An Updated Systematic Review and Meta-analysis on the Treatment of Active Tuberculosis in Patients With HIV Infection

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Background. Human immunodeficiency virus (HIV) infection increases the risk of poor outcomes in active tuberculosis. We updated a systematic review and meta-analysis assessing the effects of duration of rifamycins, schedule of dosing, and antiretroviral therapy (ART) on failure, relapse, death during treatment, and acquired drug resistance (ADR) in patients with HIV and active tuberculosis.

Methods. We searched for randomized control trials (RCTs) and observational studies published between January 2008 and November 2011. We pooled risk differences (RD) from RCTs comparing rifampin for ≥9 months and 6 months. Within strata of the 3 treatment covariates, we calculated pooled risks and adjusted odds ratios (aORs) using outcomes from RCTs and observational studies.

Results. After screening 2293 citations, 7 studies were added in the update. Risk of relapse was lowered with rifampin treatment for ≥9 months compared with 6 months (pooled RD = −9.1%; 95% CI, −16.5, −1.8). Odds of relapse were higher with shorter durations of rifamycins (aOR 2 vs ≥8 months = 5.0 [1.9, 13.2]; 6 vs ≥8 months = 2.4 [1.2, 5.0]) and in the absence of ART (aOR = 14.3, [2.1, 97.8]). Post hoc meta-regression restricted to arms with ART demonstrated no associations between rifamycin duration, dosing schedule, and outcomes.

Conclusions. In patients with HIV and active tuberculosis, ART reduces the risk of TB relapse. Use of rifamycins for ≥8 months and daily dosing in the intensive phase also improve TB treatment outcomes; however, a paucity of evidence makes their importance less clear for patients on ART. There is an urgent need to increase the number of coinfected patients receiving ART.

In 2010, persons with human immunodeficiency virus (HIV) infection comprised 13% of incident cases of tuberculosis and 25% of tuberculosis-associated deaths [1]. The HIV pandemic disproportionately impacts tuberculosis control efforts in areas of the world with limited medical and public health resources; Africa alone bears 82% of the global burden of HIV-tuberculosis coinfection [1].

Infection with HIV increases the risk of poor tuberculosis treatment outcomes including death [2–7], relapse [8–13], and acquired drug resistance to antituberculosis medications [12–16]. These worse outcomes have raised concerns surrounding the use of standard tuberculosis treatment regimens in patients with HIV.

In 2010, we published a systematic review and meta-analysis on the effects of rifamycin duration, intensive-phase dosing schedule, and antiretroviral therapy (ART) on the tuberculosis treatment outcomes of failure, relapse, and death among patients with HIV infection [17]. Few clinical trials address these basic aspects of tuberculosis treatment in patients living with HIV. Pooling of outcomes from randomized controlled trials (RCTs) and observational studies demonstrated that use of rifamycins for only 2 months and
use of intermittent dosing in the intensive phase increased the risk of poor treatment outcomes. The use of rifamycins for at least 8 months and ART were associated with nonsignificant trends toward improved treatment outcomes. Based on these findings and those of systematic reviews in predominantly HIV-negative populations [18], the fourth edition of the World Health Organization’s (WHO’s) guidelines for the treatment of tuberculosis recommends the use of rifamycins for 6 months, daily dosing in the intensive phase, and ART (regardless of CD4 lymphocyte count) in the treatment of active tuberculosis in HIV-positive patients [19].

**OBJECTIVE**

Our objective was to update a systematic review and meta-analysis on the effects of (1) the duration of rifampicin, (2) the schedule of dosing in the intensive phase, and (3) the use of ART on the following tuberculosis treatment outcomes in HIV-infected patients: failure, relapse, and death during tuberculosis treatment. A new objective for the update was to assess the effects of the 3 covariates on the outcome of acquired drug resistance (ADR) at failure or relapse.

**METHODS**

Search strategies and study selection criteria for this update were the same as previously described [17]. We searched for studies that addressed the treatment of active tuberculosis in patients living with HIV that were published between January 2008 and November 2011. We included cohort studies and RCTs in which patients with HIV infection and active tuberculosis were assigned tuberculosis treatment regimens that used rifamycin (rifampin or rifabutin) and in which the medications, duration of treatment, and schedule of dosing could not be modified. In included studies, the initial tuberculosis diagnosis and all treatment outcomes were confirmed microbiologically (via either smear or culture). We excluded patients with multidrug-resistant tuberculosis from all analyses (when possible). Authors were contacted for additional data.

**Data Extraction and Quality Assessment**

Methods of data extraction, quality assessment, and outcome definitions for the update were identical to those used in the previous systematic review [17]. In accordance with WHO definitions, death was defined as death due to any cause during the course of antituberculosis treatment, treatment failure as a positive smear or sputum culture after 5 months of treatment, and relapse as the occurrence of a positive smear or culture following successful completion of tuberculosis treatment [1]. If initial or pretreatment drug-sensitivity testing (DST) was not reported, we assumed that the proportion with initial drug resistance would be the same as that in published drug-resistance surveillance data from the same country [20, 21].

The proportion of patients lost to follow-up, defaulted, or transferred out was an indicator of study quality. For RCTs, concealment of allocation was an additional criterion for classification as "good" quality.

**Statistical Analysis**

In the first meta-analysis, we pooled risk differences of treatment failure, relapse, and death during tuberculosis treatment from RCTs with head-to-head comparisons of different durations of rifampin (rifampin was the rifamycin used in these RCTs). We could not pool risk differences between trials of 2 months vs 6 months because there was only 1 such study [22]. Because we wanted to determine if extending the duration of rifampin beyond the current recommendation of 6 months is beneficial, we pooled risk differences from the study comparing rifampin durations of 12 months and 6 months [23] with studies comparing 9 months and 6 months [24, 25]. We used a random-effects model (DerSimonian and Laird) to calculate pooled risk differences and estimated heterogeneity with the $I^2$ statistic [26]. To calculate the $I^2$ statistic, zero cells were corrected by 0.5. We calculated numbers needed to treat as 1/risk difference. We used SAS software for statistical analyses (version 9.2, SAS Institute Inc., Cary, NC) and Review Manager to create forest plots (version 5.1, Nordic Cochrane Centre, Cochrane Collaboration, 2011).

In the second meta-analysis, we combined data from all studies using a random-effects model (the procedure NLMIXED in SAS software) to calculate pooled risks and 95% confidence intervals (CIs) for treatment failure, relapse, death during tuberculosis treatment, and ADR within substrata of rifampin duration, schedule of dosing in the intensive phase, and by use of ART [27]. This method uses the exact binomial likelihood approach, which accounts for study size, includes a random effect to account for intrastudy heterogeneity, and produces fewer biased estimates of pooled effects and between-study variability [27]. For rifampin duration, we pooled study arms of 8 months with arms receiving ≥9 months. For ADR, we included only studies in which DST was performed at baseline and at failure or relapse and stratified study arms by baseline drug resistance. A fixed-effects model was used for ADR because a random-effects model estimated the variance of the between-study effect to be zero. The $I^2$ statistic, calculated using conventional meta-analysis techniques, was used to quantify heterogeneity within subgroups [26].

In the final meta-analysis, we performed multivariable metaregression (procedure PROC NLMIXED in SAS software) to determine the effects of each treatment factor (rifampin duration, intensive-phase dosing schedule, and ART) and of interstudy heterogeneity after adjusting for the other...
covariates. We assessed the significance of the following study level characteristics on our outcomes: mean or median age, prevalence of any drug resistance, use of directly observed treatment (DOT), loss to follow-up during and post-treatment, and duration of post-treatment follow-up (for relapse). The final model only included characteristics significantly associated with the outcomes of interest. For ADR, the study restrictions and fixed-effects model used when estimating pooled risks were also applied in the meta-regression.

The first post hoc analysis restricted the metaregression to patients with no history of prior tuberculosis treatment and patients with documented pan-sensitive tuberculosis at baseline. In so doing, we hoped to minimize the effects of unreported inequalities in the distribution of baseline drug resistance without relying on imputed values for the prevalence of baseline drug resistance in the model. In the second sensitivity analysis, we performed the metaregression stratified by use of ART to assess for effect modification by ART on the other covariates.

All analyses excluded patients who did not complete therapy due to adverse reactions, default, or loss to follow-up. Patients who died during or after treatment were excluded when risks of failure and relapse, respectively, were calculated.

RESULTS

Study Selection and Assessment

Our literature search and study selection process added 7 studies (see Figure 1 and Table 1). We removed 1 study from the previous meta-analysis after noting that rifampin duration could have been prolonged in some cases [28]. The updated systematic review includes 33 studies. The Supplement provides reasons for exclusion of studies from the update (Supplementary Table 1), characteristics of all 33 studies (Supplementary Tables 2 and 3), and schematic representations of outcomes (Supplementary Figure 1).

We added 2 RCTs and 5 cohort studies. One RCT compared 6 months and 9 months of rifampin for the treatment of active tuberculosis in subjects with HIV [25]. The other assessed HIV outcomes between ART regimens; in this trial, all patients received the same tuberculosis treatment regimen and are treated as a single study arm in our review [29]. We added 3 retrospective cohort studies [30–32] and 2 prospective cohort studies [33, 34]. All studies reported failure and death during tuberculosis treatment, and 3 studies also reported relapse [25, 30, 33]. Baseline DST was not performed in 4 of the 7 added studies [30–32, 34]. In 2 studies added in the update, testing for ADR at baseline, failure, and relapse was performed [25, 33]. Five of the new studies enrolled patients with no history of prior tuberculosis treatment [25, 29, 30, 32, 34] and 2 enrolled only retreatment patients [31, 33].

Follow-up was of “good quality” during tuberculosis treatment in all 7 added studies (<10% of enrolled patients lost to follow-up). Post-treatment follow-up was “good quality” for both arms of the RCT comparing rifampin durations and “poor quality” in the other studies reporting relapse. In the RCT comparing rifampin durations, treatment allocation was of “good quality” [25].
### Table 1. Characteristics of Studies Added in the Update

<table>
<thead>
<tr>
<th>Ref</th>
<th>Country</th>
<th>Year&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Number of Patients</th>
<th>Tuberculosis Site&lt;sup&gt;b&lt;/sup&gt;</th>
<th>History&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Initial Drug Resistance&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Age&lt;sup&gt;e&lt;/sup&gt;</th>
<th>CD4 Count (Cells/mm&lt;sup&gt;3&lt;/sup&gt;)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Rifamycin Duration,&lt;sup&gt;f&lt;/sup&gt; Months</th>
<th>Dosing in Initial Phase, Continued Phase&lt;sup&gt;g&lt;/sup&gt;</th>
<th>ART&lt;sup&gt;h&lt;/sup&gt;</th>
<th>Outcomes Reported</th>
<th>Follow-up,&lt;sup&gt;i&lt;/sup&gt; Months</th>
<th>% Lost During Treatment</th>
<th>% Lost After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>India</td>
<td>2005</td>
<td>110</td>
<td>P</td>
<td>N</td>
<td>M</td>
<td>34</td>
<td>167 (88–280)</td>
<td>9</td>
<td>None</td>
<td>F, R</td>
<td>27</td>
<td>6</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34</td>
<td>144 (80–304)</td>
<td>6</td>
<td></td>
<td></td>
<td>30</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>29</td>
<td>India</td>
<td>2008</td>
<td>122</td>
<td>P</td>
<td>N</td>
<td>M</td>
<td>36</td>
<td>84 (40–110)</td>
<td>6</td>
<td>None</td>
<td>F</td>
<td>NA</td>
<td>9</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Rwanda</td>
<td>2007</td>
<td>47</td>
<td>P</td>
<td>N</td>
<td>NS</td>
<td>36</td>
<td>129 (NR)</td>
<td>6</td>
<td>7,7</td>
<td>Some</td>
<td>F, R</td>
<td>12.8</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>33</td>
<td>Uganda</td>
<td>2007</td>
<td>133</td>
<td>P</td>
<td>RT</td>
<td>M</td>
<td>35.6</td>
<td>120 (34–287)</td>
<td>8</td>
<td>7,7</td>
<td>Some</td>
<td>F, R</td>
<td>16.5</td>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>34</td>
<td>Kenya</td>
<td>2007</td>
<td>50</td>
<td>P</td>
<td>N</td>
<td>NS</td>
<td>31</td>
<td>NR</td>
<td>2</td>
<td>7,7</td>
<td>All</td>
<td>F</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>31</td>
<td>Nigeria</td>
<td>2008</td>
<td>42</td>
<td>P</td>
<td>RT</td>
<td>M</td>
<td>35.6</td>
<td>NR</td>
<td>8</td>
<td>7,7</td>
<td>All</td>
<td>F</td>
<td>NA</td>
<td>5</td>
<td>NA</td>
</tr>
<tr>
<td>32</td>
<td>Nigeria</td>
<td>2008</td>
<td>199</td>
<td>P</td>
<td>N</td>
<td>NS</td>
<td>35.3</td>
<td>NR</td>
<td>2</td>
<td>7,7</td>
<td>All</td>
<td>F</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: ART, antiretroviral therapy; F, failure; M, mix of pan-sensitive and drug-resistant tuberculosis excluding multidrug-resistant tuberculosis; N, only patients with no history of prior tuberculosis treatment; NA, not applicable; NR, not reported; NS, not specified; P, patients with pulmonary tuberculosis; R, relapse; RCT, randomized control trial; Ref, reference; RT, only retreatment patients.

<sup>a</sup> The year in which enrollment of patients ended.

<sup>b</sup> Site of tuberculosis infection.

<sup>c</sup> History of prior tuberculosis treatment.

<sup>d</sup> Drug resistance of initial isolates.

<sup>e</sup> Age and CD4 values reported as mean or median (range).

<sup>f</sup> Frequency of dosing in the initial phase and the continuation phase, in days per week. For example, “3,3” means that treatment was 3 times weekly in the initial phase and 3 times weekly in the continuation phase.

<sup>g</sup> Use of ART: All = all patients received ART; Some = some patients received ART and others did not; None = no patients received ART.

<sup>h</sup> Duration of follow-up after the completion of tuberculosis treatment.
### Table 2. Characteristics of Trials With Head-to-Head Comparisons of Rifampin Duration

<table>
<thead>
<tr>
<th>Author, Country (Ref)</th>
<th>Rifampin Duration (months)</th>
<th>Number Initiating Treatment</th>
<th>Mean or Median CD4 Count (cells/mm³)</th>
<th>Prevalence of Baseline Drug Resistance (%)</th>
<th>Proportion Lost to Follow-up Post-Treatment (%)</th>
<th>Duration of Follow-up Post-Treatment (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perriens, Zaire (23)</td>
<td>12</td>
<td>168</td>
<td>413</td>
<td>4a</td>
<td>40</td>
<td>12</td>
</tr>
<tr>
<td>El Sadr, United States (24)</td>
<td>9</td>
<td>50</td>
<td>98.5a</td>
<td>0</td>
<td>14</td>
<td>15.2</td>
</tr>
<tr>
<td>Swaminathan, India (25)</td>
<td>9</td>
<td>110</td>
<td>167</td>
<td>15</td>
<td>1</td>
<td>27</td>
</tr>
</tbody>
</table>

Abbreviation: Ref, reference.

* Values not reported by treatment arm.

### Figure 2.
Individual and pooled risk differences from head-to-head trials comparing rifampin durations of ≥9 months and 6 months for the treatment of active tuberculosis in patients with human immunodeficiency virus. Negative risk differences indicate that risk was lower with ≥9 months. Results in bold font indicate 95% confidence intervals that do not include a risk difference of 0. Abbreviations: CI, confidence interval; Ref, reference.
Findings of Trials With Head-to-Head Comparisons of Rifampin Duration

Patients with HIV were included in 4 RCTs with head-to-head comparisons of different durations of rifampin in the treatment of active tuberculosis [22–25]. The rifampin durations compared were 6 months and 9 months [24, 25], 6 months and 12 months [23], and 2 months and 6 months [22]. To calculate pooled risk differences, we excluded the RCT of 2 months and 6 months. DST was not universally performed at failure or relapse in 1 trial [23]. Consequently, we did not calculate pooled risk differences for ADR.

Table 2 describes the head-to-head trials of rifampin duration. The only head-to-head trial that included patients on ART (25% of trial participants) took place before highly active ART (HAART) regimens were standard of care [24]. The pooled risk of relapse was significantly lower among patients receiving ≥9 months of rifampin, and heterogeneity was minimal for all outcomes (Figure 2). Preventing 1 case of relapse would require treating between 6 and 56 patients with ≥9 months of rifampin instead of 6 months.

Findings of Pooled Results Across All Studies

Point estimates for risk of relapse decreased with increasing duration of rifamycin and were lower with daily dosing compared with intermittent dosing in the intensive phase, but CIs were wide and overlapping (Table 3). All patients on ART were treated with HAART, with the possible exception of patients in the RCT from the pre-HAART era [24]. The risk of relapse was significantly lower in arms where some or all patients received ART compared with arms in which no patients received ART. Heterogeneity was moderate to high in the majority of substrata for all outcomes.

To estimate risks of ADR, we stratified the 3 studies that performed DST at time of diagnosis and at failure/relapse by baseline drug resistance [24, 25, 33]. Pooling outcomes from 10 arms (5 pan-sensitive, 3 isoniazid monoresistant, and 2 multidrug-resistant) demonstrated that the risk of ADR at failure or relapse was significantly lower in arms using ART (Table 3).

Differences in reporting and in aggregate values for CD4 and drug resistance are detailed in Supplementary Table 4. Arms receiving intermittent treatment had a lower group mean CD4 than arms on daily dosing schedules. However, caution should be used when interpreting this difference because the reporting of CD4 values was significantly more common in the former group than in the latter.

Metaregression

Results of metaregression are shown in Table 4. Age, CD4 count, DOT, proportion lost to follow-up, and duration of follow-up were not associated with the outcomes and were excluded from the final models. Prevalence of baseline drug resistance was included in the models and remained significant for all outcomes. However, the prevalence of baseline drug resistance increased in the former group than in the latter.

Table 3. Pooled Risks of Failure, Relapse, Death During Tuberculosis Treatment, and Acquired Drug Resistance in Patients With Active Tuberculosis and HIV Coinfection From Randomized Control Trials and Observational Studies

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Risk of Failure (%), 95% CI (Events/Subjects # of Arms</th>
<th>Risk of Relapse (%), 95% CI (Events/Subjects # of Arms</th>
<th>Risk of Death (%), 95% CI (Events/Subjects # of Arms</th>
<th>Risk of ADR (%), 95% CI (Events/Subjects # of Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Rifamycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 months</td>
<td>3.5:1.5, 5.8 (479/999, 13, 69%)</td>
<td>10.8:2.7, 19.7 (1215, 13, 94%)</td>
<td>9.2:0.9, 12.5 (209/1282, 22, 77%)</td>
<td>13.9:7.3, 20.4 (107/765, 12, 89%)</td>
</tr>
<tr>
<td>6 months</td>
<td>2.6:1.4, 4.0 (66/280, 22, 33%)</td>
<td>9.1:1.4, 12.8 (193/1808, 14, 95%)</td>
<td>4.7:0.7, 7.9 (2824, 22, 57%)</td>
<td>13.9:7.3, 20.4 (107/765, 12, 89%)</td>
</tr>
<tr>
<td>≥8 months</td>
<td>2.7:1.5, 5.0 (260, 12, 69%)</td>
<td>9.1:1.4, 12.8 (193/1808, 14, 95%)</td>
<td>4.7:0.7, 7.9 (2824, 22, 57%)</td>
<td>13.9:7.3, 20.4 (107/765, 12, 89%)</td>
</tr>
<tr>
<td>Frequency of tuberculosis treatment in the intensive phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily</td>
<td>2.7:1.6, 4.0 (88/239, 22, 17%)</td>
<td>6.2:0.6, 11.7 (127, 22, 50%)</td>
<td>10.1:0.6, 15.8 (251, 16, 9.6%)</td>
<td>11.6:7.0, 17.7 (1, 02, 58%)</td>
</tr>
<tr>
<td>Three times weekly</td>
<td>5.2:1.8, 8.8 (294, 12, 79%)</td>
<td>2.6:0.6, 5.7 (472, 10, 68%)</td>
<td>1.4:0.2, 2.7 (92, 16, 21%)</td>
<td>11.6:7.0, 17.7 (1, 02, 58%)</td>
</tr>
<tr>
<td>Use of antiretroviral therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>2.7:1.6, 5.7 (88/239, 22, 17%)</td>
<td>6.2:0.6, 11.7 (127, 22, 50%)</td>
<td>10.1:0.6, 15.8 (251, 16, 9.6%)</td>
<td>11.6:7.0, 17.7 (1, 02, 58%)</td>
</tr>
<tr>
<td>Some or all patients</td>
<td>2.0:1.3, 3.9 (37/93, 16, 44%)</td>
<td>1.1:0.2, 2.1 (9283, 8.8%)</td>
<td>11.6:7.0, 17.7 (1, 02, 58%)</td>
<td>11.6:7.0, 17.7 (1, 02, 58%)</td>
</tr>
</tbody>
</table>

Values in bold font indicate nonoverlapping confidence intervals. *p* calculated using conventional meta-analysis techniques (see the Methods section).
Table 4. Adjusted Odds Ratio of Failure, Relapse, Death, and Acquired Drug Resistance in Cohorts With HIV and Active Tuberculosis From Randomized Control Trials and Observational Studies

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Failure, aOR (95% CI)</th>
<th>Relapse: aOR (95% CI)</th>
<th>Death During Tuberculosis Treatment: aOR (95% CI)</th>
<th>ADR at Failure or Relapse aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of rifamycin¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 months</td>
<td>1.4 (0.6, 3.2)</td>
<td>5.0 (1.9, 13.2)</td>
<td>0.9 (0.5, 1.6)</td>
<td>No studies</td>
</tr>
<tr>
<td>6 months</td>
<td>0.8 (0.4, 1.5)</td>
<td>2.4 (1.2, 5.0)</td>
<td>0.7 (0.5, 1.1)</td>
<td>0.75 (0.3, 1.9)</td>
</tr>
<tr>
<td>≥8 months (reference)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Overall significance of factor (P value)²</td>
<td>0.34</td>
<td>&lt;0.01</td>
<td>0.24</td>
<td>0.55</td>
</tr>
<tr>
<td>Frequency of dosing in the intensive phase</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrice weekly</td>
<td>2.0 (0.8, 5.0)</td>
<td>2.2 (0.7, 7.3)</td>
<td>0.7 (0.3, 1.4)</td>
<td>3.7 (0.7, 18.9)</td>
</tr>
<tr>
<td>Daily (reference)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Overall significance of factor (P value)³</td>
<td>0.13</td>
<td>0.18</td>
<td>0.33</td>
<td>0.11</td>
</tr>
<tr>
<td>Use of antiretroviral therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None or not stated</td>
<td>1.7 (0.7, 4.0)</td>
<td>14.3 (2.1, 97.8)</td>
<td>1.4 (0.7, 2.8)</td>
<td>2.0 (0.5, 7.9)</td>
</tr>
<tr>
<td>Some or all patients (reference)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Overall significance of factor (P value)⁴</td>
<td>0.22</td>
<td>&lt;0.01</td>
<td>0.33</td>
<td>0.33</td>
</tr>
<tr>
<td>Variance of the random-effects parameter for between study heterogeneity⁵</td>
<td>0.7 (0.1, 1.3)</td>
<td>2.2 (0.2, 4.3)</td>
<td>0.7 (0.1, 1.3)</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Statistically significant differences between substrata are in presented in bold font.
Abbreviations: ADR, acquired drug resistance; aOR, adjusted odds ratio; CI confidence interval.

¹ Estimates of aOR derived from multivariable metaregression using a random-effects model. Estimates shown from final models that included the 3 covariates. Age, prevalence of baseline drug resistance, CD4 count, use of directly observed treatment, proportion lost to follow-up, and duration of follow-up were not associated with any of the outcomes of interest and were not included in the final model.

² Estimates of aOR derived from multivariable metaregression using a fixed-effects model. Final model included the 3 covariates and baseline drug resistance. Age, CD4 count, use of directly observed treatment, proportion lost to follow-up, and duration of follow-up were not associated with ADR and were not included in the final model.

³ Rifabutin was used in 1 study; all of the other studies used rifampin (see Supplementary Table 2).

⁴ Significance in model from approximate F test using the delta method in the procedure PROC NLMIXED in SAS software.

⁵ An estimate greater than 0 suggests significant between-study heterogeneity.

resistance was only associated with ADR and is included in the model for this outcome. After adjusting for the other covariates, the odds of relapse were significantly higher with 2 months or 6 months of rifamycin compared with at least 8 months and in the absence of ART. Between-study heterogeneity was significant for each outcome. There were trends toward increased odds of ADR with intermittent treatment in the initial intensive phase and in the absence of ART. The odds of ADR at failure or relapse were significantly higher in subjects with drug-resistant tuberculosis at baseline compared with those initially infected with pan-sensitive strains (adjusted odds ratio [aOR] = 14.5; 95% CI, 4.8, 44.0).

In the first post hoc sensitivity analysis, we restricted the metaregression for failure, relapse, and death to subjects with no history of prior tuberculosis treatment and those with pan-sensitive tuberculosis at baseline (39 study arms for failure and death and 24 for relapse). The odds of failure were significantly higher with the use of intermittent dosing compared with daily dosing in the intensive phase (aOR = 2.6; 95% CI, 1.2, 5.6), suggesting that unequal distribution of baseline drug resistance confounded the effect of intermittent dosing schedule in the main model toward the null. In this analysis, between-study heterogeneity was only significant for death. Associations between other covariates and outcomes were unchanged from the main model.

To investigate possible effect modification by ART on associations between the other covariates and our outcomes of interest, we repeated the metaregression stratified by use of ART (Table 5). In the absence of ART, failure was associated with use of intermittent dosing, relapse with rifamycin durations of 2 months and 6 months, and death with rifamycin duration of 2 months. Between-study heterogeneity was significant only for relapse. In the analysis restricted to the arms in which patients received ART, none of the associations between the other covariates (rifamycin duration and dosing schedule) and the outcomes of interest were statistically significant.

**DISCUSSION**

Our updated systematic review and meta-analysis adds to the growing body of evidence that ART improves tuberculosis...
treatment outcomes. We demonstrated that ART lowers the risk of tuberculosis relapse and may modify the effects that duration of rifamycins and schedule of intensive-phase dosing have on tuberculosis treatment outcomes. In the absence of ART, tuberculosis treatment outcomes are improved with use of rifamycins for at least 8 months and daily dosing in the intensive phase. It is unclear whether the lack of associations between rifamycin duration, dosing schedule, and tuberculosis treatment outcomes in the presence of ART is due to true effect modification or a paucity of published data.

Trials with head-to-head comparisons are the strongest design for inference; at the time of our original meta-analysis, only 2 trials had compared longer durations to 6 months of rifampin. Following the publication of a new study comparing 9 months and 6 months of rifampin in patients with HIV, we decided to pool outcomes among head-to-head trials in this update and demonstrated a lower risk of relapse when the duration of rifampin treatment was for ≥9 months. Although the number of such studies remains small (only 3), associations between longer treatment and reduced relapse were also seen in the metaregression of 27 studies. The consistency of this finding within our analysis and between our study and a previous systematic review [11] suggests that the association is real rather than an artifact. However, 2 important points should be considered. First, the majority of evidence comes from patients with untreated HIV infection. Only 1 head-to-head trial of rifampin duration included patients on ART during tuberculosis treatment [24]. Also, overall, only 8 (30%) of the study arms reporting relapse included patients on ART. Second, it remains unclear which of the 2 forms of relapse, reinfection by exogenous tuberculosis or reactivation of the original infection, is prevented by extending the duration of rifamycins beyond 6 months. Only 1 study added in the update differentiated between the types of relapse; in that study, reinfection was more common than reactivation [25, 35]. Similar findings have been reported in studies from other high-burden areas [36–38]. If the effect is primarily to lower the risk of reinfection, it is unknown whether extending rifamycin duration to ≥8 months will provide any benefit over the use of isoniazid preventive therapy post-tuberculosis treatment [39, 40].

In our update, as in our original review, intermittent intensive-phase treatment was associated with increased odds of treatment failure and with trends toward increased odds of

### Table 5. Adjusted Odds Ratio of Failure, Relapse, and Death Stratified by Use of Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Failure, aOR (95% CI)a</th>
<th>Relapse, aOR (95% CI)a</th>
<th>Death During Tuberculosis Treatment, aOR (95% CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of rifamycin</td>
<td>ART</td>
<td>ART</td>
<td>ART</td>
</tr>
<tr>
<td>2 months</td>
<td>None/NRb</td>
<td>All/Somec</td>
<td>None/NRb</td>
</tr>
<tr>
<td>6 months</td>
<td>0.9 (4, 2.0)</td>
<td>3.8 (7, 21.2)</td>
<td>6.7 (2.4, 18.5)</td>
</tr>
<tr>
<td>≥8 months (reference)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Overall significance of factor, P valuea</td>
<td>0.63</td>
<td>0.30</td>
<td>0.001</td>
</tr>
<tr>
<td>Frequency of dosing in the intensive phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrice weekly</td>
<td>4.1 (1.9, 9.1)</td>
<td>0.4 (1, 2.7)</td>
<td>2.1 (6.6, 9.9)</td>
</tr>
<tr>
<td>Daily (reference)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Overall significance of factor, P valuea</td>
<td>&lt;0.001</td>
<td>0.32</td>
<td>0.23</td>
</tr>
<tr>
<td>Variance of the random-effects parameter for between study heterogeneityf</td>
<td>0.3 (0, 0.7)</td>
<td>0.5 (0, 1.5)</td>
<td>1.7 (1, 3.4)</td>
</tr>
</tbody>
</table>

Statistically significant differences between substrata are presented in bold font.

Abbreviations: aOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; NR, not reported.

a Estimates of aORs derived from multivariable metaregression using a random-effects model. Estimates shown from final models that included rifamycin duration and intensive-phase dosing schedule.

b “None/NR”: Study arms where subjects did not receive ART or where use of ART was not reported (n = 32 arms for failure and death, n = 19 arms for relapse).

c “All/Some”: Study arms where either all subjects or a proportion of subjects received ART (n = 15 arms for failure and death, n = 8 arms for relapse).

d Among studies with all or some patients on ART, only 1 study arm with 2 months of rifampin reported relapse. There were 0 occurrences of relapse in this arm.

e Significance in model from approximate F test using the delta method in the procedure PROC NLMIXED in SAS software.

f An estimate greater than 0 suggests significant between-study heterogeneity.
relapse. A new finding from the update is the trend toward increased ADR with intermittent treatment, which is an association that has been reported in HIV-tuberculosis–coinfected patients in other studies [14–16]. The consistency of this association argues against the use of intermittent dosing in the initial intensive phase of tuberculosis treatment in patients with HIV.

Increasing evidence suggests that ART improves tuberculosis treatment outcomes. Our meta-analysis is the first study to demonstrate that ART lowers the odds of relapse after adjusting for tuberculosis treatment regimen and is consistent with associations seen in retrospective studies where tuberculosis regimens were not standardized [41]. Since the publication of our original review, 3 RCTs have demonstrated that early ART initiation in patients with active tuberculosis reduces mortality [42–44] (Supplementary Table 1 describes why these trials were excluded in our meta-analysis). The lack of association between ART and death during tuberculosis treatment in our study has a number of potential reasons, which include (1) pooling of outcomes from studies in which all patients received ART and studies in which only a proportion of patients received ART, (2) ART being started only in those with low CD4 counts, and (3) ART being started at variable time intervals after initiating antituberculosis treatment.

In 2010, only 46% of active tuberculosis patients with HIV were started on ART [1]. Thus, despite the recommendation that all HIV-infected tuberculosis patients start ART regardless of CD4 count and as early as possible during the initial phase of antituberculosis treatment, this intervention occurs in the minority of patients. Both the paucity of published evidence and our post hoc findings that ART modifies the effects of the other covariates underscore the need for head-to-head trials to assess rifamycin duration and dosing schedule in patients on ART. Expanding ART coverage and starting treatment early in the intensive phase among coinfected patients will not only lower mortality but is likely to assist tuberculosis-control efforts by reducing tuberculosis relapse. Rapid expansion of ART coverage for coinfected patients is urgently needed.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. We express our deepest gratitude to the following individuals for providing us with data used to update the systematic review and meta-analysis: Soumya Swaminathan, Gopalan Narendran, Padmapriya Darsini, Edward C. Jones López, Jonathan Levin, Irene Ayakaka, Molly Franke, Assiatiou Diallo, Ige Olusoji Mayowa, and Regina Oladokun. We thank Madhukar Pai, Bill Burman, and Sarah Royce for their contributions as coauthors of the original review and Angella Lambrou for assistance with formulation of search strategies. To the many people who provided information for the original study—thank you, again.

Potential conflicts of interest. All authors: No reported conflicts.

All 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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