Author's response to reviews

Title: Higher pre-infection vitamin E levels are associated with higher mortality in HIV-1-infected Kenyan women: a prospective study

Authors:

Susan M Graham (graha00@earthlink.net)
Jared M Baeten (ibaeten@u.washington.edu)
Barbra A Richardson (barbrar@u.washington.edu)
Daniel D Bankson (daniel.bankson@va.gov)
Ludo Lavreys (llavreys@wanadoo.fr)
Jeckoniah O Ndinya-Achola (Ndinya-Achola@kaviuon.org)
Kishorchandra Mandaliya (kishor@ikenya.com)
Julie Overbaugh (joverbau@fhcrc.org)
R. Scott McClelland (mcclell@africaonline.co.ke)

Version: 4 Date: 10 June 2007

Author's response to reviews: see over
Dear Dr. Phillips:

Re: MS: 2130750475129914
Title: Higher pre-infection vitamin E levels are associated with higher mortality in HIV-1-infected Kenyan women: a prospective study

Thank you and your reviewers for your preliminary acceptance of our manuscript. We have carefully reviewed the minor essential revisions suggested, and have modified the manuscript in response to these points. Below, please find our responses to the points made by Dr. Corbeau, followed by a point-by-point listing of changes to the manuscript. In our responses, the numbers in parentheses refer to changes detailed in the point-by-point listing.

REVIEWER 1
1. We found no point #1. Please let us know if something was erroneously left out.

2. As compared with previously published CD4 slopes (e.g. Ann. Intern. Med. 126(12):946-54, 1997) the rate of CD4 decline observed in the authors cohort is low. Hypotheses accounting for this difference must be at least proposed in the discussion (HIV subtype? Genetic background?...)
Several hypotheses may account for the low rate of CD4 count decline we reported in this study. The majority of the women in the cohort are infected with HIV-1 subtype A, which has been associated with a lower rate of disease progression in our own and other cohorts.\(^1\)\(^2\) In addition, our seroconverter cohort consists of individuals followed from before HIV-1 acquisition; this group may have a lower median CD4 count decline compared to cohorts of individuals enrolled later in infection. Genetic background, mode of transmission, and medical care given (e.g., co-trimoxazole prophylaxis) may
all have affected the rate of CD4 decline in these women, especially as compared to earlier cohorts consisting predominantly of gay men.

The CD4 count decline we initially reported had a broad confidence interval, reflecting a small sample size and the high variability of CD4 counts. We found that neither CD4 count decline nor time to CD4 count <200 cells/μl was significantly associated with vitamin E levels. In our revision, we have chosen to present the data on CD4 count <200 cells/μl only, and have removed the text on CD4 count decline. In the discussion, we mention the primary limitation of our immunologic data (i.e., CD4 counts not available before April 1998). We have added to this limitation a statement that the rate of disease progression may be different in our cohort due to the predominance of subtype A (3).

3. The fact that the set point viral load tended to be linked to the time to CD4 count<200 cells/ml should be stated in the text and the numbers given.
We have added this information to the results, as requested (1). We have also included the association between set point viral load and mortality.

4. The paper by Glynn et al. should be cited in the discussion. The argument will then be: in this cohort the survival among HIV-infected subjects is similar to that among other seroconverter cohorts (Clin. Infect. Dis. 42(9):1333-9, 2006), in which HIV has been causally related to death among those who are infected (AIDS 21(5):625-32, 2007).
A reference for the Glynn paper has been added (4), and the sentence on HIV and survival edited as suggested by the reviewer (2).

We have reviewed the journal style information per the editors’ request, and carefully formatted our files according to the guidelines provided.

**Point-by-point listing of changes to the manuscript**
Changes to the manuscript are numbered in the order that they appear. Text from the manuscript is shown in italics, with revisions shown in bold italics. References are provided in square brackets, as they are numbered in the manuscript.

1. Results, page 7. We have added the following sentence: “Each 1-unit increase in log_{10} set point viral load was associated with a hazard ratio of 1.31 (95% CI, 0.83-2.07, p = 0.248) for the risk for progression to a CD4 count <200 cells/μl and 1.66 (95% CI, 0.80-3.45, p = 0.176) for the risk of death.”

2. Discussion, page 10. We have revised the sentence on the limitation regarding cause of death as follows: “Third, the cause of death was unknown for most of the women included, and not all deaths can be attributed to HIV-1 disease despite rigorous efforts to trace women. However, survival among HIV-1-seroconverters in our cohort prior to antiretroviral therapy is similar to that
of other seroconverter cohorts, in which HIV-1 has been causally related to
death among those infected [17, 18].”

3. Discussion, page 10. We have added the following text: “Fourth, most of the
women in our cohort are infected with HIV-1 subtype A, which has been
associated with a slower rate of disease progression, compared to other
subtypes [19]; this may have influenced the associations we detected.”

4. References, page 14. We have added two references, and renumbered
accordingly.

Thank you for your provisional acceptance of this manuscript for publication in BMC
Infectious Diseases. We hope that the revisions we have made adequately address the
reviewer’s concerns, and that you will now find the manuscript acceptable for
publication. Please do not hesitate to contact us if you have any further questions.

Sincerely,

Susan M. Graham, MD MPH

References
with Faster Disease Progression than Subtype A in Spite of Similar Plasma HIV-1 Loads.
2. Vasan A, Renjifo B, Hertzmark E, et al. Different rates of disease progression of
HIV type 1 infection in Tanzania based on infecting subtype. Clin Infect Dis
cell count, and CD4 Cell count slope for progression to AIDS and death in untreated