The relationships between antituberculosis drug exposure and treatment effects on humans receiving multidrug therapy are complex and nonlinear. In patients on treatment, an analysis of the rate of decline in the sputum bacillary burden reveals two slopes. The first is the α-slope, which is thought to reflect bactericidal effect, followed by a β-slope, which is thought to reflect sterilizing activity. We sought to characterize the effects of standard first-line treatment on sterilizing activity. Fifty-four patients receiving combination therapy for pulmonary tuberculosis in a clinical trial had drug concentrations measured and Mycobacterium tuberculosis isolates available for MIC identification. Sputum sample cultures were performed at baseline and weekly for 8 weeks. A time-to-event model based on the days to positivity in the liquid cultures was used to estimate the β-slope. The pharmacokinetic parameters of rifampin, isoniazid, ethambutol, and pyrazinamide were determined for each patient. Multivariate adaptive regression splines analyses, which simultaneously perform linear and nonlinear analyses, were used to identify the relationships between the predictors and the β-slope. The potential predictors examined included HIV status, lung cavitation, 24-h area under the concentration-time curve (AUC), peak drug concentration (Cmax), AUC/MIC ratio, Cmax/MIC ratio, and the time that that concentration persisted above MIC. A rifampin Cmax of >8.2 mg/liter and a pyrazinamide AUC/MIC of >11.3 were key predictors of the β-slope and interacted positively to increase the β-slope. In patients with a rifampin AUC of <35.4 mg · h/liter, an increase in the pyrazinamide AUC/MIC and/or ethambutol Cmax/MIC increased the β-slope, while increasing isoniazid Cmax decreased it, suggesting isoniazid antagonism. Antibiotic concentrations and MICs interact in a nonlinear fashion as the main drivers of a sterilizing effect. The results suggest that faster speeds of sterilizing effect might be achieved by omitting isoniazid and by increasing rifampin, pyrazinamide, and ethambutol exposures. However, isoniazid and ethambutol exposures may only be of importance when rifampin exposure is low. These findings need confirmation in larger studies. (This study has been registered at controlled-trials.com under registration no. ISRCTN80852505.)

Received 21 July 2014 Returned for modification 31 August 2014 Accepted 3 October 2014 Accepted manuscript posted online 13 October 2014


Address correspondence to Helen McIlerton, helen.mcilleron@uct.ac.za.

* Present address: Emmanuel Chigutsa, Global PK/PD and Pharmacometrics, Eli Lilly and Company, Indianapolis, Indiana, USA.

Supplemental material for this article may be found at http://dx.doi.org/10.1128/AAC.03931-14.

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doi:10.1128/AAC.03931-14
physical models identified two bacterial subpopulations in 154 patients with pulmonary tuberculosis (12). The first subpopulation, in which bacteria were killed rapidly, with a half-life of 1.8 days, was 41-fold larger than the second. The second population, with bacterial kill rates described by the $\beta$-slope, declined, with a half-life of 39 days (12). In this study, the $\beta$-slope was used as a surrogate marker of sterilizing activity. Here, we investigated the effect of drug concentrations on the $\beta$-slope, with the assumption that the $\beta$-slope reflects sterilizing activity.

Several studies have shown the importance of antituberculosis drug concentrations on the rate of kill of $M. \text{tuberculosis}$ in hollow fiber systems (13, 14), animal models of tuberculosis (15, 16), and patients (10, 11). Some clinical studies have also shown low drug concentrations to be associated with poorer outcomes in patients receiving combination therapy (17, 18). However, the magnitude and range of the relationships between drug exposure and sterilizing activity and the speed of the sterilizing effect have yet to be elucidated in tuberculosis patients on a multidrug regimen. In general, the relationship between drug concentrations and their effects in biological systems is nonlinear (19, 20), characterized by discontinuities, and of a higher order of complexity. Standard linear regression methods offer a limited approach to the analysis of such relationships. Here, we utilized multitarget adaptive regression splines (MARS) to identify factors that are predictive of sterilizing activity in patients with pulmonary tuberculosis. By allowing for possible nonlinear patterns in the data and being able to detect interactions between variables, MARS can uncover complex data structures often hidden in high-dimensional data (21). MARS has been used to successfully identify the predictors of disease progression or the efficacy of therapeutic interventions in a variety of medical contexts (22–24), and it outperforms other methods in identifying complex nonlinear disease-risk relationships (25). We used the $\beta$-slope as a measure of the sterilizing effect occurring during the first 8 weeks of therapy. Mathematical modeling has enabled the separation of the lower rate of kill of the persisting subpopulation from that of more susceptible organisms (12), thereby providing a powerful measure against which to evaluate the sterilizing activities of the drugs (i.e., using the $\beta$-slope).

Materials and Methods

Study participants. Patients were randomized to receive micronutrient or placebo intervention in a previously conducted prospective double-blind controlled study of 154 patients from Cape Town, South Africa (26). The study received ethical approval from the University of Cape Town ethics committee and was done in accordance with the Helsinki Declaration. The micronutrient intervention had no effect on the outcomes (26). A description of the primary study has been published (26). The patients were recruited at baseline and followed up weekly for 8 weeks after starting treatment. There were no study visits beyond these 8 weeks of treatment; hence, long-term outcomes were not available.

Patients with sputum smear-positive pulmonary tuberculosis were treated with weight-based doses of rifampin, isoniazid, pyrazinamide, and ethambutol as a fixed-dose combination (FDC) of tablets containing 150 mg of rifampin, 75 mg of isoniazid, 400 mg of pyrazinamide, and 275 mg of ethambutol (27). Patients weighing 38 to 54 kg received 3 tablets, those weighing 55 to 70 kg received 4 tablets, and those >70 kg received 5 tablets once daily. Of these 154 patients, 54 had drug plasma concentrations and baseline MICs determined for each drug. Consecutive patients were invited to participate in the pharmacokinetic study, for which separate consent was obtained. The analysis described here includes these 54 patients who were a random subset of the parent study.

Pharmacokinetic analyses. Blood was drawn from patients for pharmacokinetic sampling ≥1 month after the patients commenced treatment. Each patient had between 4 and 8 samples drawn over a period of 7 h after the drugs had been administered. Twenty-four patients had pharmacokinetic samples drawn on a second occasion (one month after the first sampling had been done), thereby enabling the testing of within-subject variability of the drug exposures. Individual patient steady-state 24-h area under the concentration-time curve (AUC) and peak drug concentrations ($C_{\text{max}}$) were identified from pharmacokinetic models implemented in NONMEM 7.2 (Ellicott City, MD). The models built using data from patients in this cohort have been published elsewhere for rifampin (28) and pyrazinamide (29), while those used to describe the pharmacokinetics of isoniazid (30) and ethambutol (31) were modified from the literature. Further details on the pharmacokinetic models are delineated in the supplemental material.

Determination of bacillary kill rates. The sputum specimens were processed for culture on liquid medium using the Bactec MGIT 960 system (Becton Dickinson, Sparks, MD). Further details on the sputum processing can be found in the supplemental material. The TTP was recorded in days. These data were used to build a time-to-event model to describe the treatment response in patients, as outlined in our earlier work (12). In this model, the likelihood of having a positive sputum culture was estimated for patients who had a positive culture result at a particular time, while the survival (probability of no event) was estimated for patients who had a negative culture result. The hazard of a positive culture result was directly related to the bacillary load predicted from the model. A biexponential model described the decline in bacillary load using the $\alpha$- and $\beta$-slopes, with the $\beta$-slope reflecting terminal sterilizing activity. Individual estimates of the $\beta$-slope were generated by the model for evaluating the effects of drug exposure on sterilizing activity in a MARS analysis.

MIC determination. The Bactec MGIT 960 system with the EpiCenter software and TBxIST application were used to determine the MICs of the $M. \text{tuberculosis}$ isolates prior to therapy (32). The Bactec MGIT 960 SIRE kit was used to make stock solutions for isoniazid, rifampin, and ethambutol, while pyrazinamide was prepared from the Bactec MGIT 960 PZA kit (Becton Dickinson Biosciences, Sparks, MD). Further details can be found in the supplemental material.

Data analysis. The MARS analysis was implemented using the Salford Predictive Modeler 7.0 (Salford Systems, San Diego, CA) to identify the drug exposures linked to the $\beta$-slope. MARS is a nonparametric regression data analysis technique that combines recursive partitioning with fitting of splines to variables in the data set. The method identifies the significant predictor variables, which enables splitting of the data into subregions of interest, while the spline fitting enables the determination of relationships within the subregions (33). This can be viewed as piecewise linear regression models in small ranges of values, with transition points at hinges, which are described by the lines of best fit for subregions of the data. The location and number of hinges are automatically determined by the data (33). Here, “interaction” refers to the effect of a drug on the dependent variable as a consequence of its association with exposure to another clinical factor, such as another drug. Such interactions can be additive, synergistic, or antagonistic. The splines and interactions are described by basis functions (BFs). MARS works by first fitting an overly large model with BFs (forward selection), as long as they improve the fit (higher $R^2$), with no penalty for inclusion. This leads to overfitting. The next step is backward deletion, whereby MARS identifies one BF whose removal will have the least impact on the residual sum of squares; this pruning process is repeated with each BF in the model. BFs are thus eliminated based on generalized cross-validation error (GCV), which is the average squared residual multiplied by a penalty that is proportional to the number of BFs in the model (33). The MARS analysis is further explained in the supplemental material.

The potential predictors of the primary outcome (i.e., the $\beta$-slope) included in the MARS analysis were AUC, $C_{\text{max}}$/AUC/MIC, $C_{\text{max}}$/MIC, individual drug MICs, the percentage of the 24-h dosing interval that

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concentration exceeded MIC (%$T_{\text{MIC}}$), HIV status, and the presence/absence of lung cavitation. The effects of the predictors on the $/H$-slope were related in a series of BFs that describe the data in linear combination.

The secondary clinical outcome measured was 2-month sputum conversion (defined as both week-7 and week-8 culture results being negative after 8 weeks of treatment). Based on the MARS findings, standard statistical tests were used to determine the odds ratios of 2-month sputum conversion using contingency tables in Prism 4.0 (GraphPad Software, La Jolla, CA).

RESULTS

Patient demographics. Of the 54 study participants, 63% were male, 13% were HIV positive, 88% had lung cavities present at baseline, and 28% had converted to 2 consecutive negative sputum culture results by the end of the follow-up period (8 weeks of treatment). The median (range) for weight, body mass index, and age were 52 (38 to 73) kg, 19 (14 to 29) kg/m², and 28 (18 to 55) years, respectively. The clinical characteristics of this subset of patients did not differ substantially from those in the larger study of 154 patients (26).

Patient pharmacokinetic measures and MICs. The final parameter estimates of the population pharmacokinetic models used to describe the pharmacokinetics of rifampin, isoniazid, pyrazinamide, and ethambutol are shown in Tables S1 to S4 in the supplemental material, respectively. The 4 drugs exhibited substantial pharmacokinetic variability, as shown in Fig. 1a to h. The ranges of the observed concentrations and the parameters are shown in Table 1; more details are shown in the supplemental material. Table S5 in the supplemental material shows that the primary pharmacokinetic measures of the different drugs did not significantly covary, indicating that multicollinearity would be unlikely to complicate the interpretation of the effects of the different drugs on the $/H$-slope. Figure 2 shows the distribution of the MICs among the $/H$-tuberculosis isolates. For purposes of calculations and data analysis, the 2 patients with an isoniazid MIC of $>0.1$ mg/liter were assumed to have an $/H$-tuberculosis MIC of 0.2 mg/liter, and the 2 patients with a pyrazinamide MIC of $>100$ mg/liter were assumed to have an $/H$-tuberculosis MIC of 200 mg/liter. When MIC variability was taken into account by indexing the

<table>
<thead>
<tr>
<th>Drug</th>
<th>$C_{\text{max}}$ (mg/liter)</th>
<th>AUC (mg · h/liter)</th>
<th>$C_{\text{max}}$/MIC</th>
<th>AUC/MIC</th>
<th>% time drug concn is above MIC (h)</th>
<th>MIC (mg/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>2.5 (0.7–7.7)</td>
<td>14 (6.2–63)</td>
<td>43 (8.2–187)</td>
<td>272 (52–1,252)</td>
<td>79 (54–100)</td>
<td>0.05 (0.025–0.2)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>7.3 (3.7–11)</td>
<td>48 (18–126)</td>
<td>69 (13–401)</td>
<td>454 (80–3,934)</td>
<td>58 (26–100)</td>
<td>0.125 (0.016–0.5)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>34 (11–90)</td>
<td>420 (153–798)</td>
<td>1.0 (0.17–4.6)</td>
<td>12 (2.6–60)</td>
<td>0 (0–88)</td>
<td>25 (12.5–200)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>3.1 (1.6–5.1)</td>
<td>32 (16–73)</td>
<td>2.0 (0.46–5.5)</td>
<td>20 (5.8–79)</td>
<td>25 (0–73)</td>
<td>1.25 (0.6–5)</td>
</tr>
</tbody>
</table>
AUC and $C_{\text{max}}$ in each patient to the MIC of the $M. \text{tuberculosis}$ isolate in each patient, so as to take into account both microbial and pharmacokinetic variability, variability further increased, as shown in Fig. 3a to h. None of the MIC indexed parameters were normally distributed, apart from the ethambutol $C_{\text{max}}$/MIC ratio (Shapiro-Wilk W test, $P = 0.06$).

**MARS analysis for primary outcome.** The $\beta$-slope had a median (interquartile range) value of 0.46 week$^{-1}$ (0.22 to 0.77 week$^{-1}$). Five BFs were identified as significant predictors of the $\beta$-slope in the final MARS model and are shown in Table 2. This final model describing the effects of drug concentration and MIC on the $\beta$-slope was described by the equation $\beta$-slope = 0.49 - $0.80 \times BF1 + 0.05 \times BF2 + 0.71 \times BF3 - 0.32 \times BF4 + 0.02 \times BF5$. When a basis function has a positive coefficient, it means that higher drug exposure results in a steeper $\beta$-slope. If it has a negative coefficient, it means that higher drug exposure results in a shallower incline of the $\beta$-slope (i.e., poorer sterilizing activity). The $R^2$ for the predictions of the $\beta$-slope based on the equation above against the actual $\beta$-slopes in patients was 0.85, which we consider a good fit. The cross-validated $R^2$ (used to assess the reliability of the parameter estimates and robustness of the final model) was 0.72. The BFs are described in Table 2. The expressions are conditional at the hinges. BF1, for example, describes the effect of increasing rifampin AUC, which increases the $\beta$-slope until a hinge is seen at an AUC of 35.4 mg/liter, whereupon the effect of the basis function becomes zero. The multiplication of $\beta$-slopes than $\text{max}$ threshold of 8.2 mg/liter; otherwise, the value is $C_{\text{max}}$ = 8.2 mg/liter, multiplied by BF6. If the pyrazinamide AUC/MIC is $>11.3$ and the rifampin $C_{\text{max}}$ is $>8.2$ mg/liter, exposures to the two drugs interact synergistically to enhance sterilizing activity.

**Odds of secondary outcome based on thresholds predicted by MARS.** Patients with 2-month sputum culture conversion (defined as both week-7 and week-8 culture results being negative after 8 weeks of treatment) had higher estimated $\beta$-slopes than patients who failed to convert ($\beta$-slope median, 1.1 versus 0.26 week$^{-1}$; Mann-Whitney U test, $P < 0.0001$). Based on the threshold values predicted by MARS, contingency tables were generated to determine whether there were differences in the 2-month sputum conversion rates between patients with drug concentration exposures above and below those identified by MARS, with the results shown in Table 3. The rifampin $C_{\text{max}}$ threshold of 8.2 mg/liter was significantly associated with the 2-month sputum culture conversion (odds ratio [95% confidence interval {CI}], 3.8 [1.1 to 13.3]). The odds of a negative culture were further increased when a patient also achieved a pyrazinamide AUC/MIC ratio of $>11.3$ (odds ratio [95% CI], 6.0 [1.5 to 23.7]), confirming the positive interaction between pyrazinamide and rifampin exposures in their effect on treatment response.

**DISCUSSION**

To our knowledge, this is the first report that investigates in totality the effects of antituberculosis drug exposure together with MIC, as well as the interaction between these drug exposures, on
the sterilizing activity and 2-month sputum conversion in patients with pulmonary tuberculosis receiving a multidrug regimen. We identified the concentration thresholds at which the concentration-effect relationships occur in patients. Important predictors of sterilizing activity included rifampin AUC and $C_{\text{max}}$, pyrazinamide AUC/MIC, ethambutol $C_{\text{max}}$/MIC, and isoniazid $C_{\text{max}}$.

![Figure 3](http://aac.asm.org/)

**FIG 3** Histograms showing distribution of drug area under the concentration-time curve (24 h) and peak plasma concentration adjusted by the corresponding MIC in study participants. The ratios shown are isoniazid $C_{\text{max}}$/MIC (a) and AUC/MIC (b), rifampin $C_{\text{max}}$/MIC (c) and AUC/MIC (d), pyrazinamide $C_{\text{max}}$/MIC (e) and AUC/MIC (f), and ethambutol $C_{\text{max}}$/MIC (g) and AUC/MIC (h).

**TABLE 2** Basis functions identified in final MARS model

<table>
<thead>
<tr>
<th>Basis function</th>
<th>Function</th>
<th>Coefficient in model</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BF1</td>
<td>max (0, 35.4 mg · h/liter - rifampin AUC)</td>
<td>-0.80</td>
<td>Higher rifampin exposure results in increased β-slope, until the AUC reaches 35.4 mg · h/liter, whereupon the effect of the basis function becomes zero. The effect is exerted in 11 of the 54 patients with a rifampin AUC of &lt;34.5 mg · h/liter. In the remaining patients, the basis function is 0.</td>
</tr>
<tr>
<td>BF2</td>
<td>max (0, pyrazinamide AUC/MIC - 2.6) × BF1</td>
<td>+0.05</td>
<td>Higher pyrazinamide AUC/MIC results in increased β-slope, starting at 2.6. The effect is exerted in 11 of the 54 patients with a rifampin AUC of &lt;35.4 mg · h/liter (because of interaction with BF1). In the remaining patients, the basis function is 0.</td>
</tr>
<tr>
<td>BF3</td>
<td>max (0, ethambutol $C_{\text{max}}$/MIC - 0.46) × BF1</td>
<td>+0.71</td>
<td>Higher ethambutol $C_{\text{max}}$/MIC of &gt;0.46 results in increased β-slope. The effect is exerted in 11 of the 54 patients with a rifampin AUC of &lt;35.4 mg · h/liter (because of the interaction with BF1). In the remaining patients, the basis function is 0.</td>
</tr>
<tr>
<td>BF4</td>
<td>max(0, isoniazid $C_{\text{max}}$/0.72 mg/liter) × BF1</td>
<td>-0.32</td>
<td>Higher isoniazid $C_{\text{max}}$ results in decreased β-slope. The effect is exerted in 11 of the 54 patients with a rifampin AUC of &lt;35.4 mg · h/liter (because of the interaction with BF1). In the remaining patients, the basis function is 0.</td>
</tr>
<tr>
<td>BF5</td>
<td>max (0, rifampin $C_{\text{max}}$/8.2 mg/liter) × BF6</td>
<td>+0.02</td>
<td>Higher rifampin $C_{\text{max}}$ (&gt;8.2 mg/liter) results in increased β-slope. The effect is exerted in 12 of the 54 patients with rifampin $C_{\text{max}}$ &gt;8.2 mg/liter and pyrazinamide AUC/MIC &gt;11.3 (BF6). In the remaining patients, the basis function is 0.</td>
</tr>
<tr>
<td>BF6</td>
<td>max (0, pyrazinamide AUC/MIC - 11.3)</td>
<td>Nil</td>
<td>Higher pyrazinamide AUC/MIC (&gt;11.3) results in increased β-slope. The effect is exerted in 30 of the 54 patients with a pyrazinamide AUC/MIC of &gt;11.3. In the remaining patients, the basis function is 0. BF6 serves solely to interact with rifampin $C_{\text{max}}$ (BF5).</td>
</tr>
</tbody>
</table>
TABLE 3 Association between drug exposure above the MARS-predicted threshold and 2-month sputum culture conversion

<table>
<thead>
<tr>
<th>Drug threshold</th>
<th>Odds ratio of negative 2-month culture (95% CI)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin $C_{\text{max}}$ &gt;8.2 mg/liter and pyrazinamide AUC/MIC ratio &gt;11.3</td>
<td>6.0 (1.5–23.7)</td>
<td>47</td>
<td>87</td>
</tr>
<tr>
<td>Rifampin $C_{\text{max}}$ &gt;8.2 mg/liter regardless of pyrazinamide AUC/MIC ratio</td>
<td>3.8 (1.1–13.3)</td>
<td>60</td>
<td>72</td>
</tr>
<tr>
<td>Pyrazinamide AUC/MIC ratio &gt;11.3 regardless of rifampin $C_{\text{max}}$</td>
<td>2.9 (0.78–10.7)</td>
<td>73</td>
<td>51</td>
</tr>
<tr>
<td>Rifampin AUC alone</td>
<td>1.0 (0.7–1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethambutol $C_{\text{max}}$/MIC regardless of rifampin $C_{\text{max}}$</td>
<td>0.80 (0.02–27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid $C_{\text{max}}$ regardless of rifampin $C_{\text{max}}$</td>
<td>0.45 (0.04–4.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$95% CI, 95% confidence interval.
$^b$Ability to correctly identify 2-month sputum culture conversion, i.e., the proportion of patients with culture conversion who were predicted to convert based on the MARS thresholds.
$^c$Ability to correctly identify failure to convert to negative sputum, i.e., the proportion of patients who failed to convert who were predicted to fail based on the MARS thresholds.
strengthened the analysis, allowing definition of the roles of pyrazinamide and ethambutol. Our current study demonstrates that for pyrazinamide, for which AUC has been shown to be associated with a sterilizing effect (19), the inclusion of MIC data added to the ability to predict the effect on the β-slope and 2-month sputum conversion rate. The inclusion of MIC data also adds useful information that can aid in determining M. tuberculosis susceptibility breakpoints (epidemiological cutoffs) for clinical decision making (45).

Lung cavitation was not a significant predictor of β-slope. This finding is not unexpected, given that lung cavitation influences initial bacillary burden rather than kill rates, as we have shown before (12). The small proportion of patients with HIV infection (13%) may explain the failure to identify HIV infection as a significant covariate. However, other clinical studies have also shown that HIV infection does not appear to have an effect on sputum conversion rates (46, 47).

Our study has several limitations. First, the limited sample size in this study means that the results of the MARS model should be interpreted with caution, and our findings need confirmation in larger data sets. The findings related to isoniazid and ethambutol were limited to 11 patients who had low rifampin exposures. However, the use of a continuous measure of sterilizing activity, such as the β-slope, means that even in those confirmatory studies, relatively small sample sizes will be adequate, compared to those in studies employing dichotomous endpoints, such as relapse. A second possible concern is that our analysis had many possible predictors that might be collinear. However, in Table S5 in the supplemental material, we show that pharmacokinetic parameters were not colinear between the different drugs, thus obviating that concern. Moreover, where different basis functions were included for the same drug as those for rifampin, there was no overlap in the respective data subregions in which the effects of the different measures of a drug were apparent (e.g., there were no patients with a C_{max} of >8.2 mg/liter and AUC of <35.4 mg·h/liter).

In summary, we show the effects of rifampin, pyrazinamide, isoniazid, and ethambutol concentrations and MICs on sterilizing activity. These effects were elucidated for each drug as part of a multidrug regimen in patients, and the findings are thus directly applicable to the clinical setting. In patients with low rifampin exposure, isoniazid had a detrimental effect on sterilizing activity, and clinical studies to confirm the effect of the removal of the drug from regimens are warranted. A rifampin C_{max} of >8.2 mg/liter coupled with a pyrazinamide AUC/MIC ratio of >11.3 is associated with both higher sterilizing activity and higher 2-month sputum conversion rates. Last, the sterilizing effect of ethambutol is evident but only at low rifampin exposures. This work suggests that higher drug exposures (except for isoniazid) result in higher sputum conversion rates.

ACKNOWLEDGMENTS
This work was supported by grants from the Clinical Infectious Diseases Research Initiative (CIDRI) Wellcome Trust Fund 412164 (to E.C.), the National Research Foundation (NRF) South Africa (2067444 and Research Council of Norway [RCN] 180353/S50), the Norwegian Programme for Development, Research, and Higher Education (NUFUPRO-2007/10183), Research Council of Norway (RCN) (183694/S50), the South African Medical Research Council, and the National Institutes of Health (RO1AI079497) to J.G.P. and T.G.

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