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Are the effects of isoniazid preventive therapy and HAART additive in preventing of HIV-associated tuberculosis?

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Golub *et al.* recently reported a retrospective analysis of rates of incident tuberculosis (TB) in a large observational cohort of 2778 patients accessing HIV care in rural and urban South Africa [1]. The TB incidence rate was highest (7.1/100 person-years; 95%CI 6.2–8.2) during the period of care when patients did not receive isoniazid preventive therapy (IPT) or highly active antiretroviral therapy (HAART). The rates were lower during person-time that accrued during follow-up after initiation of IPT (5.2/100 PYs; 95%CI 3.4–7.8) and during follow-up on HAART alone (4.6/100PYs, 95%CI 3.4–6.2). The rate was lower still (1.1/100 PYs 95%CI 0.2–7.6) during person-time accrued during sequential IPT and HAART (IPT +HAART). The authors concluded that TB risk was significantly reduced by IPT in HAART-treated adults. It was further concluded that “the dramatic reduction in TB risk” demonstrated in this study together with supportive data from a similarly analysed study from Brazil [2] indicate that widespread use of IPT should be implemented in conjunction with the roll-out of HAART.

Firstly, it is notable that HAART alone but not IPT alone was associated with significantly lower TB incidence rates compared to the non-intervention group in both adjusted and unadjusted analyses. In addition, no significant difference was observed in the incidence rates comparing the HAART only and the IPT+HAART groups. Thus, these analyses do not demonstrate a significant additive effect in TB prevention by treating patients with both IPT and HAART.

In further analysis, Kaplan-Meier survival estimates appeared to support a significant difference between TB-free survival in the IPT+HAART group and all other treatment groups. Surprisingly, however, the Kaplan-Meier analysis showed that no TB events occurred among patients in the IPT+HAART group during the first 3 years of observation despite low CD4 cell counts (median, 176 cells/ μ L at the time of HAART initiation). We are concerned that these conclusions may have been erroneously drawn as a result of analysis of groups with significant selection bias.

Among 62 patients within the IPT+HAART group, 61 had initiated IPT a median of 1.0 years (IQR 0.5–1.9) before starting HAART. In this analysis, person-time of observation was censored when patients developed TB. Thus, only selected patients who remained alive and free of TB during the period between IPT initiation and HAART initiation would be eligible for inclusion in the IPT+HAART group. Thus, the TB incidence rate during the median of 1.0 years (IQR 0.5–1.9) of observation before HAART would have been inappropriately assessed as zero cases/100 PYs. However, the IPT-HAART group had markedly lower CD4 cell counts than the IPT alone group and therefore the true incidence rate would very likely have exceeded 5.2 cases/100 PYs in the pre-ART period, potentially adding several more cases to the single case reported in this treatment group. Furthermore, no deaths were reported in this survival analysis and additional cases of TB may have remained unascertained among those who died. Inclusion of such additional TB cases would likely have negated the apparent observed group differences in the Kaplan-Meier analysis.

The benefits of IPT in HIV-infected patients included in randomised controlled trials have been clearly demonstrated [3,4]. However, the lack of significant effectiveness of IPT alone in this South African study and in the large Brazilian cohort study [2] raises concerns about the effectiveness of this intervention in routine clinical practice. Potential explanations for lack of IPT efficacy may include poor adherence and the inclusion of TST-negative individuals. However, in both these studies the strongest predictor of TB incidence rates was the baseline CD4 cell count, with 60-90% lower rates in those with CD4 cell strata above 200 cells/uL. Furthermore, there are no data from randomised controlled trials that specifically demonstrate the efficacy of primary IPT at low CD4 cell counts. We wonder therefore whether the inclusion of significant numbers of individuals with CD4 cell counts under 200 cells/uL may partially explain the apparent lack of statistically significant reduction of TB rates during and after IPT.

In view of the clear benefits of HAART on survival and TB incidence [5], it would be unethical to perform studies of 6 months IPT or placebo before initiating HAART in eligible patients. TB rates during early HAART are very high and are related to the baseline CD4 cell count at treatment initiation, remain high in those with sub-optimal CD4 cell recovery and continue to be elevated even in those with optimal CD4 cell recovery [7,8,9]. There remains an urgent need to demonstrate an additive benefit of IPT over and above CD4 cell recovery after initiation of HAART and to identify the optimal timing of IPT before this can be scientifically justified as an integrated component of HAART roll-out.

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