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Cardiovascular toxicity of contemporary antiretroviral therapy

Alinda G. Vos[a,b] *and W.D.F. Venter*[b]

Purpose of review
HIV treatment has evolved since the introduction of antiretroviral therapy (ART) in the 1990s. Earlier treatment strategies, and the introduction of integrase inhibitors in preferred first-line ART have fundamentally changed cardiovascular side effects due to HIV infection and ART. This review provides an update on cardiovascular toxicity of contemporary ART.

Recent findings
Cardiovascular disease (CVD) risk, including heart failure, is still increased in people living with HIV (PLWH). Exposure to older antiretrovirals, including stavudine and zidovudine, still impact on CVD risk through persistent changes in body fat distribution years after discontinuation. Protease inhibitors (PI) and efavirenz have associated metabolic disturbances and increased risk of CVD, although use is decreasing worldwide. Integrase inhibitors and CCR5 antagonists seem to have negligible immediate CVD toxicity. Weight gain on newer antiretrovirals including integrase inhibitors is a reason for concern.

Summary
CVD risk should be monitored carefully in PLWH who were exposed to first generation ART, efavirenz or to PIs. Registries should capture ART use and CVD events to stay informed on actual clinical risk in the current era of rapid initiation on integrase inhibitor-based ART.

Keywords
antiretroviral therapy, cardiovascular disease, heart failure, HIV, side effects

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INTRODUCTION

Life expectancy of people living with HIV (PLWH) has improved steeply in the past decades with the introduction of safe and effective antiretroviral therapy (ART), resulting in a near-normal life expectancy for PLWH [1▪]. As a result, treatment focus has shifted from preventing AIDS related conditions and mortality to healthy aging with HIV. Initial antiretroviral drugs were effective in reducing viral load and restoring the immune system, but at the cost of substantial side effects, including cardiovascular toxicity [2▪].

Over the past years, ART combinations and dosages have been refined to increase efficacy, reduce pill burden and reduce side effects. This review will focus on cardiovascular side effects of contemporary ART in the light of what is known about CVD risk in PWLH and cardiovascular toxicity of previous ART regimens.

HIV AND CARDIOVASCULAR DISEASE

HIV infection is associated with an increased risk of cardiovascular disease (CVD). The risk of CVD, including myocardial infarction and stroke, is increased 2.2 times in PLWH compared to people without HIV infection [3]. The Strategies for Management of Antiretroviral Therapy (SMART) study demonstrated that interruption of ART resulted in an increased risk of myocardial infarction, possibly due to rebound viraemia and subsequent inflammation [4]. Nadir CD4 count and duration of uncontrolled viraemia have been found to be associated with poorer outcomes and increased CVD risk, and initiating ART at a CD4 count >500 cells/ul resulted in an increase in healthy life expectancy compared to starting ART at lower CD4

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Curr Opin HIV AIDS 2021, 16:286–291

DOI:10.1097/COH.0000000000000702

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KEY POINTS

- CVD risk, including heart failure, is increased up to two times in people living with HIV.
- Exposure to older ART regimens including thymidine analogues impacts negatively on CVD risk, even years after discontinuation.
- The increase in CVD risk relies next to ART also on traditional CVD risk factors and duration of untreated HIV infected.
- Contemporary ART seems to have far less cardiovascular toxicity than older regimens, although weight gain is a concern for INSTIs.
- Nationwide registries should capture ART use and CVD events to stay informed on CVD risk in the current era with timely initiation of contemporary ART.

counts [1▪,5]. The pathogenesis of CVD in HIV is multifactorial and includes direct effects of HIV itself, side effects of ART, and traditional CVD risk factors that accumulate with the natural process of ageing. These factors all act, at least in part, through inflammation and an imbalance in the immune system. Initiation of ART restores immunity, but immune markers do not return to levels seen in healthy HIV-negative individuals. Initiation of ART early in HIV infection seems to restore the immune balance better than ART initiation later in the course of disease [6]. In PLWH, traditional CVD risk factors, such as smoking exceed the prevalence of CVD risk factors seen in the HIV-negative populations in Western countries [7▪]. The situation in Sub-Saharan Africa is less clear, with reports indicating a higher prevalence of CVD risk factors in PLWH than seen in the general population but also studies indicating a more beneficial CVD risk profile in PLHW [8].

CONTEMPORARY ANTIRETROVIRAL THERAPY

Currently, there are eight categories of marketed ART, including nucleoside reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), protease inhibitors (PI), integrase strand transfer inhibitors (INSTIs), CC-chemokine receptor 5 (CCR5) antagonists, fusion inhibitors, CD4-directed postattachment inhibitors and GP120 attachment inhibitors. International guidelines currently recommend first-line ART combinations including 2 NRTIs, usually tenofovir disoproxil fumarate (TDF), or tenofovir alafenamide (TAF), or abacavir (ABC) with either lamivudine (3TC) or emtricitabine (FTC). This should be combined with an INSTI. An NNRTI or PI with a booster such as ritonavir or cobicistat may be used as an alternative to an INSTI [9]. The World Health Organizations first-line recommendation consists of dolutegravir (an INSTI) with a TDF/3TC backbone, and as alternative low-dose efavirenz to dolutegravir [10].

CARDIOMETABOLIC SIDE EFFECTS

Cardiometabolic side effects differ by ART class and sometimes even by individual drug. A comprehensive overview of metabolic side effects by ART drugs has been described by Hsue *et al.* [11] and by Dominick *et al.* [12▪]. Overall, it is difficult to disentangle the exact effects of HIV and different types of ART on CVD risk. Differences between study populations, changes in regimens, altered adherence over time, and distinct risk profiles by gender and race make association and causation assessments complex. In general, ART toxicity can induce new CVD risk factors or exacerbate the negative impact of existing CVD risk factors like hypertension, insulin resistance, diabetes mellitus, lipid disturbances and obesity [2▪]. HIV and ART both influence the function of adipose tissue, leading to inflammation and metabolic syndrome. ART has been associated with oxidative damage to DNA, also leading to metabolic syndrome [13▪].

Of all NRTIs, abacavir has attracted the most clinical concern regarding its CVD risk profile for over a decade. Recent studies show that abacavir is associated with increased risk of myocardial infarction, independent of traditional CVD risk factors [5,14]. This was already seen in the Data Collection on Adverse events of anti-HIV drugs (D:A:D) study in 2010, where use of abacavir, as well as lopinavir (PI), was found to result in altered glucose and lipid metabolism, mitochondrial toxicity, cardiac myopathy and impaired left ventricular function [15]. However, in a pooled analysis of clinical trial data abacavir was not associated with CVD risk in younger people with low CVD risk [16]. This might indicate that the contribution to increased CVD risk is most pronounced in older patients with existing CVD risk factors. The mechanism through which abacavir increases CVD risk is unclear, but may include altered platelet function. Platelet dysfunction is associated with CVD risk. Abacavir is associated with changes in platelet-collagen interaction linked to platelet activation [17,18▪]. This effect seems to be specific for abacavir as these proinflammatory changes were not observed for TDF and TAF. In the general population, an increased immature platelet fraction has been associated with CVD events. This fraction was increased in ART naïve PLWH but was lower in PLWH on ART, implying that ART reduces CVD risk [19▪]. More research is needed to unravel the link between ART, platelet function and CVD events.

TAF has been associated with weight gain and treatment related obesity, and TDF wit mitigation of weight gain, although impact on traditional metabolic factors such as glucose or lipids has not been seen [20▪,21▪▪].

Of the NNRTIs efavirenz and rilpivirine are commonly used. Efavirenz is known to increase lipid levels including low-density lipoprotein (LDL) and triglycerides, as well as to promote insulin resistance, with less of an effect by rilpivirine. However, rilpivirine is associated with greater weight gain [21▪▪]. Nevirapine, a legacy NNRTI, was regarded to be more lipid friendly as it increased high-density lipoprotein (HDL) to a larger extend than LDL, and did not increase insulin resistance [22].

PI, in general, are associated with an increased risk of CVD including myocardial infarction [23]. The use of PIs has also been linked to increased CVD mortality and 30-day hospital readmission for heart failure [24]. The adverse CVD risk in PIs might partly be caused by disturbances in the lipid metabolism [25▪]. Atazanavir, unboosted or boosted by ritonavir, is an exception in the PI class as it was not associated with an increased risk of CVD in several studies [23,26]. Compared to darunavir, another PI, and raltegravir (an INSTI), atazanavir had the slowest rate of increase in carotid intima-media thickness (CIMT), an intermediate marker for CVD risk. This effect was hypothesized to be mediated by an increase in bilirubin levels seen in people on atazanavir. Bilirubin is an antioxidant and was found to delay the progression of atherosclerosis [27].

The newer drugs including INSTIs and maraviroc, a virus-entry inhibitor (CCR5 antagonist), have generally, less to no measurable cardiovascular toxicity compared to older ART regimens drugs. Lipid profiles in patients using dolutegravir were significantly better than in people using a ritonavir-boosted PI or efavirenz [28]. In people who switched from a PI based regimen to a raltegravir based regimen lipid levels improved significantly and markers of endothelial damage decreased [29]. However, the main concern for INSTIs is excessive weight gain, and this effect seems to be most pronounced in black women [21▪▪]. This topic is discussed in depth in another review in this journal and hence not included in our discussion.

Prolonged use of maraviroc in PLWH was significantly associated with a decline in triglyceride levels and fewer comorbidities compared to nonmaraviroc containing ART over a period of three years, although this was not statistically significant, probably due to the low number of events [30]. However, maraviroc is rarely used in modern ART regimens, due to lack of coformulation and expense, as well as requirements for tropism testing.

ANTIRETROVIRAL THERAPY AND CAROTID INTIMA MEDIA THICKNESS

In multiple publications, ART has been linked to an increase in CIMT, a surrogate outcome marker for CVD. This has been well summarized in a systematic review and meta-analysis by Msoka *et al.* [31] including publications between 2000 and 2014. In this period ART was initiated when HIV infection had already significantly impaired the immune system, as the CD4 count needed to drop below the preset threshold of 350 or later 500 cells/mm^3 before ART could be initiated. Besides, ART regimens in that time were known for mitochondrial toxicity and adverse metabolic effects [2▪].

The assumption that contemporary ART regimens have less CVD toxicity than older regimens is supported by several recent studies using CIMT. In a multicenter study that was conducted just before the test-and-treat principle was introduced, in a 2 year period CIMT increased more steeply in treatment naïve PLWH than in HIV-negative controls, whereas the rate of CIMT progression for PLWH on ART and HIV-negative controls did not differ. The authors concluded that the increased risk of CVD was due to HIV itself, rather than to side effects of ART [32]. Similarly, our own study from South Africa, which included relatively young PLWH with adequate viral suppression on first-line and second-line therapy, did not find a difference in CIMT nor in carotid distensibility between PLWH and healthy controls [33]. A study from Thailand included PLWH $>$ 45 years, virally suppressed, with a median ART duration of 15 years. They also found no difference in CIMT compared to HIV negative sex and age matched controls [34]. The influence of HIV and ART on CIMT remains a question of debate. A large population survey including participants from different sites in Africa reported a lower CIMT in PLWH on ART compared to HIV negative people [35].

In summary, contemporary ART does not seem to induce relevant cardiovascular toxicity as measured with CIMT. The association between increased CIMT and ART use in older publications may be explained by the then used, more toxic ART regimens, or by significant immune deficiency before ART initiation, with prolonged exposure to a high viral load and hence direct toxicity of HIV on endothelial cells [11].

ANTIRETROVIRAL THERAPY AND METABOLIC CHANGES

Older ART regimens were known to result in lipoatrophy and a change from subcutaneous adipose tissue (SAT) to visceral adipose tissue (VAT). An increase in VAT is strongly associated with insulin

resistance, metabolic syndrome and CVD. A study from Denmark showed that previous exposure to thymidine analogues, like stavudine and zidovudine, and didanosine, was associated with an increase in VAT compared to PLWH who were never exposed to these drugs. This effect was still visible 9 years after discontinuation of these drugs [36]. Newer ART seems to have a more favourable metabolic profile than older ART, but it is important to consider the ART history when assessing someone's CVD risk profile.

A study from India, before the introduction of dolutegravir in 2019, reported a prevalence of metabolic syndrome in PLWH of 21.3%, with the highest prevalence in people on a PI-based regimen with a tenofovir backbone [37▪]. A study from Ethiopia had the same findings: metabolic syndrome was present in 23.5% of all HIV positive participants. Use of ART for more than 6 years and use of older ART regimens, that included stavudine, were both significantly associated with the occurrence of metabolic syndrome [38]. In a study from the United States of America (USA), metabolic syndrome was present in 34% of PLWH, all treated with ART. The prevalence increased with age and was higher in women than in men [39]. The introduction of the INSTIs has raised a new concern as INSTIs, and particularly dolutegravir and bictegravir, are associated with excessive weight gain and fat accumulation, mainly in the trunk, and more in women than in men [21▪▪]. The long term impact of weight gain on the occurrence of metabolic syndrome, diabetes mellitus type 2 and CVD risk has yet to be established, but is reason for concern [40▪].

ANTIRETROVIRAL THERAPY AND HEART FAILURE

In the pre-ART period cardiomyopathy with clinically manifest heart failure was frequently observed, and this was strongly linked to early mortality. This changed drastically with the introduction of ART. However, PLWH still have an up to 2 times higher risk of heart failure, both with preserved and reduced ejection fraction, compared to HIV-negative individuals [12▪]. Sudden cardiac death is also reported more often in PLWH and both heart failure and sudden cardiac death have been associated with low nadir CD4 count and peak viral load levels [41]. The prevalence of systolic dysfunction among PLWH decreased with increasing ART coverage [42]. No specific class of ART was associated with risk of heart failure in a nationwide cohort study in Taiwan [43]. For PLWH who are virally suppressed on ART the risk of sudden cardiac death levels out to the risk seen in the general population [44].

For older ART regimens mitochondrial toxicity impacted negatively on the myocardium and in a cardiac magnetic resonance imaging study in 2012, cardiac steatosis and cardiac fibrosis was seen frequently. Myocardial lipid levels were almost double in PLWH compared to healthy controls and about 75% of PLWH had any degree of myocardial fibrosis [45]. In a recent study, the level of intramyocardial triglycerides was three times higher in women living with HIV who were virally suppressed on ART (42% PI use, 63% INSTI use) than in HIV-negative women, although lipid levels in the blood did not differ. Intramyocardial triglyceride content was adversely related to diastolic function, as well as to viral load and CD4/CD8 ratio but no association with ART duration was seen [46]. A study in South Africa included 134 PLWH virally suppressed on ART and 95 uninfected people. Almost all participants (92%) used an NRTI/NNRTI based ART regimen. PLWH had more myocardial fibrosis on cardiac magnetic resonance imaging than HIV-negative people, although in subgroup analysis this effect was only seen in women [47▪▪]. A study in the USA included 22 women living with HIV and 14 non-HIV infected women. All women were virally suppressed and the majority was using an INSTI/NRTI based ART regimen. Women living with HIV had more myocardial fibrosis and reduced diastolic function compared to the HIV-negative women [48▪▪].

Taken together, in the current ART era the prevalence of heart failure and prestages of heart failure are still higher in PLWH compared to HIV negative people. However, there is no specific ART class or drug that seems to be responsible, but rather HIV related characteristics like (nadir) CD4 count and viral load.

CONCLUSION

For newly diagnosed PLWH who are initiated on a contemporary ART regimen early in the course of HIV infection, cardiovascular toxicity might become negligible, unless the weight gain signal related to INSTIs remains an issue. For PLWH who initiated ART when there was already significant immune derailment and/or who were exposed to older ART regimens, there should be awareness of the increased risk of CVD including heart failure. To attenuate this risk strict monitoring and treatment of modifiable CVD risk factors, like dyslipidemia and hypertension, is recommended.

Ongoing monitoring of PWLH, preferably in nationwide registries, is needed to inform CVD risk in the era of contemporary ART and the contribution of weight gain on INSTIs to CVD risk.

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Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Marcus JL, Leyden WA, Alexeeff SE, *et al.* Comparison of Overall and ■ comorbidity-free life expectancy between insured adults with and without HIV infection, 2000-2016. JAMA Netw Open 2020; 3:e207954.

This paper addresses that life expectancy in PLWH in the current ART era is near normal compared to that of individuals without HIV. This is important as it indicates on macro level that ART becomes more efficient, and that benefits clearly outweigh side effects

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This in vitro study shows the effects of three commonly used antiretrovirals on endothelial function. One drug has protrombotic, proinflammatory properties whereas the other two have cardio-protective properties. This is an important study as it highlights differential effects of ART on cardiovascular function, despite all three drugs are from the NRTI class

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Immature platelet fraction represents young platelets with a prothrombotic expression profile. An increase in this fraction is observed in people with CVD. The immature platelet fraction was increased in PLWH not on ART, but returned to normal in PLWH on ART, where the majority was on a INSTI/NSTI regimen. Immature platelet fraction might be a biomarker in predicting CVD risk

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This randomized controlled trial shows that upon initiation of dolutegravir PLWH had substantial weight gain, most pronounced in the group that used it in combination with tenofovir alafenamide, and more in women than in men. This urges the need for further research on the clinical consequences of weight gain as dolutegravir is part of first line ART worldwide

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47. ▪▪ Shuldiner SR, Wong LY, Peterson TE, *et al.* Myocardial fibrosis among antiretroviral therapy-treated persons with human immunodeficiency virus in South Africa. Open Forum Infect Dis 2020; 8:ofaa600.

PLWH in South Africa, virally suppressed on ART (almost all on a NNRTI/NRTI combination) had greater myocardial fibrosis compared to healthy controls, and this effect was most pronounced in women. This is an important finding as the largest part of the HIV positive population resides in sub Saharan Africa. In indicated the need for further research into drivers of myocardial fibrosis, the role of contemporary ART in promoting or reducing cardiac fibrosis and ways to prevent it

48. ▪▪ Zanni MV, Awadalla M, Toribio M, *et al.* Immune correlates of diffuse myocardial fibrosis and diastolic dysfunction among aging women with human immunodeficiency virus. J Infect Dis 2020; 221:1315–1320.

Women with HIV on ART (the majority on INSTI/NRTI based ART) had increased myocardial fibrosis and reduced diastolic function compared to healthy women. In women with HIV sCD163 and CD14+CD16+ monocyte CCR2 expression were related to cardiac parameters. This prompt further research to understand the increased risk of heart failure and directs research towards immunomodulatory strategies aiming to prevent heart failure in PLWH

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