Reply to Daskapan et al

TO THE EDITOR—We agree with the views of Daskapan et al on lower blood levels of antituberculosis drugs in human immunodeficiency virus/tuberculosis coinfection facilitating emergence of drug resistance. Pharmacokinetic studies must become an integral part of all randomized controlled clinical trials.

A possible explanation for highly active antiretroviral therapy (HAART) not being a significant factor for preventing acquired rifampicin resistance, in our logistic regression analysis, is the varied timing of HAART initiation in the cohort that received HAART [1]. Seventy-seven patients in clinical trial NCT00332306 [2] were initiated on HAART at 2 months after antituberculosis therapy (ATT) initiation, whereas 39 patients from clinical trial NCT00933790 [3] (ongoing) had HAART initiated within the 2 months, according to prevailing national antiretroviral therapy guidelines. Acquisition of ATT drug resistance could have occurred early in the treatment period, thus offsetting the protective effect of HAART that was started subsequently.

Our study, NCT00376012, [4] was the first report of a thrice-weekly ATT regimen associated with acquired rifampicin resistance. In our ongoing trial, low drug levels were found in patients on daily as well as intermittent regimens [5]. Emergence of drug resistance in the context of dual infection is multifactorial where lower drug concentrations also contribute to selective propagation of mutant strains [6]. The most important research question in our ongoing study (NCT00933790) is to relate blood levels of ATT with treatment outcomes, helping to ascertain the need for therapeutic drug monitoring and adjusting dosages appropriately.

Regarding the role of cotrimoxazole on acquired rifampicin resistance, most patients received it, as the median CD4 count of the cohort was 156 cells/µL (interquartile range [IQR], 80–290 cells/µL). Notably, patients who developed acquired rifampicin resistance had a significantly lower CD4 count at baseline (median, 101 [IQR, 54–185] vs 165 [IQR, 86–297]) compared to those without acquired rifampicin resistance [4].

Ideally, therapeutic drug monitoring should be made available (eg, with the use of dried blood spot analysis). But in its absence, optimization of drug dosing based on local pharmacokinetic studies is another feasible option.

Note

Potential conflict of interest. Both authors: No potential conflict of interest.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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Clinical Infectious Diseases® 2015;61(1):138–9
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DOI: 10.1093/cid/civ240