 (5.94–6.89)	0.85 (0.17–1.52)	0.014
Mitral Ea (cm/s)	10.56 (9.78–11.33)	11.70 (11.15–12.25)	–1.01(–1.87–0.15)	0.022
RV basal diameter	34.2 (33.2–34.7)	34.8 (33.5–35.6)	–0.6 (–1.8–0.48)	0.262
RVFW GLS (%)	–22.4 (–21.3 to –23.4)	–24.2 (–23.3 to –25.1)	1.91 (0.53–3.30)	0.007
PSP (mmHg)	26.4 (25.3–27.6)	25.7 (24.2–27.2)	0.96 (–1.15–2.64)	0.584
LAVI (ml/m ²)	24.9 (23.2–26.6)	24.9 (22.1–27.7)	0.32 (–2.2–2.9)	0.740
RAVI (ml/m ²)	18.0 (16.7–19.3)	18.3 (16.5–20.1)	–0.81 (0.93– –2.67)	0.225
LASr (%)	33.09 (31.2–34.98)	35.56 (33.69–37.42)	2.54 (–0.12–5.1)	0.061

Mean (95%CI). LVED: Left ventricular end-diastolic index. LV: left ventricle. LVEF: left ventricular ejection fraction. LV GLS: left ventricular global longitudinal strain. GWI: global work index. GWE: global work efficiency. MPI: Myocardial performance index. E: Early diastolic mitral wave velocity. Ea: Averaged early diastolic mitral annulus velocity. RV: Right ventricle. RVFW GLS: right ventricular free wall global longitudinal strain PAP: estimated pulmonary artery pressure LAVI: Left atrium volume index. RAVI: Right atrium volume index. LASr: left atrial reservoir strain.

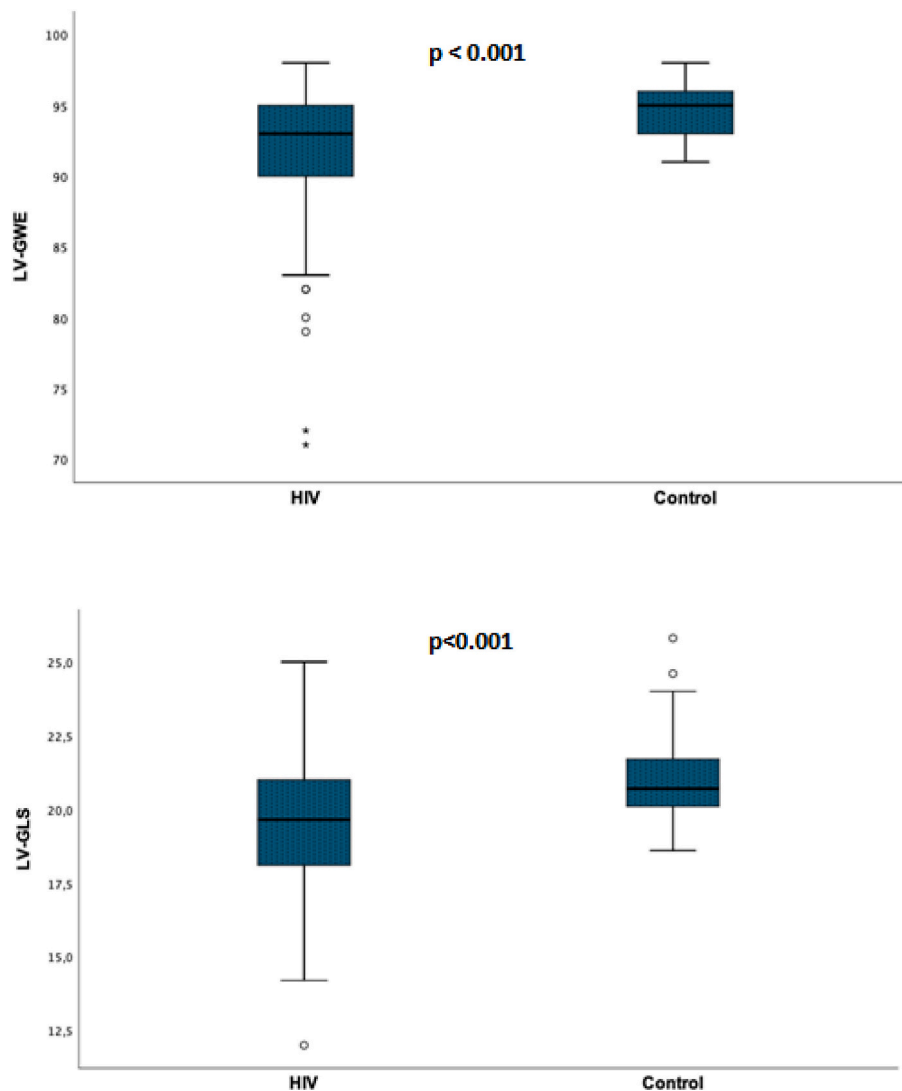


Fig. 1. - Comparison between GWE and LV GLS among HIV patients and control group.

LV-GWE: left ventricle global work efficiency. HIV: human immunodeficiency virus. LV-GLS: left ventricle global longitudinal strain.

Table 3
Significant predictors of GWE by linear regression analysis.*

Predictors of impaired GWE	Univariate analysis		Multivariate analysis	
	β (95%CI)	p	β (95%CI)	p
Age (years)	-0.11 (-0.20 to -0.02)	0.017	-	
Diabetes	-7.1 (-12.82 - -1.40)	0.015	-	
Score2 (%)	-0.66 (-1.01 - -0.31)	<0.001	-0.5 (-0.91 - -0.08)	0.020
Time from diagnosis (years)	-0.12 (-0.22 - -0.02)	0.026	ns	
QRS duration (ms)	-0.10 (-0.18 - -0.02)	0.014	-0.11 (-0.19 - -0.03)	0.007
Long QTc Interval	-4.0 (-7.7 - -0.36)	0.003	ns	
CD4-count nadir (cells/ μ L)	0.007 (0.001-0.01)	0.023	ns	
Initial viral load (log)	-1.2 (-2.25 - -0.15)	0.026	ns	
Maximum viral load (log)	-1.35 (-2.28 - -0.42)	0.05	-0.86 (-1.86 - -0.14)	0.04
DDI exposure	-2.33 (-4.54 - -0.12)	0.039	ns	

GWE: global work efficiency. Beta: DDI: didanosine. ns: non-significant.

* Variables expressed as n (%). All other variables expressed as mean (95% CI).

B: Change in GWE for each unit of change in predictors of impaired GWE.

QRS duration (another possible marker for cardiac damage) and maximal viral load. Although causation cannot be inferred from an observational study, it deserves further investigation and GWE could offer additional diagnostic value to GLS in HIV patients, without previous studies in this clinical setting.

Some studies have found differences in cardiac damage regarding retroviral therapy [11]. Drugs most commonly related to adverse cardiac effects are abacavir and protease inhibitors such as darunavir and ritonavir, linked to dyslipidemia and myocardial infarction. Non-nucleoside reverse transcriptase inhibitors, particularly efavirenz, are associated with the development of conduction disorders and arrhythmias [28]. We found a relationship among subclinical myocardial damage and exposure to didanosine in univariate analysis in our group, but none of the patients were currently receiving it, and the study lacks the power to establish causality. Didanosine, less commonly used nowadays, is a nucleoside reverse transcriptase inhibitor that has previously been associated with mitochondrial damage and ischemic heart disease [28,29]. However, there are no specific strategies for these patients beyond close clinical and electrocardiographic monitoring [28].

From a clinical perspective, our findings have significant implications. Although there is a well-established association between HIV infection and cardiovascular disease, there are unique characteristics inherent to this population, so conventional risk stratification tools or imaging parameters may not be sufficient in this group of patients. Advanced echocardiographic techniques may play a role in early risk stratification of patients without apparent cardiovascular disease but subclinical myocardial dysfunction. In the setting of breast cancer treatment, an unicentric study [30] with serial GLS and myocardial work measurements, found that the latter predicted cardiotoxicity, and a relative reduction of 5% in GWE in patients with moderate cardiotoxicity. We found a relative mean difference of 8% in GLS values, and 3% in GWE, both in the grey zone, but our study was cross-sectional. Patients with subclinical myocardial damage diagnosed by reduced myocardial work indices, specially GWE, may benefit from serial cardiovascular follow-up and targeted preventive measures if needed.

There are currently no prospective studies that have connected lower strain parameters to clinical events in HIV patients, but studies have linked lower GLS values to fibrosis and weakened immune system (lower CD4 count), which have been connected to heart failure, arrhythmias, and increased cardiovascular mortality. Furthermore, no research has shown that HIV patients with subclinical myocardial damage identified

by strain techniques benefit from a particular treatment (such as beta-blockers or ACE inhibitors), so this approach should be further investigated [28,29].

Major strengths of our study were the use of a matched control group, inclusion of multiple clinical, electrocardiographic and a wide variety of variables related to infectious history and treatment, and implementation of advanced echocardiographic techniques including both myocardial strain and myocardial work.

Nevertheless, certain limitations must be acknowledged: it is an observational, relatively small study from one center, and lack of longitudinal follow-up and assessment of clinical cardiovascular outcomes, which limits generalizability. Although patients were asymptomatic, no CT scan or coronary detection was performed, and there were more smokers in the HIV group. The echocardiographic software is to date available from one vendor, operators were not blinded to HIV condition, although no technical difference existed regarding acquisition, and studies were not repeated for interobserver variability. Overall, our study's results contribute to current knowledge and emphasize the high prevalence of subclinical myocardial impairment, particularly determined by global myocardial efficiency, in asymptomatic patients with longstanding HIV infection, even with preserved LVEF. This suggests a direct role for viral myocardial damage, although causation is not warranted in an observational study. Troponin was not measured due to local restrictions, and it could have added diagnostic value for subclinical damage. Although statistically significant, clinical impact of these differences was not relevant at the moment. It highlights the importance of advanced imaging techniques and specific tools that allow prompt identification of individuals at risk to facilitate early diagnosis and treatment.

5. Conclusions

Subclinical myocardial dysfunction is present in long standing HIV infection even in patients with appropriate ART and viral suppression. Myocardial work is a novel technique that allows assessment of myocardial efficiency, which may represent a sensitive marker of subclinical myocardial dysfunction, even in patients with preserved LVEF and GLS values. In our study, impaired efficiency was associated with maximum viral load.

Author Contribution

Study design: RGR, JGD. Data collection: all authors. Data review and statistical analysis: JGD, RGR. Manuscript drafting: JGD, RGR. Review, editing, and acceptance of the manuscript: all authors.

Introduction and Clinical Context

Due to the success of antiretroviral therapy (ART), infectious and immunosuppression-related complications have decreased drastically over time, and cardiovascular disease has emerged as a leading cause of mortality in people living with HIV.

The pathogenesis of this increased cardiovascular risk is multifactorial, involving a high prevalence of classic risk factors, low-grade chronic inflammation, continuous immune activation, endothelial dysfunction, prothrombotic states, and the potential toxicity of certain antiretroviral drugs. While coronary artery disease is the most common presentation, the risk of developing heart failure is also doubled in these patients. Currently, the predominant profile features asymptomatic patients with preserved ejection fraction who already exhibit diastolic dysfunction and altered subclinical mechanical parameters detectable through advanced echocardiography based on strain (*Speckle Tracking*) and myocardial work analysis.

Key Findings of the Study

- 1. Demonstrated Subclinical Dysfunction:** Despite both groups (HIV and controls) having similar and normal chamber sizes, left ventricular mass, and LVEF, HIV patients presented clear impairment in myocardial deformation indices (LV GLS and RV-FW GLS) and diastolic function parameters.
- 2. Sensitivity of Myocardial Work:** The study highlights that global work efficiency (GWE) identifies myocardial energetic inefficiency before traditional ejection fraction is impacted. The mean GWE value was significantly lower in the HIV group (92.49%) compared to the control group (94.98%).
- 3. The Weight of Virological Memory:** The finding that an impaired GWE depends on the **historic maximum viral load** suggests that prior exposure to uncontrolled viremia leaves long-lasting metabolic or structural scars on the myocardium, regardless of whether the patient currently achieves strict virological control and an undetectable viral load under ART.
- 4. Didanosine Exposure:** The univariate analysis also identified an association with past exposure to didanosine, a drug traditionally linked to mitochondrial damage.

Clinical Implications

Because conventional risk stratification tools may be insufficient for the HIV population, incorporating advanced echocardiographic techniques like myocardial work provides substantial diagnostic value. Identifying patients with subclinical dysfunction (GWE < 93%) enables closer cardiovascular follow-up and the timely optimization of preventive measures before clinical heart failure develops.

CRedit authorship contribution statement

Julia Gómez-Diego: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Raúl Gascueña-Rubia:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Carlos De Blas-Ruiz:** Writing – review & editing, Investigation, Data curation. **Miguel Cervero-Jiménez:** Validation, Investigation. **Belén Jiménez-Azzaoui:** Data curation. **Teresa Morales-Martínez:** Supervision, Data curation. **Giancarlo Ernest Candela-Ganozabe:** Investigation, Data curation. **Carlos Giraldo Carrasco-Muñoz:** Data curation. **Alberto Esteban-Fernández:** Writing – review & editing, Validation, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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