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Comment on: Predictors of immune recovery and the association with late mortality while on antiretroviral treatment in Cambodia

We read with great interest the article by van Griensven and Thai, who report on the risk factors for late mortality after antiretroviral therapy (ART) initiation in a cohort of 2840 patients in Cambodia.[1] The main risk factor identified was time-updated CD4 cell count, which is consistent with the findings of other studies in different settings. They also analysed predictors of immune recovery, including the use of different non-nucleoside reverse transcriptase inhibitors (NNRTI). Their analysis showed a negative effect of the use of nevirapine (NVP) versus efavirenz (EFV) on CD4 recovery over time. This finding is very interesting as it is contradictory to other reports, including a randomised open-label trial[2] and a meta-analysis.[3]

We are concerned that the reported finding is due to bias by indication: the prescription of a EFV- or NVP-based regimen is not due to chance alone but related to multiple factors, possibly leading to systematic differences between the two groups. This bias is common in observational cohort studies estimating causal effects of treatment.[4]

In our prospective research cohort in Kampala, Uganda, we did a similar analysis of factors associated with CD4 recovery over a period of 6 years in 356 patients initiating first-line NNRTI-based ART who were virologically suppressed from 6 months onwards (J. Sempa et al., unpublished data). Observations stopped when patients were switched to second-line therapy. To minimise bias by indication by ART regimen, we calculated a propensity score for the use of NVP versus EFV using a multivariable logistic model including all the factors potentially associated with NNRTI assignment in our setting: gender, age, baseline CD4 count, weight, year of ART initiation and ART funding source, and any interactions between these factors.

A bivariable linear mixed effects model with and without the use of the propensity score as a weighting factor was used to calculate coefficients representing the effect of EFV versus NVP on the slope of CD4 count change. The unweighted analysis showed a negative effect of EFV (−52.88, 95% CI −80.67 to −25.08; $p < 0.001$), but the weighted analysis showed no association (63.43, 95% CI −171.96 to 298.82; $p = 0.597$).

Use of propensity scores showed the association of different NNRTIs and CD4 recovery in our cohort to be similar to those observed in the 2NN Study[2] and a subsequent meta-analysis.[3] This exemplifies the strong bias by indication effect that can be present in observational cohort studies. Estimating causal effects of treatment in such a setting should therefore be done with utmost caution.

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Comment on: The seroprevalence of *Helicobacter pylori* and its relationship to malaria in Ugandan children

Gupta et al.[1] present seroprevalence of *Helicobacter pylori* in 200 children living in Kampala, Uganda, more specifically in the area of Mulago III, without attention to our previously published work in children living in the adjacent neighbourhood of Mulago II,[2] where we studied the prevalence of *H. pylori* antigen in 427 apparently healthy children using a non-invasive faecal monoclonal antibody test. Gupta et al.[1] are confirming our three main findings: increasing prevalence with age; boys are more frequently colonized with *H. pylori* compared with girls; and that children living in households with the lowest wealth index are more often colonized. However, we found a remarkably lower prevalence of 44.3% in children aged 0–12 years old. We have also studied 219 HIV-infected, HAART-naive children admitted to the Mulago National Referral Hospital[3] which is within walking distance of the Mulago III neighbourhood. These children had an overall *H. pylori* prevalence of only 22.5%.

The monoclonal antibody test has the advantage of showing an ongoing and not cleared infection which might not be the case if using a test based on serology. Consequently, the new (August 2011) joint European and American guidelines on *H. pylori* in children in high-income countries[4] do not recommend the use of serology in a clinical setting in children due to highly variable sensitivity and specificity for detection of antibodies (IgG or IgA) against *H. pylori* in children. Even if these guidelines are for clinical use and for children in high-income countries, the methodological issues relating to the use of serology to detect *H. pylori* merited a broader discussion than the one provided by Gupta et al.[1] The most reliable non-invasive test to use in children in all ages today is a monoclonal antibody test.

Our clinical experience in our study group is that airway infections in children living in the Mulago area in Kampala are frequently treated with antibiotics. Amoxicillin is frequently used. Deworming campaigns take place (1–2 per year), in the whole country of Uganda, with partially free treatment in school. If this coincides with an ongoing treatment for airway infections, an accidental treatment of *H. pylori* can take place, but serology tests might remain positive for a long time after.

Further, to the best of our knowledge, there is no strong evidence that *H. pylori* infections are associated with frequent diarrhoea as indicated in the introduction of the paper by Gupta et al.[1]

From a research ethical point of view, it is remarkable that such a large study was carried out next to well-established research institutions such as Makerere University and Mulago Hospital in this millennium without involving any local researchers.

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