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ORIGINAL RESEARCH

No Evidence for an Association of HIV and Antiviral Treatment With Changes in Framingham Cardiovascular Risk Score in the Ndlovu Cohort Study

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BACKGROUND: HIV and antiretroviral therapy (ART) have been associated with increased cardiovascular disease (CVD) risk in high-income countries. The authors studied the longitudinal association between HIV and ART and nonlaboratory Framingham Risk Score (FRS) in a middle-income country.

METHODS AND RESULTS: This longitudinal analysis of the NCS (Ndlovu Cohort Study), South Africa used baseline to 36-month follow-up data. Demographics, HIV, ART status, and cardiometabolic measures were obtained. FRS was used as a CVD risk measure. Through linear mixed models, FRS trends over time and the association with HIV were studied. Analysis included 1136 participants, with 609 (54%) having HIV, and 495 (81%) taking ART. At baseline, 9.8% of participants had a high FRS. People living with HIV (PLHIV) had a 3.2% lower FRS than HIV-negative participants (P<0.001). FRS increased similarly for both groups over time. Other factors associated with FRS were secondary and higher education (ß value: −0.075, P<0.001; ß value: −0.084, P<0.001) and alcohol consumption (ß value: 0.011, P<0.001).

CONCLUSIONS: CVD risk increased for all participants over 36 months, suggesting classic risk factors rather than HIV status or ART to be drivers of CVD risk. People living with HIV had a significantly lower FRS than their HIV-negative counterparts, possibly related to HIV itself or a more frequent interaction with healthcare services. No association of HIV and ART with changes in FRS over 36 months was observed, suggesting the need for research using clinical endpoints to elucidate the effects of HIV and ART on CVD risk. Population-based prevention of CVD risk factors in sub-Saharan Africa is warranted, regardless of HIV status.

Key Words: antiretroviral therapy ■ cardiovascular risk factors ■ Framingham Risk Score ■ HIV ■ sub-Saharan Africa

In 2021, ≈38.4 million people worldwide were living with HIV.[1] Even though antiretroviral therapy (ART) has significantly increased the life expectancy of people living with HIV (PLHIV), in 2021 alone, as many as 650 000 people died from AIDS-related illnesses. Sub-Saharan Africa (SSA) shoulders the biggest burden (more than two-thirds) of HIV infections worldwide. In 2021, at least 78% of the PLHIV in SSA had access to ART.[1]

Currently, a composite of communicable, maternal, neonatal, and nutritional diseases are the number 1 cause of death in SSA, followed by noncommunicable diseases (NCDs), which account for ≈35% of all deaths.[2] With the increasing treatment coverage for

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CLINICAL PERSPECTIVE

What Is New?

- This study showed a longitudinal increase in cardiovascular disease risk in a rural South African population for both people living with HIV and the HIV-negative population.
- Baseline cardiovascular disease risk was higher for the HIV-negative population compared with people living with HIV.
- HIV and antiretroviral therapy were not associated with changes in Framingham Risk Score over 36 months, suggesting the need for research using clinical end points to elucidate the effects of HIV and antiretroviral therapy on cardiovascular disease risk.

What Are the Clinical Implications?

- Population-based prevention of cardiovascular disease risk factors in sub-Saharan Africa is warranted, regardless of HIV status.

Nonstandard Abbreviations and Acronyms

FRS	Framingham Risk Score
IPAQ	International Physical Activity Questionnaire
NCS	Ndlovu Cohort Study
NIDS	National Income Dynamics Study
PLHIV	people living with HIV
SSA	sub-Saharan Africa
STEPS	STEPwise approach to surveillance
WHO	World Health Organization

HIV and rapid changes in lifestyle resulting from economic growth and globalization in SSA, the burden of NCDs is rapidly rising.[3,4] Of the NCDs, cardiovascular diseases (CVDs) are the primary cause of death worldwide.[5] In 2019, >1 million deaths were caused by CVDs in SSA, thereby contributing to ≈5.4% of CVD deaths worldwide.[6] With the ongoing fall of communicable, maternal, neonatal, and nutritional diseases, >50% of all deaths in SSA are projected to be attributed to NCDs by 2030, with CVDs as the most common cause of death for NCDs.[2] This epidemiological shift in SSA calls for thorough investigation of the growing burden of CVDs to advance the needed interventions and aid the formulation of policy.[7]

With current ART, PLHIV are living longer and experiencing a rise in CVD burden.[8–10] The number of disability-adjusted life-years attributed to CVD associated with HIV status has tripled over the past 2 decades.[10] An increased risk of CVDs has been mainly shown in PLHIV in high-income countries,[11–14] suggesting that either the immune activation due to the (suppressed) chronic HIV infection or the antiretroviral medication is linked to the reported increased risk.[10,15] The high prevalence of HIV in SSA could therefore further increase CVD, emphasizing the need for further studies to elucidate the relationship between HIV, ART, and CVDs, thereby taking into consideration changes in cardiovascular risk factors at the population level in SSA, including HIV-infected populations.[11]

Cardiovascular risk assessment and treatment can improve disease prevention and CVD outcomes.[16,17] The estimation of each individual's CVD risk allows for stratification into risk categories, which enables health care workers to recommend appropriate measures. Furthermore, absolute CVD risks, shown as a percentage, are easier for the patient to interpret and aid in increasing CVD awareness, as well as treatment adherence as opposed to relative risks.[18]

Traditional CVD risk factors include smoking, alcohol consumption, hypertension, diabetes, obesity, hyperlipidemia, low physical activity, and poor diet.[2,18,19] Risk factors can be combined into a multivariable CVD risk model, used to estimate absolute CVD risk. The Framingham Risk Score (FRS) includes age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure (BP), antihypertensive medication, current smoking, and diabetes.[20,21] For use in primary health care in resource-limited settings,[22] a simpler, nonlaboratory FRS has been developed without the necessity for laboratory testing.[21] Total and high-density lipoprotein cholesterol are replaced by body mass index (BMI) in the nonlaboratory FRS.[21] Several cross-sectional studies in SSA have shown good agreement between nonlaboratory FRS with laboratory FRS as well as other standard risk scores for both individuals with and without HIV.[23–25]

This study aims to assess trends in the nonlaboratory FRS (denoted as FRS) over a 36-month period and to assess the association between FRS and HIV status and ART in a rural South African population.

METHODS

Study Setting and Population

Data were collected as part of the NCS (Ndlovu Cohort Study), a prospective cohort study in a rural area, in Elandsdoorn, Limpopo Province, South Africa. Baseline assessment of the NCS was undertaken from November 2014 to August 2017. Both HIV-negative and HIV-positive participants were recruited at local events.

All underwent HIV testing on enrollment and those who tested positive were consequently enrolled in the HIV-positive group. Next to this, participants were recruited at the local clinic (Ndlovu Medical Center), both at the HIV treatment facility as well as at the general clinic. The majority of HIV-positive participants, especially those taking ART at enrollment, were enrolled from the HIV clinic.[26] Overall, 1927 participants were included in the study, among which 46% (887) were PLHIV, and 55% (1056) were women. The inclusion criteria were age 18 years or older, ability to give written informed consent, and intent of long-term follow-up. Ethical approval for the NCS was given by the Human Research Ethics Committee at the University of Pretoria in South Africa and the Limpopo Department of Health Ethics Committee. A more detailed description of the design and methods of the NCS has been previously published.[26]

Measurements

After the baseline assessment, participants were called 6 months later and yearly thereafter to inquire about medical conditions, medication use, and lifestyle characteristics.[26] Participants were also invited to the research center annually for follow-up questionnaires and physical measurements.

Information was obtained on general characteristics, cardiovascular risk factors, HIV status, and ART. These were collected through questionnaires and included age, sex, demographics, and socioeconomic status. The 2012 NIDS (National Income Dynamics Study) Wave 3 Adults Questionnaire was used to assess employment and revenue.[27] Physical activity was measured using the International Physical Activity Questionnaire (IPAQ).[28] Employment was categorized as employed/unemployed, where the unemployed category included participants who identified as students, disabled or retired people, and volunteers. Cardiovascular risk factors including family history of CVD, alcohol use, and smoking were assessed by use of the World Health Organization (WHO) STEPwise approach to surveillance (STEPS) instrument.[29] Participants were considered to have a positive family history of CVD when a first-degree relative had experienced a stroke and/or heart attack younger than 60 years. A medical history and information on chronic medication use was collected, including diabetes and hypertension treatment.

Anthropometric measurements included height (cm) and weight (kg). Height was measured using a fixed stadiometer. Height and weight were used to calculate BMI as weight (kg)/height (m)^2. BMI category cutoffs were based on WHO guidelines: underweight (BMI <18.5), normal weight (18.5 ≤BMI <25), overweight (25≤ BMI <30), and obese (BMI ≥30).[30]

BP was measured 3-fold after a 5-minute rest with a sphygmomanometer device. The average of the second and third measurements was used for further analysis. The measurements were taken on both arms and repeated on the arm resulting in the highest values.[31]

Participants were invited to come to the research site while fasting and blood samples were drawn at baseline and used to determine fasting lipids and glucose levels, HIV viral load, and CD4$^+$ cell counts. Participants were indicated to have diabetes if either their glucose levels were ≥11.1 mmol/L, or their glycated hemoglobin (average blood sugar levels for the past 2 to 3 months) was ≥6.5%, or by the use of medication to lower blood glucose levels.[32,33] Blood samples were analyzed within 2 days at a certified laboratory (TogaLabs). In addition, viral load and CD4$^+$ were obtained at each follow-up visit to the NCS research center.

All participants who were HIV-negative or had an unknown HIV status underwent HIV testing on enrollment and at each follow-up visit using an antibody-based point-of-care test. Positive tests were confirmed with a second, different, point-of-care test according to the Department of Health guidelines.[26,31] ART treatment status was assessed by self-report and complemented with data from the electronic HIV registry (TIER.net).[26] TIER.net is an HIV and tuberculosis monitoring system developed to harmonize disease registration and treatment processes in low- and middle-income countries.[34] Details regarding ART treatment such as time between diagnosis and treatment initiation and which medications were prescribed were recorded.[26] If only the year of HIV diagnosis and/or treatment initiation was known, the date was set to July 1. If only the date of start of HIV diagnosis was unknown, the date was set to the start date of HIV treatment. Furthermore, treatment responses were measured through plasma viral loads and CD4 counts.

Cardiovascular Risk Profile

Nonlaboratory FRS was used to estimate 10-year CVD risk.[21] The FRS was originally geared towards a population between the ages of 30 and 74 years. The FRS can be categorized into low (<10%), medium (10%–20%), and high risk (>20%). Table S1 provides the respective weights of each risk factor to estimate the FRS for men and women separately.

Data Analysis

Data for analysis comprised all participants enrolled in the study at baseline and attending at least one of the follow-up time points. A comparison between the analytic sample (n=1591) and the population lost to follow-up (n=336) is shown in Table S2. After exclusion of individuals lost to follow-up (n=336), the

data set consisted of 1591 participants, with on average between 3 and 4 time points per individual. Baseline descriptive statistics separated by HIV status are shown in Table S3. Considering that the FRS was developed for a population aged between 30 and 74 years, all participants outside of that range at baseline were removed from the data set (n=455). The final data set for analysis comprised 1136 participants (Figure 1).

Continuous population characteristics with a normal distribution are reported as mean and SD, whereas skewed data are shown using medians and interquartile ranges (IQRs). Categorical variables are represented with numbers and percentages. The nonlaboratory FRS was calculated for each participant at each time point according to D'Agostino et al.[21]

The distribution of low (<10%), medium (10%–20%), and high (>20%) 10-year CVD risk is shown using frequency counts and percentages between baseline and the end of the 36-month follow-up period.[35] Subsequently, average FRS per HIV group (positive versus negative) and HIV subgroup (HIV-negative, HIV-positive taking ART, HIV ART-naïve) were compared over time to investigate the association between HIV, ART, and FRS over time. The Kruskal-Wallis test was used to test for differences between the HIV (sub) groups at each time point, followed by a pairwise comparison using Wilcoxon rank sum test.

A linear mixed effects model with a random intercept and a random slope per participant was used to fit the data to account for baseline differences and different rates of change in logarithmic FRS over time, respectively. A logarithmic transformation of the FRS was used to correct for a skewed distribution of the FRS. An interaction between time point and HIV group was added to allow the effect of time to differ between HIV groups. The model was adjusted for known confounders of CVD risk and mortality: alcohol consumption, employment, education, and physical activity.[36] These were tested as categorical covariates with a bivariate variable for employment and alcohol consumption: yes or no; 3 levels for physical activity: low, moderate, and high; and 4 levels for educational attainment: none, primary, secondary or matric, or college or university. Model selection was based on the Akaike information criterion and run in R Studio version 1.4.1106 (Posit Software).

To assess FRS trends over time, 2 approaches were used to categorize the population: (1) according to HIV status (HIV positive, HIV negative) and (2) according to ART treatment (HIV negative, HIV positive on ART, HIV positive, and ART naïve). Classification into the different groups was based on self-reported treatment and updated by use of information recorded in TIER.net, as described in Vos et al (2020).[31] These classifications were flexible over time, meaning that the participants could change between treatment groups between follow-up time points. The final models for both approaches were estimated using maximum likelihood. The fixed effects for the models were: HIV (sub) group, visit (as categorical), an interaction between HIV (sub)group and visit, education, employment, and alcohol consumption over the past 30 days. The reference category was the HIV-negative group, at baseline, without education, without employment, and no alcohol consumption over the past 30 days. Results are presented as back transformed (from logarithmic-transformed dependent variable) regression coefficients with 95% CIs and marginal means. A 2-sided P value ≤0.05 was considered significant. R Studio version 1.4.1106 was used for all data analysis and visualization.[37]

Between January 1, 2016 and November 31, 2017, BP measurements were obtained by use of a nonvalidated wrist device, which resulted in ≈52% of nonstandard BP measurements. This included 41% and 97% of BP measurements for baseline and 12-month follow-up, respectively. Due to the high percentage of nonstandard measurements for 12-month follow-up, this time point was completely removed from the analysis. For all other population characteristics and HIV-related variables, percentage missing data was ≤0.1% missing, except for the variables categorical income per month (under the poverty line, which is defined as <648 South African Rand[31]), alcohol use in the past 30 days, glycated hemoglobin levels, and total cholesterol, which had 6.5%, 17.3%, 24.6%, and 0.7% missing values, respectively. Linear mixed models were built based on a reduced number of observations, without imputation of the missing data.

Data that support the findings of this study are available from the corresponding author upon reasonable request.

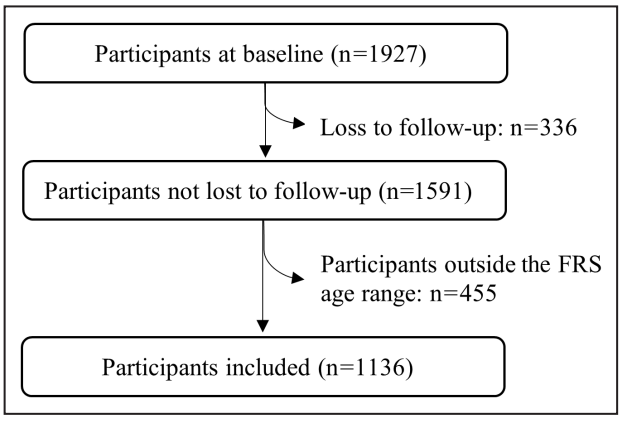

Figure 1. Flow chart for patient exclusion.
Excluded patients were removed from all time points for analysis.

RESULTS

Baseline population characteristics for the 1136 study participants (56% women; average age, 45 years [SD, 9.5 years]) are shown in Table 1. The average BMI at baseline was 25 kg/m^2 (SD, 6.5 kg/m^2). The mean systolic BP was 121 mm Hg (SD, 23.4 mm Hg). Smoking was reported by 481 participants (42%), of whom 324 (67%) were current smokers. A positive family history for CVD was indicated by 2.8% of the population. Alcohol consumption during the preceding 30 days was reported by 355 (31%) of the participants. At baseline, the number of participants per HIV treatment category was 527 (46%) HIV-negative, 114 (10%) HIV-positive and ART-naïve, and 444 (39%) HIV-positive taking ART. PLHIV taking first- and second-line ART were merged due to the small number of participants taking second-line ART (n=51). A comparison of baseline population characteristics showed significant differences between PLHIV and the HIV negative population for the variables age, sex, education, employment, relationship, smoking, and family history of CVD. Both groups were compared using Mann–Whitney *U* test and Fisher exact test for continuous and categorical data, respectively (Table S3). Table 2 shows baseline characteristics acquired through medical assessment per HIV subgroup. For PLHIV, the median CD4 cell count at baseline was 585 (IQR, 384–764). Of the participants living with HIV, 413 (68%) had an undetectable viral load (<50 copies/mL).

Table 1. Study Population Characteristics at Baseline (n=1136) in the NCS—South Africa

Variable	Distribution
Demographics and socioeconomic background	
Age, mean (SD), y	45 (9.51)
Women, No. (%)	638 (56.2)
Highest level of education	
None, No. (%)	61 (5.4)
Primary	303 (26.7)
Secondary and matric	676 (59.5)
College and university	96 (8.4)
Employment	
Unemployed, No. (%)	839 (73.9)
Employed	297 (26.1)
Income per person/mo in ZAR*	
<648	749 (65.9)
648–992	87 (7.6)
>992	300 (26.9)
Stable relationship (married, life partner, cohabiting)	685 (60.3)
Cardiovascular risk factors	
Alcohol use, ever	729 (64.2)
Alcohol use, past 30 d	355 (31.3)
Smoking	
Ever	481 (42.3)
Current	324 (28.5)
Cigarettes/cigars per day, median (IQR)	0 (0–2)
Positive family history for CVD	32 (2.8)
Physical activity, MET-min/wk†	
Low	488 (43.0)
Moderate	401 (35.3)
High	247 (21.7)

CVD indicates cardiovascular disease; NCS, Ndlovu Cohort Study; IQR, interquartile range; and ZAR, South African Rand.

*Lower bound poverty line: <648, upper bound poverty line: >992, as defined at baseline.[27]

†The metabolic equivalent task (MET)-min/wk is a weighted average calculated by average duration×frequency per week×intensity (MET) summed for all physical activity domains. MET is a measure for intensity of physical activity that enables comparison of different types of exercise/movement. MET-min/wk are categorized into low, moderate, and high categories for respective values of <600 MET-min/wk, 600–3000 MET-min/wk, and >3000 MET-min/wk.

FRS at Baseline and Over Time

At baseline, 75%, 16%, and 9% of the participants were at low, medium, and high CVD risk, respectively. The median FRS for the entire population at baseline was 0.044 (IQR, 0.018–0.101). Median FRS for the complete population changed from 0.044 to 0.060 during the follow-up period. No changes in the distribution over the FRS categories over time were observed (Figure 2).

FRS by HIV Groups Over Time

A comparison of the stratified median FRS by HIV status (PLHIV versus HIV-negative population) showed no change in FRS over time by group. The median FRS from baseline to 24- and 36-month follow-up was 3.2% (IQR, 5.9%), 4.2% (IQR, 6.8%), and 3.9% (IQR, 6.3%) for the HIV-positive group, respectively. For the HIV-negative group, these values were 6.4% (IQR, 10.7%), 8.0% (IQR, 10.6%), and 8.4% (IQR, 10.7%), respectively (Figure 3). However, the linear mixed model results did show a significant increase of FRS over time, when corrected for other covariates (Table 3). The HIV-positive group had roughly a 50% lower median FRS at each time point compared with the HIV-negative group (Kruskal-Wallis test, $P \leq 0.05$) (Figure 3).

Patterns in FRS by HIV Treatment Groups Over Time

A significant increase in median FRS from baseline to 36-month follow-up was observed for the HIV-negative group and PLHIV taking ART. The HIV-positive, ART-naïve group showed a significant increase in median FRS from baseline to 24-month follow-up (+0.053, P=0.04), followed by no significant change from 24 to 36 months (–0.050, P=0.08) (Figure 4). Analysis

Table 2. HIV-Related Population Characteristics at Baseline in the NCS—South Africa

Variable	HIV-negative (n=527)	ART-naïve (n=114)	HIV-positive, taking ART (n=495)
Physical examination			
Average systolic BP, mean (SD), mm Hg*	128 (24.9)	120 (22.3)	115 (19.9)
Average diastolic BP, mean (SD), mm Hg*	80 (14.1)	78 (13.2)	74 (13.0)
BMI, mean (SD), kg/m^2	26.4 (6.7)	24.0 (6.7)	23.8 (5.8)
Waist circumference, mean (SD), cm	87.8 (13.6)	84.1 (13.6)	85.5 (12.4)
Hip circumference mean (SD), cm	102.9 (14.4)	100.6 (15.2)	99.9 (13.6)
Laboratory analysis			
Fasting glucose, mean (SD), mmol/L	5.50 (3.47)	4.72 (0.90)	4.90 (1.17)
Glycated hemoglobin, mean (SD), %	5.81 (1.18)	5.55 (0.39)	5.62 (0.62)
Total cholesterol, median (SD), mmol/L	4.5 (1.06)	4.0 (0.94)	4.4 (0.98)
Nonlaboratory FRS			
Median FRS (IQR), %	6.4 (2.6–13.2)	3.5 (1.6–7.0)	3.2 (1.3–7.3)
HIV-related characteristics			
Time since HIV diagnosis,, mean (SD), mo		15 (36.3)	78 (50.7)
Newly diagnosed at enrollment, No. (%)		82 (72)	0 (0.0)
Time on ART, median (SD), mo		0 (0.2)	64 (44.1)
CD4$^+$ cell count, cells/mm^3, mean (SD)		445 (273)	528 (248)
CD4$^+$ <200 cells/mm^3, No. (%)		22 (19.3)	36 (7.3)
Viral load, copies/mL, No. (%)			
<50		24 (21.1)	389 (78.6)
50–1000		18 (15.8)	44 (8.9)
>1000		71 (62.3)	56 (11.3)

ART indicates antiretroviral therapy; BMI, body mass index; FRS, Framingham Risk Score; IQR, interquartile range and NCS, Ndlovu Cohort Study.
*All of the blood pressure (BP) measurements were taken; however, 41.3% of these were with a nonvalidated device.

allowed for participants to change treatment groups over time, resulting in 114, 21, and 16 ART-naïve PLHIV at baseline, 24-month, and 36-month follow-up, respectively.

Modeling FRS by HIV Groups Over Time

Table 3 shows the results of the linear mixed model analysis investigating the association between FRS and HIV status and time, corrected for education, employment, and alcohol consumption. An overall increase in FRS over time was observed for the entire population. The reference category (HIV-negative, unemployed, no education, no alcohol consumption) at 24- and 36-month follow-up had a respective 36% and 35% increase (P<0.001) in FRS compared with baseline. The interaction effect between HIV status and time was only significant for the 24-month follow-up time point. For PLHIV, the effect of time at 24-month follow-up increases the FRS by an additional 16%. Compared with the HIV-negative population, the effect of living with HIV reduced the FRS by 38% at baseline and 36-month follow-up, whereas the reduction was (38% minus 16%) 22% at 24-month follow-up. Compared with no education, secondary and matric and college and university education significantly changed (P<0.001) the FRS, with a respective decrease of 57% and 61%. Primary education attainment reduced the FRS by 10% but was not statistically significant. Being employed significantly increased the FRS by 8%. Alcohol consumption over the past 30 days significantly increased the FRS by 19%.

DISCUSSION

In the NCS, the HIV-negative population was observed to have a higher FRS at baseline and over time compared with PLHIV. This difference in FRS between both groups was primarily seen at baseline. However, based on the significant interaction between HIV status and time at 24 months it seems that there is also a difference in FRS trajectory between the HIV-positive and HIV-negative participants. The proposed explanation for the increase in FRS with employment is that employment is associated with income, and hence being better off economically, which was shown in the INTERHEART Africa study conducted in South Africa, to be positively associated with myocardial infarction in Black Africans, while the inverse was true for Europeans.[38] Another study conducted in South Africa showed a positive association between BMI (as a

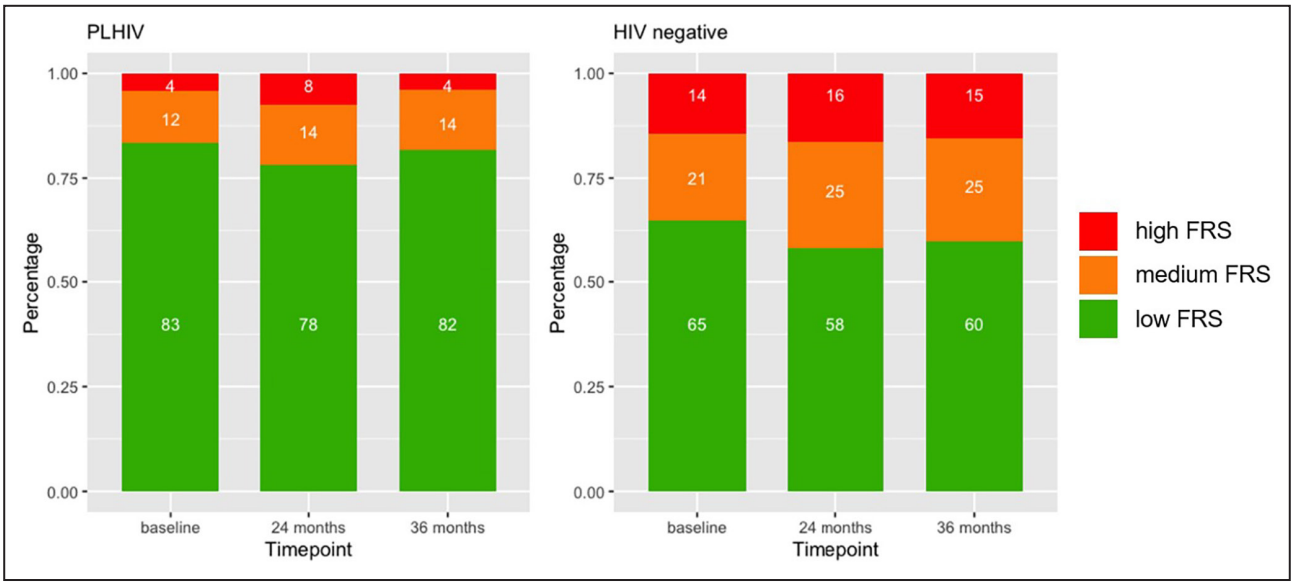

Figure 2. Distribution Framingham Risk Score (FRS) risk categories in the Ndlovu Cohort Study according to HIV status over time.
Low, medium, and high FRS are categorized by FRS values of <10%, 10% to 20%, and >20%, respectively. PLHIV indicates people living with HIV.

marker of CVD risk) and being employed, although this result was significant only for the male population.[39]

For PLHIV, median FRS for the HIV-positive ART-naïve group peaked at 24-month follow-up (Figure 4); however, given the small number of HIV-positive ART-naïve participants in the current study, this finding should be interpreted with caution. This observation was further supported by the presence of a significant interaction between HIV status and time at 24-month follow-up. Future analysis comparing different ART regimens can provide insight into the possible effect of ART on FRS. The absence of a significant interaction at 36-month follow-up is believed to be related to loss of follow-up of the study population over time. The percentage of participants lost from baseline to 36-month follow-up for the HIV-negative and HIV-positive population was 18.6% and 29.7%, respectively, which might have limited the power to detect a difference in trend in FRS development over time.

For PLHIV, we observed an ≈50% smaller median FRS for each time point after baseline, compared with the HIV-negative population. Previous cross-sectional results from the NCS observed HIV positivity to be associated with a better CVD risk profile,[31,40] and other studies in SSA have consistently found lower BP values (an

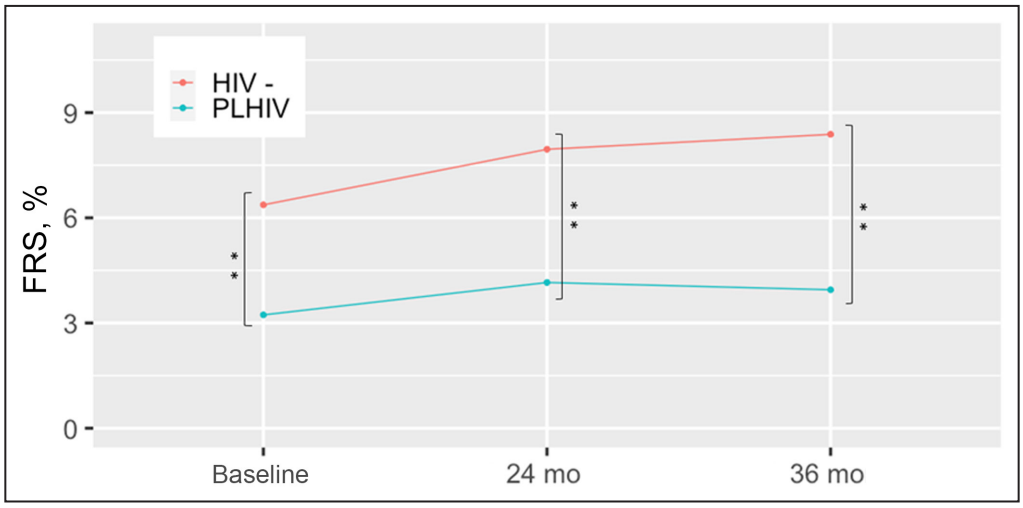

Figure 3. Median Framingham Risk Score (FRS) for people living with HIV (PLHIV) and those who are HIV-negative from baseline to 36-month follow-up in the Ndlovu Cohort Study, South Africa.
Statistical significance for the difference in FRS between HIV groups at each time point was tested using the Kruskal-Wallis test. * $P>0.05$; ** $P\leq0.05$.

Table 3. Results From the Multivariable Linear Mixed Model Showing Estimates for FRS in Relation to Time, HIV Status, Education, Alcohol Consumption, and Employment

Fixed effects		
	Regression coefficient (95% CI)	*P* value*
Intercept	0.095 (0.072–0.123)	<0.001
Time point		
Baseline	Reference	
Follow up visit at 24 mo	1.362 (1.291–1.437)	<0.001
Follow up visit at 36 mo	1.345 (1.271–1.423)	<0.001
HIV status		
Negative	Reference	
PLH	0.621 (0.546–0.705)	<0.001
Highest level of education		
None	Reference	
Primary	0.901 (0.679–1.195)	0.468
Secondary and matric	0.426 (0.325–0.559)	<0.001
College and university	0.393 (0.285–0.542)	<0.001
Employment		
No	Reference	
Yes	1.084 (1.020–1.151)	0.010
Alcohol use, past 30 d		
No	Reference	
Yes	1.192 (1.121–1.267)	<0.001
Interaction HIV status×time point		
PLHIV×24-mo follow-up visit	1.159 (1.067–1.259)	<0.001
PLHIV×36-mo follow-up visit	1.068 (0.978–1.166)	0.143

Back-transformed (logarithmic transformation of Framingham Risk Score (FRS) regression coefficients. To be interpreted as mulitplicative effects. PLHIV indicates people living with HIV.

*Statistical significance was considered as a 2-sided $P<0.05$.

important marker for CVD risk) for PLHIV.[41–43] A likely explanation may be the possibility of a more frequent contact with health care workers and hence being more likely to receive counseling on CVD risk factors.[25,44] However, the percentage of people reporting the use of antihypertension treatment in the NCS was 2- to 3-fold higher for the HIV-negative population compared with PLHIV for all time points. This suggests that the use of medication to lower BP is not the main driver for the reduced CVD risk in PLHIV and that there might be a direct effect of HIV infection (or ART) in reducing BP for PLHIV.[45,46] This could also explain the reduced FRS observed for PLHIV, as BP is one of the covariates used to calculate FRS. How this affects the development of CVD is currently unknown.

To date, longitudinal studies on the association of HIV and CVD are scarce and have reported inconsistent results. The best evidence so far, a systematic review by Shaw et al,[10] reported a 2-fold increase in the likelihood of CVD for PLHIV as compared with their HIV-negative counterparts in the SSA region, despite the fact that studies using surrogate outcomes or risk scores found an equal or even lower CVD risk for PLHIV. Hence, the use of FRS and other surrogate markers as reliable tools for predicting CVD risk/events still needs to be elucidated as they have not been validated in the SSA PLHIV population. Furthermore, these tools do not take into account the effects of inflammation, which even though reduced by ART, do generally not return to normal levels for PLHIV.[47]

Two studies in high-income countries show varying results. A study by Hsue et al[48] reported differential rates of carotid intima-media thickness over time, with a steeper increase for PLHIV compared with HIV-negative participants (San Francisco, CA). Another study from the United States with HIV-positive ART-naïve participants and matched HIV-negative controls reported similar progression in carotid intima-media thickness levels between both groups (Cleveland, OH).[49] However, as PLHIV in SSA represent a different population and risk factor profile, the trends in CVD observed in PLHIV in high-income countries are likely different than trends expected in the SSA population of PLHIV.

Strengths and Limitations

The main strength of the current study is the longitudinal analysis along with the inclusion of HIV-negative controls aimed to determine the long-term effect of HIV infection and/or it treatment on CVD risk. Another strength is inclusion of participants at both local events and the hospital, likely resulting in good representation of the community in the study population. An important limitation was the absence of BP measures from a standard device between January 2016 and November 2017, with the resulting exclusion of the 12-month follow-up time point from the analysis. A further limitation of the current analysis is related to the small sample size of the ART second-line treatment groups, which foreclosed any assessment of CVD risk related to HIV treatment at the time. Over time, the ART second-line treatment group may increase, allowing for future analysis based on a larger sample size. As of 2017, every person diagnosed with HIV should be able to start ART immediately, thus the disentanglement of the effects of HIV diagnosis and ART on CVD risk will be of little importance. The current data reflect ART used at the time of inclusion in the cohort study along with regimens with possibly more side effects for people who had been taking ART for a longer time prior to inclusion. Furthermore, before implementation of immediate ART treatment on HIV diagnosis and the current test-and-treat strategy, PLHIV were more likely to have uncontrolled viral loads for longer time periods, resulting in lower nadir CD4 cell counts, which has been associated with an increased CVD risk. This

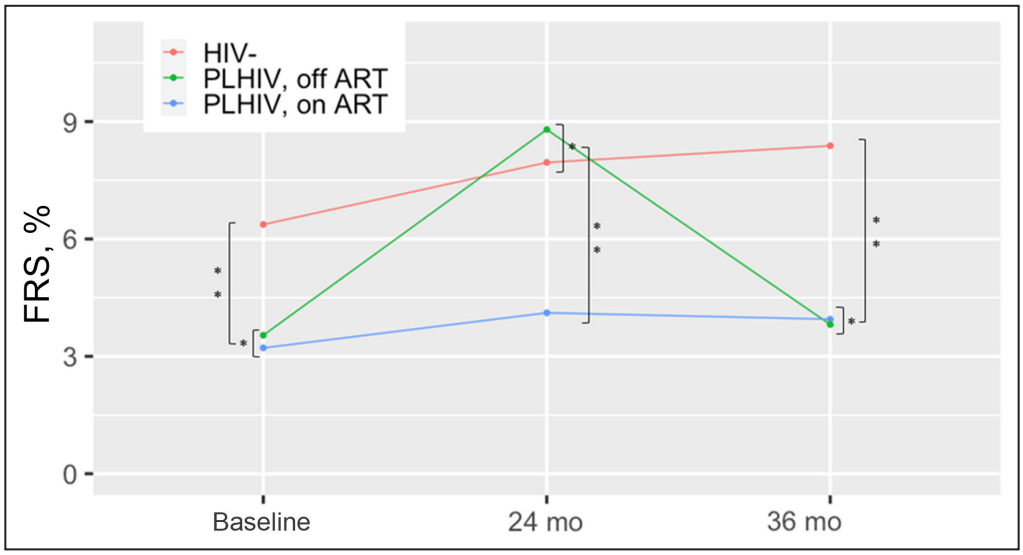

Figure 4. Median Framingham Risk Score (FRS) for HIV treatment groups: people living with HIV (PLHIV) taking antiretroviral therapy (ART), PLHIV off ART, and HIV-negative participants from baseline to 36-month follow-up in the Ndlovu Cohort Study, South Africa.
The results for PLHIV off ART should be interpreted with caution due to the small sample size at 24- and 36-month follow-up visits (n=21 and n=16, respectively). Statistical significance for the difference in FRS between HIV subgroups at each time point was tested using the Kruskal-Wallis test, followed by the Wilcoxon rank sum test. * $P>0.05$; ** $P\leq0.05$.

means that the current instruments evaluating CVD risk might not accurately predict CVD risk in PLHIV. Last, FRS estimates 10-year CVD risk; only future inclusion of CVD outcomes will allow us to validate the predictive ability of the FRS in the Ndlovu cohort and similar SSA-based populations.

Future Research

There is a clear need for further longitudinal large-scale studies assessing the association of HIV and its treatment with CVD risk in order to reconcile the perceived lower risk profiles for PLHIV in SSA with actual observations of a higher incidence of cardiovascular events. Furthermore, new data in the test-and-treat era, where patients have not been exposed to prolonged viremia and older, more toxic drug regimens, might also show different patterns of CVD risk. The high frequency of conventional CVD risk factors (eg, tobacco use, unhealthy diets, low physical activity, and increased use of alcohol) among PLHIV and those without HIV calls for a population-based approach for CVD prevention.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S3

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