Subclinical cardiac disease in children with perinatally acquired HIV is associated with inflammation

Sepiso K. Masenga[a], Hélène C.F. Côté[b] and Peter W. Hunt[c]

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Introduction of antiretroviral therapy (ART) in children with perinatally acquired HIV (PHIV) has attenuated the adverse effects of untreated HIV infection such as opportunistic infections, acute inflammation, progression to AIDS as well as reduced mortality [1–4]. However, children with PHIV continue to experience elevated risk of chronic conditions including subclinical cardiovascular disease (CVD) that may eventually progress to symptomatic cardiac disease [5].

Growing evidence suggests that despite viral suppression, suboptimal inflammation still persists [6,7] and contributes to the genesis and progression of subclinical cardiac disease in more than 25% of children with PHIV [8,9]. Structural and functional cardiac abnormalities on echocardiographic findings reported in children with PHIV include right ventricular (RV) and left ventricular (LV) dilation, septal hypertrophy, LV posterior wall hypertrophy, LV systolic dysfunction, reduced LV global longitudinal strain, and higher end-systolic wall stress [5,8,9].

Identifying biomarkers of inflammation and cardiac injury that contribute to subclinical cardiac disease is, therefore, cardinal to understanding its risk and pathophysiology. Nevertheless, few studies have reported specific biomarkers as correlates of subclinical cardiac disease in this population.

Majonga *et al.* [10] aimed to address this gap in a cross-sectional study where they recruited 195 PHIV and 211 HIV-uninfected children 6–16 years. PHIV had been on ART at least 18 months after initiation. The authors measured cardiovascular and proinflammatory biomarkers, and determined their association with echocardiographic abnormalities among the children with PHIV only. They reported persistent systemic inflammation despite use of ART, as evidenced by plasma levels of C-reactive protein (CRP), tumour necrosis factor α (TNF-α), suppression of tumorigenicity 2 protein (ST2), vascular cell adhesion molecule 1 (VCAM-1), and growth differentiation factor 15 (GDF-15) that were significantly higher in the children with PHIV compared with the uninfected controls. Persistent inflammation may have been exacerbated by delayed initiation of ART as viral suppression was associated with reduced TNF-α and interleukin (IL)-6.

Among children with PHIV, Majonga *et al.* [10] found that 42% showed cardiac abnormalities including LV dilatation and hypertrophy, LV diastolic dysfunction and systolic dysfunction, left atrial dilatation, dilated cardiomyopathy, RV dilatation and systolic dysfunction. The biomarkers that were increased and correlated significantly with cardiac abnormalities (LV diastolic dysfunction and LV hypertrophy) were CRP and GDF-15. The latter is a member of the transforming growth factor (TGF) family [11]. In the general population, increased GDF-15 levels have been reported in myocardial injury and pressure cardiac overload, and it has been shown to be an independent predictor of mortality in

[a]HAND Research Group, School of Medicine and Health Sciences, Mulungushi University, Livingstone, Zambia, [b]Department of Pathology and Laboratory Medicine, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada, and [c]Division of Experimental Medicine, Department of Medicine, University of California San Francisco, CA, USA.
Correspondence to Sepiso K. Masenga, PhD, Mulungushi University Livingstone, Zambia.
E-mail: smasenga@mu.ac.zm
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patients with CVD, especially in heart failure and acute coronary syndromes [12,13]. CRP is generally raised in the context of acute inflammation, and although is not a specific marker of CVD, it is a predictor of adverse cardiac injury and mortality in patients with CVD [14,15].

Although echocardiographic measures were not available in the controls without HIV, the study by Majonga *et al*. [10] confirms that a substantial proportion of children with PHIV develop subclinical echocardiographic evidence of cardiac disease. This study also raises the possibility that cardiovascular and proinflammatory biomarkers could eventually be used to risk stratify children with PHIV for potential interventional strategies, and monitor high-risk patients, especially those who experienced delayed ART initiation and/or fail to achieve viral suppression. Indeed, the findings by Majonga *et al*. [10] support the hypothesis that persistent systemic inflammation contributes to the pathogenesis of HIV-related cardiac disease in children living with HIV. It will be of great interest to determine whether the biomarkers identified in this exploratory study predict the eventual development of clinical cardiac disease in children who are exposed to HIV and its effects so early in life. Lastly, most clinical trials of interventions to reduce cardiovascular events in people with HIV like the REPRIEVE trial of pitavastatin will likely continue to be restricted to older adults, most of whom acquired HIV during adulthood, primarily because the cardiovascular event rates are too low in young adults to achieve a feasible number of clinical endpoints. Nevertheless, there are likely over two million young adults with PHIV around the world who are expected to age into later adulthood and may eventually be at particularly high risk for cardiovascular complications. Studies of inflammatory and cardiovascular surrogate markers as performed in the study by Majonga *et al*. [10] may be particularly important in identifying subpopulations who may plausibly benefit from earlier treatment.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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