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EDITORIAL



Early vascular aging in the HIV infected: Is arterial stiffness assessment the ideal tool?

Carla M. T. Fourie^{a,b} and Aletta E. Schutte ^{a,b}

^aHypertension in Africa Research Team (HART), North-West University, Potchefstroom, South Africa; ^bMRC Unit for Hypertension and Cardiovascular Disease, North-West University, Potchefstroom, South Africa

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The human immunodeficiency virus (HIV) epidemic has been a scientific challenge for over 35 years, and despite great strides forward, there is still no cure or proven vaccination available. Worldwide, almost 40 million people are infected with HIV.¹ Great advances were made in the management of people living with HIV, with antiretroviral treatment (ART) significantly improving life expectancy, resulting in HIV infection becoming a manageable chronic disease.

However, as the HIV infected population aged, it became clear that comorbidities seem to develop earlier than in HIV free populations² with an increased risk for the development of cardiovascular disease (CVD). Although the absolute event rates remain low in the younger HIV infected,³ the incidence and prevalence of CVD rise with age,² since HIV is accompanied by metabolic abnormalities,⁴ endothelial dysfunction,⁵ increased arterial stiffness,⁶ and carotid wall thickness.⁷ Furthermore, despite viral suppression by ART, premature CVD may result from a combination of viral injury, low-grade inflammation and abnormalities in immune activation.^{3,8} Vascular alterations may be initiated by the direct effect of the virus on the vasculature, leading to altered endothelial function, inflammation and modification of the aortic smooth muscle cells and the extracellular matrix.⁶ Although treatment may reduce endothelial activation, it does not seem to ameliorate the effects of HIV infection, thus endothelial dysfunction may persist and promote atherosclerosis, even among those with low viral loads.⁹



Carotid intima-media thickness (IMT) is a marker of sub-clinical atherosclerosis and CVD.¹⁰ Abd-Elmoniem *et al.* reported increased IMT's in young adults infected with HIV.¹¹ But it remains controversial whether these individuals will develop accelerated atherosclerosis.¹⁰

Large artery stiffness – assessed by aortic pulse wave velocity (PWV) – is a validated surrogate marker of arteriosclerosis and atherosclerosis.¹² Ridker *et al.* found that HIV infection independently predicts increased PWV,⁶ but whether aortic stiffness and vascular aging are influenced by HIV remains a topic of debate.³

Strategies implemented by health authorities to reduce CVD risk among HIV infected patients include anti-inflammatory medication, ART regimens known for the least adverse metabolic effects and potential immunomodulatory benefits, as well as careful management of traditional cardiovascular risk factors.^{2,8} Early identification of subclinical atherosclerosis may therefore provide insight into the risk of developing overt CVD and may be central for both prevention and treatment of CVD development in the HIV infected population.¹¹

This issue of *Virulence* features an article by Eckard *et al.* evaluating arterial stiffness in HIV-infected youth.¹³ The paper is timely, since the majority of studies on atherosclerotic risk among people living with HIV, focus on the elderly. Eckard *et al.* addressed this knowledge gap by including HIV infected children and young adults on stable ART and with low levels of viremia. They specifically assessed whether arterial stiffness (carotid-femoral PWV) relates to IMT and HIV-related variables. Although this was a cross-sectional study and had a small sample size, the study benefits by including a comparable healthy control group – an aspect that many similar studies on HIV and CVD lack.

Eckard and co-authors found thicker IMTs in HIV infected youths compared with those uninfected, but found no differences in arterial stiffness upon adjustment for blood pressure.¹³ Only in the HIV infected youths they found a positive association between IMT and

CONTACT Carla M. T. Fourie  carla.fourie@nwu.ac.za  Hypertension in Africa Research Team (HART), North-West University, Private Bag X6001, Potchefstroom, 2520, South Africa.

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arterial stiffness. This relationship does provide some new insight, but precludes one from using arterial stiffness (PWV) as an early marker of vascular function in this population, due to similar PWV in the HIV infected and uninfected groups. When evaluating the findings from this study, the following aspects need to be reviewed carefully.

Age and substance use

Arterial stiffness is primarily associated with blood pressure and age,^{14,15} and may also be influenced by unhealthy lifestyles. The HIV infected youths and the control groups' mean age was similar in this study, but unfortunately the age range was wide, ranging from 8–25 y. The percentage of these young patients consuming alcohol was high, 45% of those infected vs. 34% among the control group. Interestingly, although the indicated alcohol consumption was statistically similar in the 2 groups, alcohol consumption only associated with PWV in the HIV infected participants. Alcohol consumption was assessed by questionnaires, and could have benefitted from biologic markers of alcohol intake, such as gamma-glutamyltransferase (GGT) – a marker of excessive alcohol consumption, liver disease and oxidative stress.¹⁶ Since GGT counteracts oxidative stress, elevated GGT levels are observed in conditions such as excessive alcohol consumption and HIV infection, where increased oxidative stress prevail.¹⁷ Furthermore, recent evidence indicate that marijuana use may accelerate cardiovascular aging.¹⁸ With 25% and 21% of the HIV infected and uninfected youths using marijuana, it is yet unknown what the effects on arterial stiffness was in this relatively small population.

Ethnicity

An important aspect to highlight is that the majority of the participants in both the study and control groups were black. Arterial stiffness is known to be elevated in black populations,¹⁹ even among children as young as 6–8 years,²⁰ and ethnicity should therefore be factored in when reviewing findings on arterial stiffness.

Antiretroviral therapy

The study of Eckard *et al.* represents individuals who acquired HIV early in life and is the first generation of young adults growing up with lifelong exposure to HIV and ART. Although they were on stable ART, their regimens varied widely. Antiretroviral therapy may exert an additional detrimental effect on endothelial function and contradictory results have been reported concerning the effect of ART on arterial stiffness. Protease inhibitors

have been associated with endothelial dysfunction, but more recent evidence suggests a safer cardiometabolic profile of some regimens⁸ and the newer protease inhibitors did not result in endothelial dysfunction.¹⁰

Concluding remarks

The role of arterial stiffness in CVD development has become increasingly recognized in the past decade, as arterial stiffness increases the risk of cardiovascular events. PWV is the gold standard method for the measurement of arterial stiffness²¹ and is thought to be a better predictor of all-cause mortality, cardiovascular mortality and events than blood pressure.²² Eckard and co-authors suggest that arterial stiffness assessments may have potential as a useful, non-invasive method to access CVD risk in the young generation living with HIV infection, yet HIV infected and uninfected youths differed by carotid wall thickness, but not in arterial stiffness. Their findings therefore highlight the critical need for more data, especially from longitudinal studies on the cardiovascular profile of young HIV patients.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

ORCID

Aletta E. Schutte  <http://orcid.org/0000-0001-9217-4937>

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