Reviewer's report

Title: Non-AIDS defining cancers in the D:A:D Study - time trends and predictors of survival: a cohort study

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Reviewer: Eric Engels

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Review of Worm et al, NADCs in the D:A:D cohort

The authors describe the incidence of NADCs and subsequent mortality in a consortium of HIV cohort studies. Overall, the text is clear, and the results seem sound. There are some important limitations that the authors recognize, include the grouping of NADCs together for most analyses, and lack of data on cancer treatment.

Comments and questions for authors

1. For the 408 cases that were not accompanied by a complete CRF (almost half of the cases), how well were the diagnoses documented?

2. Were any regression analyses conducted using the outcome of cancer-specific deaths? This could be very informative, particularly since it appears that a large percentage of the deaths were due to cancer.

3. In defining follow-up for NADC incidence, were only first/primary cancers considered events? Or were secondary/multiple cancers also considered? If only primary cancers were considered, the potential to miss NADCs (e.g. lung cancer that was diagnosed after a HD diagnosis) could have resulted in a small underestimate of NADC incidence over time.

4. Please clarify in the text whether the age variable was defined as age at baseline or attained age.

5. Because the sample size for each cancer type was limited, certain regression estimates may have not reached statistical significance, particularly in multivariable models. However, it would still be informative to include the point estimates for all variables investigated, not just the significant findings, according to each cancer type in Table 3. Please add in the effect estimates under lung cancer, anal cancer, and HD for all variables included assessed in regression models.

6. It appears that a low CD4 count is associated with poor survival when all cancers are considered, although the effect was strongest for HD. This is an interesting finding and since most deaths were due to cancer, it is potentially relevant to the role of immunity in the control of cancer. Alternatively, it may
reflect that some cancer patients with lower CD4 counts were not offered treatment, could not tolerate treatment, or had impaired access to medical care. Very few died of AIDS. Some text regarding immunity and cancer-specific mortality, cancer treatment and comorbidities, and the paucity of deaths due to AIDS, would be a good addition to the Discussion section.

8. Discussion. The authors comment that “it is not surprising that event rates were seen to rise as patients began to survive for longer periods.” This is misleading, because it is mentioned in the context of “a major competing cause of mortality (AIDS) was removed.” The reader is led to believe that the absence of a competing event (death) led to a higher incidence rate of cancer. This does not follow in a strict mathematical sense, contrary to what the text implies. Instead, it is better to conceive of the improved survival as allowing people to live with HIV and immunosuppression longer, and allowing them to age. Both prolonged immunosuppression and aging might plausibly lead cancer incidence to rise.

Minor issues not for publication

Page 4. “…apparently increasing incidence of NADC” is too broad and not quite accurate. For most cancers, there has been no change in the age-standardized incidence rate, although the number of cases is rising due to an aging of the population, as well as an increase in the size of the population.

Page 7. For Hodgkin lymphoma, “nodular” should read “nodular sclerosis.”

Page 10. Add “mortality” so text should read “…between the latest CD4 count and mortality from either lung…or anal cancer.”

Page 11. Mention that the study lacks data on surgical treatment of cancer, in addition to chemotherapy and radiation.

Table 1. Reorder the cancers. An alphabetical listing is not appropriate. Either list them according to the frequency, or use an ordering by system as done by SEER (http://seer.cancer.gov/siterecode/),

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.