

Letter to the editor

re: Matthew J. Feinstein et al. **Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific Statement From the American Heart Association.**

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We read the AHA Scientific Statement by Feinstein and colleagues about cardiovascular disease in people living with HIV (PLWH) with great interest. The authors conclude that rates of myocardial infarction, heart failure, stroke, and of subclinical atherosclerosis are significantly elevated in PLWH compared to HIV-negative subjects, even in the setting of modern antiretroviral therapy.

Unfortunately, Feinstein and colleagues do not provide a well-balanced assessment of the published literature. The authors do not cite reports suggesting that cardiovascular (CV) risk may not be increased in PLWH compared to HIV-negative persons. In a large cohort study from the Kaiser Permanente health system in California¹, and in Swiss HIV Cohort Study participants and population-based controls², no increased risk of myocardial infarction was seen in PLWH in recent years. In addition, 3 large studies have compared subclinical atherosclerosis prevalence in HIV+ and HIV-negative persons using coronary CT angiography (CCTA)³⁻⁵. However, Feinstein et al cite only 1 study³ that showed somewhat increased subclinical atherosclerosis in PLWH, but elect not to cite the 2 studies, from the US and from Switzerland, which suggested no increased⁴, or even decreased⁵ subclinical atherosclerosis in PLWH.

Failure to cite all relevant work provides opportunities for questionable dogmas to consolidate. Each of these “negative” CV endpoint studies¹⁻² and cardiac imaging studies⁴⁻⁵ provide arguments against the prevalent notions, also held by Feinstein and colleagues, that CV risk is increased in HIV, and that ongoing inflammation despite optimal suppressive HIV treatment may promote accelerated atherosclerosis in HIV. Our negative CCTA study⁵ even prompted an insightful editorial in the *European Heart Journal* by Cotter and Ma, who asked whether the notion of increased CV risk in HIV amounts to “much ado about nothing”.

More importantly, a selective focus on only those studies that fit the notion of increased CV risk in PLWH has direct implications for patient management. For example, not only has anti-inflammatory treatment shown no benefit in PLWH to date, but some anti-inflammatory drugs have even caused harm, such as low dose methotrexate, which was associated with infections and pulmonary toxicity in a study conducted by AHA guideline authors. Because there is no evidence of increased CV risk in well-controlled PLWH in Switzerland, we see limited interest in pursuing anti-inflammatory treatment in our patients.

References

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AHA Scientific Statement: Response to Letter to the editor

Matthew J. Feinstein, MD, MSc; Judith S. Currier, MD; Priscilla Y. Hsue, MD

We appreciate the comments by Schoepf and co-authors in the letter to the editor. In our effort to examine the literature on HIV and cardiovascular disease (CVD) as thoroughly as possible in our statement, we inevitably were unable to incorporate every study, including four of the articles cited by the co-authors, two of which they authored. The authors' main concern appears to be that we did not present enough data suggesting that cardiovascular risk is similar for people with HIV (PWH) vs. HIV-uninfected persons; the reason we did not is simply because the bulk of current evidence does not support this hypothesis espoused by Schoepf and co-authors.

The articles cited by the authors highlight the importance of considering HIV-related CVD risk enhancers to understand gradients of HIV-associated CVD risk. One of the two articles the authors discuss that investigated actual clinical CVD endpoints found declining relative risks for myocardial infarction among PWH in the Kaiser Permanente health system, which are attributed to more effective HIV therapy – in other words, a lower burden of HIV-related CVD risk enhancers. While we neglected to include this article, we did cite a similar one from the same group and same Kaiser Permanente cohort. This study found that PWH have overall elevated risks for myocardial infarction, but that the heightened risks are primarily among PWH with lower CD4 counts.¹ Indeed, a thorough investigation of our proposed approach to CVD risk stratification (as shown in Figure 4) underscores our conclusion that specific HIV-related risk enhancers (e.g., prolonged viremia, delayed antiretroviral initiation, and/or low CD4 counts) are the main drivers of elevated cardiovascular risk among PWH.

In light of the totality of evidence from investigations of HIV and CVD, we disagree with the authors' assertion that PWH no longer have significantly elevated risk for CVD. This may occur in select cohorts of PWH with excellent HIV control and near-complete immune recovery, although numerous studies (including several cited in our statement) demonstrate elevations in innate immune activation, arterial inflammation, and subclinical CVD in PWH with excellent viral control and immune recovery. Furthermore, in populations of PWH without ubiquitous HIV control, ART uptake, or immunologic recovery – the unfortunate reality in many HIV care settings – CVD risk clearly remains elevated. This is supported by the preponderance of literature from different patient populations and cohorts investigating hard CVD endpoints in well-powered analyses,²⁻⁴ as well as rigorous meta-analyses such as a recent one investigating the global burden of HIV-associated CVD.⁵ Based on our review, these and other studies outweigh the small number of studies in cohorts that may not reflect the full breadth of the HIV care spectrum which suggest no statistically significant increase in CVD risk.

As the authors indicate, our statement has direct implications for patient management. We agree. Therefore, rather than quibbling over broad differences in relative CVD risk by HIV serostatus – which depends largely on cohort composition – we focus on

understanding which risk-enhancing factors *among PWH* may confer heightened CVD risk and therefore warrant focused clinical interventions.

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Acknowledgments

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