Reviewer's report

Title: Risk factors for subclinical atherosclerosis in HIV-infected patients under and over 40 years: a case-control study

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Reviewer: Kaku Armah

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This study asks an interesting question, “Do co-morbidities associated with atherosclerosis differ among HIV-infected people of different ages?” The finding of a differential effect by age of comorbid disease on atherosclerosis is noteworthy. This finding, if valid, is a worthwhile contribution to the field of HIV and cardiovascular disease research in view of recent work describing a phenomenon termed “accelerated ageing” in this population. Enthusiasm for this study is dampened by inconsistencies in methods, interpretation, terminology and grammar.

Major Compulsory Revisions

1. The essential question is whether age interacts with atherosclerosis risk factors among HIV infected people. However, no clinically or epidemiologically valid reason is presented for the choice of 40 years as a threshold. The authors suggest that HIV prevalence among people 20-39 years in Brazil is 60%, which appears to be the rationale for the age threshold. Since they have not suggested that their study population is a representative sample of the national population, it is unclear this supports the use of the 40 years threshold. It may be more epidemiologically sound to use an internal reference e.g. above and below median age or age tertiles if the sample size permits. Alternatively, instead of splitting the sample, they could examine interaction models with age and each comorbidity. This may be statistically more efficient though possibly more involved to interpret.

2. The outcome variable was carotid intima-media thickness (cIMT). Again, the authors do not provide any justification for the choice of 0.8 mm as a threshold.

3. A fascinating finding in this paper is a differential relationship between HIV-related and non-HIV related factors and cIMT by age group. The authors suggest several reasons for this observation including a) no association between antiretroviral therapy (ART) and cIMT and b) mediation of HIV-related effects by non-HIV related effects. They neglect to discuss that almost twice as many people <40yrs were not using HAART vs. >40 years, and that there was more immunocompetence and less viremia in the younger group despite longer HAART duration in the older group. An important analysis would compare cIMT values (medians, means) separately by ART use, viremia, or immune status for different age groups. Another important sub-analysis could exclude those with traditional cardiovascular disease risk factors and to see if an HIV-related effect
is unmasked.

4. I am not familiar with this model selection procedure. Is this a variation of stepwise regression with backward and forward elimination? If so, what criteria were used to compare model fit? If not, has this method previously been described?

5. Assuming legitimacy of the model selection procedure, why not use all covariates that meet criteria for either model in both models. This enables you to discuss a similar set of covariates by the two age groups.

6. The finding of increased cIMT with lower CD4 counts is unexpected. The authors cite an analysis of the Strategies for Management of Antiretroviral Therapy (SMART) study[1] and describe an increased risk of CVD with per 100 unit elevation in CD4 level. I was unable to locate this result in this study. Perhaps the authors can assist this reviewer in finding it. The authors also suggest that comorbidities among virally suppressed participants on ART in their study “may increase the chance of subclinical atherosclerosis.” However, they present no data to support this – was the burden of comorbidities higher among virally suppressed people on ART vs. non suppressed people on/off ART?

7. The lack of association between cIMT and HDL cholesterol, LDL cholesterol and triglycerides raises the issue of confounding by lipid lowering therapy. If these data are available, the authors should account for the use of these therapies. A similar point could be made for antihypertensive therapy.

8. The time interval between cIMT and assessment of covariates is unclear. The greater the time separation, the less likely the covariates approximate biological status at the time of cIMT measurement.

Minor Essential Revisions

9. It is unclear that “consensual union” and “schooling” should be characterized as a “traditional risk factor for CHD.” The authors should provide references to support this assertion or modify this characterization.

10. Please provide a reference for the source of the validated questionnaire used to obtain self-response data.

11. Some imprecise statements made in the discussion suggest conclusions not supported by the data. “The association of male gender as a predictor of cardiovascular disease only in the younger group is in agreement with the literature…” What the data actually suggest is an association of male gender with cIMT, a marker of subclinical atherosclerosis, which is in turn a risk factor for cardiovascular disease. Likewise, “The …metabolic syndrome… was an independent factor … for the onset of subclinical atherosclerosis” implies some causal relation by chronology. Since assessment of the metabolic syndrome was likely done concurrently with or subsequently to assessment of cIMT, this characterization is likely incorrect. “…association between immunosuppression… and increased cardiovascular risk for both subclinical atherosclerosis and myocardial infarction” This statement conflates cardiovascular disease and cardiovascular disease risk. This occurs again during the discussion of data from the SMART study – to my knowledge, atherosclerosis risk has not been reported
from SMART.

Discretionary Revisions

12. The authors report differences in mean values of lipids. In my experience, lipid values are typically non-normally distributed. The authors may wish to indicate how they compared means if these values were not normally distributed.

13. “No prior coronary disease” is specified as an inclusion criterion. The authors may wish to specify events (myocardial infarction, stroke, heart failure), coronary heart disease, or coronary artery disease.

REFERENCES


Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.