Abstract

Objectives: Understanding of the interplay between human immunodeficiency virus (HIV) and cardiovascular disease, especially in Africa, is limited to evidence from longitudinal studies. Therefore the demographic profile and cardiometabolic, renal and liver function of an HIV-infected South African population were profiled from 2005 to 2015.

Methods: The study included 117 HIV-infected and 131 uninfected controls that were examined at baseline, five and 10 years.

Results: Mortality rate declined from 24% (2005–2010) to 0% (2010–2015) after the introduction of ART. Longitudinal increases in C-reactive protein \( p = 0.002 \), alanine transaminase \( p = 0.006 \) and gamma-glutamyl transferase \( p = 0.046 \) levels and estimated glomerular filtration rate \( p < 0.001 \) were seen only in the HIV-infected group. This group also showed increased high-density lipoprotein cholesterol (HDL-C) \( p < 0.001 \) and total cholesterol \( p < 0.001 \) levels and decreased triglyceride:HDL-C \( p = 0.011 \) levels. Low-density lipoprotein cholesterol decreased in both groups \( p < 0.001 \).

Conclusion: Despite trajectories of deranged lipid and inflammatory profiles, the cardiometabolic disease risk seems stable in HIV-infected South Africans. Inflammation and renal and liver function warrant regular monitoring.

Keywords: human immunodeficiency virus, antiretroviral therapy, cardiometabolic factors, renal function, liver enzymes, South Africa

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Since the discovery of the human immunodeficiency virus (HIV) in the 1980s, the global prevalence of HIV infection has increased from 7.6 million patients in 1990 to 36.7 million in 2017. Of global infections, eastern and southern Africa contributed 53% of new infections and include 19.6 million people living with HIV in these regions.

The HIV epidemic in South Africa received significant attention during the 1990s, due to the growing incidence of HIV infection and deaths related to acquired immunodeficiency syndrome (AIDS). In order to address the growing burden of HIV/AIDS, the South African government implemented the antiretroviral therapy (ART) roll-out programme for HIV-infected patients in April 2004, which is now the world’s largest ART roll-out programme. The use of ART has improved the life expectancy of people infected with HIV in a country that has seen a dramatic increase in the number of HIV-infected patients, namely 11.5% (5.35 million) in 2005 to 12.5% (6.19 million) in 2015 (Fig. 1) and 12.6% (7.1 million) in 2017. Despite various campaigns to reduce HIV infection rates, South Africa continues to bear a disproportionate share of the global burden of HIV, as the highest rates of new HIV infection are still reported in South Africa.

The era of ART has exposed new challenges, including cardiometabolic changes such as elevated blood pressure, dyslipidaemia, lipodystrophy and chronic inflammation, which are all associated with increased development of cardiovascular disease (CVD). The use of ART is associated with hepatotoxicity, which often manifests as liver disease in HIV-infected patients. In addition, renal disease, characterised by higher urinary protein excretion and elevated serum creatinine, was observed in HIV-infected individuals. With 56% of the HIV-infected patients on ART in South Africa, the prevalence of cardiometabolic and renal diseases in HIV-infected patients has increased.

The HIV-infected population is at a higher risk of developing CVD due to the complex interlinkage between HIV, ART and cardiometabolic disease. Furthermore, sub-Saharan Africa is faced with co-epidemics of HIV infection and CVD. Further research is required to understand the nexus between these conditions, and limited evidence is available from longitudinal studies in Africa.

In a cross-sectional analysis of 300 newly diagnosed HIV-infected, ART-naïve individuals individually matched with uninfected controls by age, gender, body mass index (BMI) and locality, we previously reported dyslipidaemia and inflammation in the HIV-infected group, which suggested increased risk for the development of CVD. In this study, HIV-infected black Africans and controls were followed over 10 years to profile the
demographic factors and to investigate the impact of long-term HIV infection and ART use on cardiometabolic factors, as well as liver and renal function.

Methods

This study is embedded within the Prospective Urban and Rural Epidemiology (PURE) study, which is a multinational longitudinal study examining changes in lifestyle and focusing on low-, middle- and high-income countries. In the South African leg of the PURE study, performed in the North West Province, 2 010 participants were randomly recruited from Potchefstroom (urban \(n = 1 004\)) and Ganyesa (rural \(n = 1 006\)). Data were collected on three occasions, at baseline in 2005, and follow up in 2010 and 2015. Black individuals older than 35 years were invited to take part in the study and were fully informed, procedures were explained and they gave written informed consent. Pregnant and lactating women were excluded.

During the 2010 follow up, 1 288 subjects participated in the study, while 221 died and 501 were lost to follow up. In the second follow up in 2015, 926 returned for follow up and 127 deaths were recorded, while 307 did not return for follow up. The attrition level of participants from baseline (2005: \(n = 2 005\)) to follow up (2015: \(n = 926\)) is similar to previous longitudinal studies as a result of refusal to take part, relocation to other locations of the country, ill health of older individuals and death.

In the current study, at baseline in 2005, 320 of the total study population of 2 010 were newly identified with HIV, and at the 10-year follow up, 117 were retained. The 320 newly identified HIV-infected participants were matched with uninfected controls according to age, gender, BMI and locality at baseline. For this longitudinal study, we followed 117 HIV-infected and 131 uninfected participants who participated in the 10-year follow-up data collection. The study population is outlined in Fig. 2.

In 2005, the participants who were newly diagnosed with HIV and were ART-naïve were referred for follow up and CD4 cell count determination to initiate ART according to the guidelines of the South African Department of Health. Five years later (2010), 70 were on ART, which increased to 77 in 2015. ART comprised two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) (Fig. 1).
In South Africa, the ART guidelines changed over the 10 years of follow up. In 2004, when ART was introduced, stavudine was the backbone of the ART regimen. However, it was phased out due to its association with lipodystrophy and was replaced with tenofovir in 2010. Fixed-dose combination was introduced in 2012, and a ‘test-and-treat’ programme was implemented in September 2016. The PURE study was approved by the Health Research Ethics Committee of the North-West University, South Africa. The study protocol and procedures were explained to the participants in their home language (Setswana) and they gave written informed consent.

Questionnaires were used to collect data on demographic information, current health status, medical and family history, medication as well as tobacco and alcohol use. Standardised procedures were used for anthropometric measurements, including height, weight and waist and hip circumferences. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were taken, in duplicate at an interval of five minutes on the right arm while in a sitting position. The validated OMRON HEM-757 device was used at baseline and at the 2010 follow up while the OMRON M6 device (Omron Healthcare, Kyoto, Japan) was used during the 2015 follow up. Venous blood samples were collected from the participants after fasting for at least eight hours. Serum and plasma were prepared and along with spot urine samples, stored at –80°C.

Glucose levels from fluoride plasma samples were determined using the Vitros DT6011 chemistry analyser (Ortho-Clinical Diagnostics, Rochester, New York, USA) in 2005 and the Cobas Integra 400 plus (Roche, Indianapolis, IN) at follow up. Glycated haemoglobin (HbA1c) was determined using the D-10 haemoglobin testing system from Bio-Rad (Hercules, California, USA).

Serum samples were used to analyse levels of high-sensitivity C-reactive protein (hsCRP), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), γ-glutamyltransferase (GGT), aspartate transaminase (AST), alanine transaminase (ALT) and creatinine using a Konelab20iTM auto-analyser (Thermo Fisher Scientific Oy, Vantaa, Finland) in 2005 and a Cobas Integra 400 plus auto-analyser (Roche, Indianapolis, IN) in 2010 and 2015. Low-density lipoprotein cholesterol (LDL-C) levels were calculated. Estimated glomerular filtration rate (eGFR) was determined using the chronic kidney disease epidemiology collaboration.

**Fig. 2.** Outline of the study population. ART, antiretroviral therapy; BMI, body mass index; HIV, human immunodeficiency virus; n, number of participants; PURE, Prospective Urban and Rural Epidemiology study. *Two of the participants were excluded due to incomplete data. *Participants who were not followed up in 2010 but in 2015: 11 HIV-infected and 11 uninfected participants.
The HIV status of all participants was determined from whole blood finger-prick using the first response rapid HIV card test (Premier Medical Corporation Limited, Daman, India). The HIV-infected group (Table 1) declined from 24% (2005–2010) to 0% (2010–2015). To establish whether certain attributes could be ascribed to lost or deceased participants during the 10-year follow up, baseline characteristics were compared of the HIV-infected group followed, and those lost to follow up and deceased (Table 2). The deceased HIV-infected participants were older (p = 0.002) and showed higher heart rates (p = 0.001), lower HDL-C (p = 0.024) levels, higher lipid ratios (all p ≤ 0.033), and HbA1c (p = 0.044), CRP (p < 0.001) and GGT (p = 0.046) levels compared to those followed and lost to follow up.

In Table 3 the 10-year percentage change between the HIV-infected and uninfected groups was compared. No differences were seen in the percentage change in blood pressure and body composition between the groups, however TC and HDL-C levels increased in the HIV-infected group, opposed to a decrease in the uninfected (all p < 0.001) group. Although LDL-C (–1.9 vs –16%, p < 0.001) level decreased in both groups, a lesser decrease was noted in the HIV-infected group. The change in TG:HDLC differed between the HIV-infected and uninfected groups (–8.1 vs 21%, p = 0.011).

Glucose level increased more (8.5 vs 4.7%, p = 0.046) while HbA1c level remained the same in the HIV-infected group compared to an increase in the uninfected group (0 vs 2.1%, p = 0.009). The HIV-infected group displayed a greater increase in CRP (76 vs 0.1%, p = 0.047), ALT (25 vs –19%, p < 0.001) and GGT (12 vs –34%, p < 0.001) levels compared to the uninfected group. The HIV-infected group showed an increase in eGFR (4.8 vs –2.1%, p = 0.010) while in the uninfected group, eGFR declined.

The change in cardiometabolic characteristics of the HIV-infected and uninfected participants was determined over the three data-collection time points (Table 4). For this analysis, fewer participants were available due to missing data for 2010 for some variables. In the HIV-infected group, TC, LDL-C and TG:HDLC (all p ≤ 0.88) remained the same, but HDL-C level increased (p = 0.017), whereas in the uninfected group, all the above lipids decreased over time (all p ≥ 0.023). The HIV-infected group showed no changes for AST (p = 0.11) and an increase in ALT (p = 0.006) and GGT (p = 0.046) levels, while these markers all decreased (all p ≤ 0.002) in the uninfected participants. In the HIV-infected group, CRP level increased (p = 0.002) while in the uninfected group it did not change (p = 0.45). An increase in uACR was noted in the HIV-infected (p < 0.001) and uninfected participants (p < 0.001), and eGFR (p < 0.001) increased over time in the HIV-infected group, whereas in the uninfected counterparts, no change was seen (p = 0.53).

Table 5 shows the proportion and percentage of cardiometabolic risk factors of the HIV-infected and uninfected individuals over 10 years. A smaller proportion of the HIV-infected participants had elevated blood pressure than the uninfected controls at both baseline (p = 0.011) and five years later (p = 0.043). At baseline, more of the HIV-infected men had elevated HDL-C levels compared to the uninfected men (p = 0.016). Five years later, the HIV-infected men and women presented with a smaller proportion of individuals with elevated HDL-C levels compared to the uninfected men (p = 0.046) and women (p = 0.002). A larger proportion of the uninfected women showed central obesity at the 2010 (p = 0.003) and 2015 follow up (p = 0.022) compared to the HIV-infected women.
Discussion

With 12.7% of the PURE study participants living with HIV after 10 years, the frequency of HIV is aligned with the national South African prevalence (12.5%). The aims of the Joint United Nations Programme on HIV/AIDS (UNAIDS) is to increase the number of HIV-infected patients on ART, and this is in agreement with our data, indicating an almost two-fold increase in ART, from 46% in 2010 to 85% in 2015 in our study cohort. However, in the total South African population, this is not reflected, since the use of ART is estimated at 56%. Even though only 46% of the HIV-infected cohort was on ART in 2010, a marked decline in mortality rate was observed, corresponding well with the global decline in mortality rate with ART use. The HIV-infected participants were younger compared to their counterparts, and showed no difference in chronic medication use. These factors together with the beneficial effect of ART may have contributed to the observed decline in mortality rate.

When tracking the HIV-infected participants and their
controls over 10 years, similar changes in blood pressure and body composition were noted, but notable differences were seen for lipid profile and trajectory of elevated CRP, liver enzymes and eGFR in the HIV-infected group. Contrary to expectations, the HIV-infected participants displayed an increase in eGFR, which may suggest improved renal function with ART use. However, if the data are reviewed as a trajectory towards possible future outcomes, continued increases in eGFR may reach the hyperfiltration range, which precedes the development of renal disease. Additionally, this population is exposed to risk factors such as ageing, and use of tobacco, alcohol and antihypertensive medication, which may in the future increase their CVD risk.

A previous study using the PURE study population reported dyslipidaemia in the newly diagnosed HIV-infected, ART-naïve black Africans.13 Now, based on the 10-year follow-up data with 85% of the HIV-infected participants on ART, this current study reports an increase in HDL-C and TC levels and a decrease in TG/HDL-C in the HIV-infected compared to the uninfected controls.

In support of the increase in HDL-C levels, more of the HIV-infected participants displayed an increase in eGFR, which may suggest improved renal function with ART use. However, if the data are reviewed as a trajectory towards possible future outcomes, continued increases in eGFR may reach the hyperfiltration range, which precedes the development of renal disease. Additionally, this population is exposed to risk factors such as ageing, and use of tobacco, alcohol and antihypertensive medication, which may in the future increase their CVD risk.24
with lower HDL-C levels, while after 10 years, no difference was observed. Higher HDL-C is cardioprotective, and this finding is consistent with a study that reported an increase in HDL-C level over 96 weeks in HIV-infected patients on a first-line regimen, especially nevirapine (NVP). The participants in this study were using NVP (Fig. 1), which is associated with favourable lipid changes.

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ART use, and CRP elevation was associated with HIV disease progression.31 The finding of this study supports persistent low-grade inflammation in HIV-infected patients, even after long-term ART, which may be a result of on-going viral replication or microbial translocation.7 Moreover, CRP is associated with CVD risk and all-cause mortality not only in the general population,33 but also in HIV-infected patients.9

Inflammation may be further aggravated in the presence of oxidative stress, which may be a consequence of both HIV infection and ART.4 Higher levels of GGT were seen, a liver enzyme known to play an important role in maintaining glutathione homeostasis and normal redox status,1 along with a greater increase in GFR over 10 years in the HIV-infected group. Where others reported that ART lowered serum GGT in HIV-infected patients,30 the findings of this study did not support this, which could be attributed to the effects of the nucleosides.38 The use of GGT applies beyond oxidative stress, as it is also a marker of non-fatty and alcohol-related liver disease.10 Although self-reported alcohol use was high in our study, it did not differ between these groups.

Together with GGT, higher ALT and AST levels were reported at follow up and an increase in ALT over time in the HIV-infected participants compared to a decrease in uninfected counterparts. These results are in agreement with previous findings.11 It should be noted, however, that ALT and GGT levels were not above the cut-off values of 40 and 50 U/l, respectively, for liver disease.12 Administration of NRTIs is associated with mitochondrial toxicity, while NNRTIs are metabolised by the cytochrome P450, known to increase activities of co-administered ART and hence elevating the toxic effect on the hepatocytes.13 As the HIV-infected participants will continue ART, it is expected that these liver enzymes will increase further over time, which warrants regular monitoring of liver function in the future.

In those with HIV, higher uACR and lower eGFR at baseline was indicated, while over 10 years, eGFR increased. This increase in eGFR is contrary to the normal expectations of a decrease with aging,13 but aligns well with the findings of the Multicenter AIDS Cohort Study where an increase in eGFR in HIV-infected patients was defined as hyperfiltration (eGFR \( \geq 140 \text{ ml/min/l.73 m}^3 \)).4 This finding may indicate renal deterioration and may in future lead to the observed higher prevalence of renal failure in HIV-infected populations.14 However, in this study the eGFR was not above the cut-off value as proposed by the Multicenter AIDS Cohort Study.

This increase for eGFR may also suggest a catch-up effect in renal function over time due to ART. Renal impairment occurs dependent or independent of HIV infection. In the former pattern, HIV alters renal function as a result of immune suppression and when ART is introduced, renal function improves by exerting its antiviral effects.4 In the latter pattern, patients have improved immune function due to long-term ART use, which later results in nephrotoxicity, or as a result of pre-existing renal impairment and aging.42 Although the renal function markers did not indicate renal disease over time, it is important that regular renal screening be done as this HIV-infected cohort is ageing and using life-long ART.

The findings of this study should be interpreted in the context of the strengths and limitations of our study design. Demographic and cardiometabolic profiling of HIV-infected and control participants were carefully performed over a period of 10 years, thereby contributing to longitudinal data in Africans living with HIV. HIV-infected participants (n = 20) that were newly diagnosed during the follow-up studies were also included. Regarding ART information, ART use was not available for 26 HIV-infected participants. Although this study is limited by a relatively small sample size, it is overcome somewhat by the longitudinal design of the study, but may not be representative of the HIV-infected population of South Africa.

Conclusion

South Africans living with HIV for 10 years presented with similar changes in blood pressure and body composition compared to their uninfected counterparts. However, HIV infection was accompanied by longitudinal changes in the lipid profile, which may indicate the future development of dyslipidaemia. Low-grade inflammation and oxidative stress are common in HIV-infected individuals using ART, and the changes seen may, together with the lipid changes, reflect the development of a pro-atherogenic profile, which is associated with increased risk of CVD. In addition, the trajectories of increased CRP levels, elevated liver enzymes and increased eGFR should be carefully monitored in light of HIV infection and ART use.

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