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Additive effects of isoniazid preventive therapy and HAART

Jonathan E. Golub[a,b], **Richard E. Chaisson**[a,b], and **Neil A. Martinson**[a,c]

[a]Johns Hopkins University School of Medicine

[b]Johns Hopkins University, Bloomberg School of Public Health, Baltimore, Maryland, USA

[c]Perinatal HIV Research Unit, University of Witwatersrand, Witwatersrand, South Africa

Our thanks to Wood *et al.* [1] for their interest in our study describing the benefits of isoniazid preventive therapy (IPT) and HAART for HIV-infected patients being followed prospectively in South Africa [2]. Tuberculosis is an exceedingly common opportunistic infection and the leading cause of death in HIV-infected adults, irrespective of their HAART treatment status. Given that the effectiveness of IPT has been clearly demonstrated in multiple trials and cohort analyses [3] but its uptake incredibly poor in resource-limited settings [4], we were interested in understanding the impact of both HAART and IPT in a clinical cohort in South Africa, a very high-burden area. As clearly stated in our study, clinical cohort studies are subject to a number of limitations and potential biases that are not present in randomized trials. Conversely, however, clinical cohorts represent a much more real life situation than clinical trials, in which patients are not excluded because of comorbid conditions and adherence to protocols is imperfect. We endeavored to learn the most from our data by constructing analyses that minimized potential biases and adjusted for important covariates, including time and CD4 cell counts. We believe that Wood *et al.* [1] may have misunderstood some of these analytical methods in their critique of our results.

First, we were careful to categorize all follow-up time into four categories according to exposure to IPT and/or HAART: treatment naive, IPT only, HAART only, and both IPT and HAART – the majority of whom received IPT prior to receiving HAART. Thus, we compared incidence of tuberculosis during treatment-naive follow-up with incidence in each of the different treatment categories and did not use time accrued in a different category in our calculations. For example, the patients who received both IPT then HAART (without being censored) contributed person time to three categories (treatment naive, IPT only, and IPT/HAART), and any tuberculosis event would be attributed to the IPT/HAART time period. The simple rate calculations based on these person-years can be affected by survival bias, with person-years in one exposure group tending to be earlier during follow up than those exposed to both. For the Kaplan–Meier and Cox models, however, all patients followed a time-since-cohort entry timeline, with staggered entry according to category transitions. Thus, for example, a patient who has been followed for exactly 2 years and is on both IPT and HAART is compared at that instant with all the rest who also have survived (not been censored) at least 2 years. We did not directly compare patients receiving HAART with those receiving both IPT and HAART; incidence within each of these time periods was compared with incidence among treatment-naive patients. What our data show, therefore, is that the point estimate of tuberculosis incidence for those who received both IPT and HAART is considerably lower than for those who received either intervention alone, suggesting an interaction between these two interventions.

Correspondence to Jonathan E. Golub, PhD, MPH, Johns Hopkins University School of Medicine, 1550 Orleans Street, Baltimore, MD 21231, USA Tel: +1 443 287 2969; fax: +1 410 955 0740; jgolub@jhmi.edu.

As noted by Wood *et al.* [1], CD4 cell counts are important potential confounders in an analysis such as ours, and we adjusted for baseline CD4 cell counts accordingly. The median CD4 cell count at time of IPT for everyone receiving IPT, including those who later received HAART, was 399 cells/μl. Patients who received HAART following IPT had a median CD4 cell count of 176 cells/μl at HAART initiation, similar to those patients who received HAART and no IPT (median CD4 cell count, 145 cells/μl). Our adjusted Cox proportional hazards model revealed that patients receiving both IPT and HAART had a significantly reduced risk of tuberculosis after adjustment for baseline CD4 cell count (89% reduction). The protective effect of HAART only compared with treatment-naive patients was significant as well (64% reduction). As stated above, these estimates cannot be directly compared in our analysis, but clearly suggest that patients receiving both therapies have greater protection.

Wood *et al.* [1] also wonder whether IPT alone was not significantly associated with protection from tuberculosis because of the inclusion of many patients with CD4 cell counts less than 200 cells/μl. When we examined only patients with baseline CD4 cell count more than 200 cells/μl, the effectiveness of IPT was only slightly better than in our overall model [adjusted hazards ratio (aHR), 0.81; 95% confidence interval (CI), 0.48–1.38 versus overall aHR 0.87; 95% CI, 0.55–1.36].

As noted by Wood *et al.* [1], the benefits of IPT have been clearly established, and its use is recommended by the WHO. Although it is also clear that HAART reduces the risk of tuberculosis, rates are more than 10-fold higher than in HIV-uninfected individuals, and our data suggest that IPT can further reduce this risk. Although it is reasonable to study whether IPT significantly improves protection compared with HAART alone in patients with advanced HIV infection, we do not believe that it is appropriate to withhold IPT from patients in HAART roll out programs pending the results of studies. By analogy, when HAART was first introduced and its benefits were being appreciated, guidelines for prevention of opportunistic infections remained in place, including use of cotrimoxazole and azithromycin. Only when controlled trials demonstrated that these therapies were not necessary following a response to HAART, did guidelines change. If clinical trials were to show that there is no additional benefit to IPT in patients receiving HAART (and we are skeptical of this), then Wood *et al.* [1] would be justified in recommending that IPT be omitted from HAART treatment programs. In the meanwhile, ignoring the results of controlled trials with more than 11 000 participants and the results of cohort studies with approximately 15 000 participants [2,5] that show the benefits of IPT exposes millions of patients to an unjustified risk.

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