Reviewer's report

Title: Development of a definition for Rapid Progression (RP) of renal function in HIV-positive persons: the D:A:D study

Version: 2
Date: 30 November 2013

Reviewer: Michelle Estrella

Reviewer's report:

Dr. Kamara and colleagues attempt to generate an operational definition for rapid progression among those with normal kidney function at baseline in a large multi-cohort study of HIV-infected individuals. They conducted several analyses with varying follow-up periods, number of annual eGFRs and mean annual decline in eGFR. Strengths of the study include its large sample size and availability of repeated eGFRs and careful consideration of factors that may impact the association between RP and its association with long-term outcomes. Some concerns raised during the review are as follows:

Major Compulsory Revisions:

1. Methods: It is unclear how many DAD study participants had eGFR>=90 at baseline but were excluded due to having fewer than 3 eGFRs after January 2004. Were these excluded participants similar in clinical characteristics to those included in the study?

2. The notion that the association between potential HIV treatment-related factors and RP will be evaluated at a later point seems weak, especially in light of the fact that the study already includes results evaluating the association between traditional CKD risk factors and RP. HIV treatment-related factors would be important to include in this predominantly treated HIV-infected population since a growing proportion of renal disease in this patient population is attributable to anti-retroviral nephrotoxicity.

2. Discussion - The assertion that the results "demonstrated that a RP definition can be used alongside other current measures of renal function to identify those at risk of developing more severe renal disease at an early stage" is over-reaching based on the results presented which showed that the RP definitions provided had low sensitivity and positive predictive value. While it may in the future, the study did not investigate whether the RP definition used leads to improved clinical outcome, therefore supporting its use alongside routine renal function monitoring.

Minor Essential Revisions:

1. Abstract: While the association of RP with CKD events is mentioned in the methods, no findings are reported in the results. As this would be of greatest interest to readers, a brief summary of these findings in the abstract should be considered for inclusion.
2. Introduction: The last sentence in the first paragraph may be improved by actually describing the MDRD findings which led to the authors asserting that the MDRD study "made a strong case" for RP.

3. Introduction: The "normal" age-related decline for eGFR cited by the authors pertains mainly to those aged >=50. This point should be clarified for accuracy.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.