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Clinical management of cardiovascular disease in HIV-infected patients

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Human immunodeficiency virus (HIV) is no longer a deadly disease, but is now a chronic condition since the introduction of antiretroviral therapy (ART)¹. Cardiovascular disease (CVD), specifically coronary artery disease is becoming a significant health burden in HIV-infected (HIV+) patients. Our current understanding of the mechanisms underlying HIV-associated CVD is largely obtained from clinical observations¹. ART treatment suppresses, but does not eradicate HIV. Extensive clinical evidence indicates that well-controlled HIV infection with or without ART (eg. in HIV+ patients or HIV+ elite controllers) accelerates CVD, including atherosclerosis. ART treatment, HIV-associated comorbidities such as dyslipidemia, drug abuse, opportunistic infections, and lifestyle are risk factors for HIV-associated CVD and atherosclerosis¹. However, the treatment strategies for CVD disease in HIV+ individuals still largely follow those strategies for traditional CVD. Current ongoing clinical trials in HIV+ patients include the use of lipid lowering and anti-inflammatory statin therapy² or treatment with a monoclonal antibody targeting interleukin 1 β , Canakinumab³. Since these studies are blinded and ongoing, the outcomes are forthcoming. However, therapeutic strategies specific for HIV-mediated atherogenesis remain to be developed¹. Considering the persistent and chronic nature of HIV infection, current ART treatment, elevated risk factors, increased life expectancy, and the limited specific treatment options or guidelines, one of the emerging challenges is the clinical management (prevention and treatment) of HIV+ patients with CVD^{3,4}.

The article by Ballocca et al. provides a comprehensive review of the current knowledge on the prevalence, pathophysiology, and treatment of CVD in HIV+ patients and stresses the need for better risk stratification and HIV-specific treatment guidelines. The traditional CVD risk factors (hypertension, diabetes, dyslipidemia, and smoking) are elevated in HIV+ patients potentially accelerating the pathogenesis. As illustrated in Fig. 1, complex interaction of HIV infection, ART treatment and traditional risk factors participates in the pathogenesis of HIV-associated CVD. Smoking by HIV+ patients leads to increased rates of

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CVD with a 2-fold increased risk of myocardial infarction (MI)⁵. Not only are traditional risk factors increased in this population, but HIV-specific risk factors further impact the development of CVD. HIV infection itself has a significant impact on the development of CVD as suggested by the correlation between nadir CD4 count, RNA viral counts and the risk of coronary syndromes⁶. Activation of the immune system and long-lasting inflammatory status changes by DNA methylation and alteration in gene expression may further contribute to a proatherogenic environment. Lastly, ART treatment increases levels of total cholesterol and triglycerides while reducing HDL⁷. Thus, promoting atherosclerosis through dyslipidemia as well as endothelial activation, however these effects are largely from first-generation drugs that have since been replaced.

The clinical presentation of coronary heart disease (CHD) ranging from silent ischemia to acute coronary syndrome (ACS) in HIV+ patients is not different from the general population. However, HIV+ patients with CHD tend to be younger and have more frequent ACS that often present as ST-segment elevation MI⁸. Importantly, as described in this review HIV+ patients have a “peculiar” plaque characteristic, including an increased prevalence of non-calcified inflammatory plaques⁹. This inflammatory plaque phenotype is unstable and more prone to rupture and thrombus, thus contributing to the increased rates of ACS in HIV + patients.

Since plaques in HIV+ patients are unique and patients are at an increased risk of CVD after accounting for traditional risk factors, a critical problem that still needs to be addressed is accurately determining CVD risk stratification for better prevention and treatment for individual HIV+ patients. Risk models of the general population such as the Framingham Risk Score (FRS), the Pooled Cohort Equations for atherosclerotic cardiovascular disease (ASCVD), and the European Systematic Coronary Risk Evaluation score (SCORE) underestimate the risk in HIV+ patients. The D:A:D equation was the first to include both CV risk and HIV-related variables, however there has been limited data with short follow up to compare this model with those for the general population. Risk stratification is essential to address diagnostic exams and primary prevention. To date, most of the interventions for HIV-associated CVD follow the guidelines established for HIV negative patients. First line therapies are life-style alterations, such as smoking cessation and counseling for behavioral changes. When beginning pharmacologic interventions for traditional risk factors such as hypertension, dyslipidemia and diabetes it is important to pay specific attention to medications with drug-drug interactions with ART. As nicely outlined in Table 1, the authors document specific drug-drug interactions to consider in the management of patients when prescribing anti-hypertensive, anti-diabetic, anti-thrombotic, and lipid lowering drugs in combination with ART. A pharmacologic therapy frequently prescribed in management of CVD in both the general and HIV population is statins. Statins that are not metabolized by the cytochromes P450 (CYP) system have a safer profile. Of significant note, a worldwide multicenter international clinical trial, the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) (clinicaltrials.gov: NCT-02344290) started in March 2015 and is randomizing 6500 HIV+ patients to a statin, pitavastatin (not metabolized by CYP and thus safe in HIV+ patients) or placebo. The outcome of this study will be the first and largest of its kind and will help to understand the impact of statin therapy on HIV+ patients who by current standards would not have a high enough risk for therapy. Revascularization strategies

are another treatment option in the case of ACS, and recommendations follow that of the general population. However, HIV+ patients exhibit a higher rate of recurrent ischemic events and subsequent recurrent coronary revascularization than HIV negative patients.

In summary, in ART era, we are facing new challenges with the elevated occurrence of CVD in HIV+ patients, and CVD in HIV+ patients will continue to accumulate in the coming years with the increase in life expectancy¹⁰. The pathogenesis of HIV-associated CVD is complicated by the contributions of many factors such as HIV, ART, and other traditional risk factors and the molecular mechanisms remain mostly unknown. The current clinical prevention/treatment for HIV-associated CVD for the most part follow the guidelines established for HIV negative patients. Drug interactions with ART when treating comorbid risk factors is important to guide the clinician's management of HIV+ patients. Accurate risk stratification for HIV+ patients is necessary to direct diagnostic exams and determine clinical intervention. Specific management approaches for HIV-associated CVD is much needed considering the unique feature of non-calcified inflammatory plaques in HIV+ patients. Including the assessment of subclinical atherosclerosis by measuring carotid artery intima-media thickness via ultrasound¹¹ or assessment of plaque features by coronary computed tomography angiography¹² will greatly improve risk stratification models. Further, in HIV+ patients with MI, it is important to diagnose specific types of MI as type 1 (caused by atherosclerosis) and type 2 (caused by bacteremia and recent use of recreational drugs) because they may require different treatment approaches¹³. Approximately half of myocardial infarction (MI) in HIV+ patients were type 2 MIs, which is higher than those in HIV negative patients¹³. Taken together, general as well as specific management approaches will help better diagnosis, prevent and treat CVD in HIV+ patients.

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