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Reply to "Strategy To Limit Sampling of Antituberculosis Drugs Instead of Determining Concentrations at Two Hours Postingestion in Relation to Treatment Response"

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As the number of studies examining the relationship between plasma concentrations of antituberculosis (anti-TB) drugs and treatment response is limited, our Indonesian-Dutch team performed a practical field pharmacokinetic study recently published in this journal (1). Despite large interindividual variability in plasma concentrations of TB drugs at 2 h postdose ($C_{2\ h}$), no associations were found between isoniazid, rifampin, and pyrazinamide $C_{2\ h}$ values and sputum culture results after 8 weeks of TB treatment. These results contrast with findings in several (2–6) but not all (7, 8) similar studies.

Akkerman et al. reiterate several limitations and considerations that were already mentioned by us in our publication, including that only a single sample at 2 h postdose was taken to estimate maximum concentrations in serum (C_{max}) of the TB drugs; assessment of total exposure (the area under the concentration-time curve from 0 to 24 h [$AUC_{0\text{-}24\ h}$]) would be preferable. However, sampling at 2 h was not performed to estimate C_{max}, but rather $C_{2\ h}$ values were used as a correlate of total exposure ($AUC_{0\text{-}24\ h}$) or C_{max}. Very high correlations were found between rifampin's $C_{2\ h}$ and $AUC_{0\text{-}24\ h}$ (Spearman's ρ, 0.950; $P < 0.001$) and between isoniazid's $C_{2\ h}$ and $AUC_{0\text{-}24\ h}$ (Spearman's ρ, 0.967; $P < 0.001$), yet the correlation was less for pyrazinamide's $C_{2\ h}$ and $AUC_{0\text{-}24\ h}$ values (Spearman's ρ, 0.700; $P = 0.04$), as mentioned in our paper (1). Thus, sampling at 2 h postdose was actually meant as a "limited-sampling strategy." Nevertheless, we agree that a single sample is often suboptimal for estimating $AUC_{0\text{-}24\ h}$, and any limited-sampling approach should be evaluated in terms of predictive performance (bias, precision) if enough full pharmacokinetic curves are available. Recently, we developed limited-sampling equations for simultaneous assessment of $AUC_{0\text{-}24\ h}$ values of all first-line TB drugs in Dutch patients, and similar equations may be derived for Indonesian TB patients (9).

In this respect, we also emphasize that we did not perform "classical $C_{2\ h}$ monitoring" in the sense that we used predetermined C_{max} cutoff values to classify patients as having either low or adequate drug concentrations based on their $C_{2\ h}$ values. Instead, odds ratios (ORs) for a poor treatment response were assessed for an interquartile range increase in $C_{2\ h}$, i.e., an increase in $C_{2\ h}$ values from the 25th percentile to the 75th percentile of the observed $C_{2\ h}$ values (interquartile OR).

Akkerman et al. also point to MIC values, which were not assessed in our study to calculate pharmacodynamic indices of the TB drugs. Of course, MIC values should ideally be measured when exposure-response relationships are evaluated. Our practical field study allowed only for an assessment of drug susceptibility, and patients with drug-resistant isolates were excluded. Available studies that found associations between exposure and response for TB drugs did so without taking MIC values into consideration (2–6).

Akkerman et al. question how much closer we are to predicting response based on plasma concentrations of anti-TB drugs after our study. Despite its limitations, we still believe that our study of a relatively large cohort of 181 patients suggests that such a prediction is not easily possible in Indonesian pulmonary TB patients, based on $C_{2\ h}$ values of isoniazid, rifampin, and pyrazinamide that correlate with $AUC_{0\text{-}24\ h}$ values. We are puzzled by this finding, enumerated several possible explanations in our paper, and have started follow-up research into the pharmacokinetics and pharmacodynamics of TB drugs in Indonesian TB patients.

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This is a response to a letter by Akkerman et al. (doi:10.1128/AAC.01535-13).

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