# Treatment of Active Tuberculosis in HIV-Coinfected Patients: A Systematic Review and Meta-Analysis

**Faiz A. Khan,[1] Jessica Minion,[1] Madhukar Pai,[1,2] Sarah Royce,[3] William Burman,[4] Anthony D. Harries,[5] and Dick Menzies[1]**

[1]Montreal Chest Institute, McGill University Health Centre, [2]Department of Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, Canada; [3]University of California, San Francisco; [4]Denver Public Health, Denver, Colorado; [5]International Union against Tuberculosis and Lung Disease, Paris, France; and London School of Hygiene and Tropical Medicine, London, United Kingdom

***Background.*** Patients with human immunodeficiency virus (HIV) infection and tuberculosis have an increased risk of death, treatment failure, and relapse.

***Methods.*** A systematic review and meta-analysis of randomized, controlled trials and cohort studies was conducted to evaluate the impact of duration and dosing schedule of rifamycin and use of antiretroviral therapy in the treatment of active tuberculosis in HIV-positive patients. In included studies, the initial tuberculosis diagnosis, failure, and/or relapse were microbiologically confirmed, and patients received standardized rifampin- or rifabutin-containing regimens. Pooled cumulative incidence of treatment failure, death during treatment, and relapse were calculated using random-effects models. Multivariable meta-regression was performed using negative binomial regression.

***Results.*** After screening 5158 citations, 6 randomized trials and 21 cohort studies were included. Relapse was more common with regimens using 2 months rifamycin (adjusted risk ratio, 3.6; 95% confidence interval, 1.1–11.7) than with regimens using rifamycin for at least 8 months. Compared with daily therapy in the initial phase ($n = 3352$ patients from 35 study arms), thrice-weekly therapy ($n = 211$ patients from 5 study arms) was associated with higher rates of failure (adjusted risk ratio, 4.0; 95% confidence interval, 1.5–10.4) and relapse [adjusted risk ratio, 4.8; 95% confidence interval, 1.8–12.8). There were trends toward higher relapse rates if rifamycins were used for only 6 months, compared with $\geqslant$8 months, or if antiretroviral therapy was not used.

***Conclusions.*** This review raises serious concerns regarding current recommendations for treatment of HIV-tuberculosis coinfection. The data suggest that at least 8 months duration of rifamycin therapy, initial daily dosing, and concurrent antiretroviral therapy might be associated with better outcomes, but adequately powered randomized trials are urgently needed to confirm this.

Coinfection with tuberculosis (TB) and human immunodeficiency virus (HIV) poses a tremendous challenge to TB control, particularly in resource-limited settings. Among the estimated 9.3 million new patients with TB in 2007, just over 1.3 million (14.8%) were estimated to be HIV positive. In 2007, there were an estimated 456,000 deaths from HIV-associated TB [1].

Among patients with active TB, patients with HIV coinfection have greater risk of relapse [2–5], raising concerns about the optimum duration of TB treatment [2, 4–9]. Current recommendations by the American Thoracic Society–Centers for Disease Control and Prevention–Infectious Diseases Society of America and the World Health Organization (WHO) are that the standard 6-month therapy should be used for active TB in HIV-positive patients; the former provides clinicians with the option of extending therapy on the basis of clinical judgment [10, 11]. Both guidelines state that intermittent 3-times weekly dosing schedules are acceptable alternatives to daily treatment in HIV-seropositive patients, but WHO specifically recommends against using twice-weekly dosing for HIV-seropositive patients [10].

Antiretroviral therapy (ART) has been associated with dramatic reductions in the progression to AIDS and death [12]. Studies in a variety of settings have shown that among HIV-infected persons rates of TB are significantly lower in those who receive ART and

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Reprints or correspondence: Dr Dick Menzies, Montreal Chest Institute, 3650 St Urbain, Rm K1.24, Montreal, Quebec, Canada H2X 2P4 (dick.menzies@mcgill.ca).

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progressively decline with longer duration of ART [13, 14]. However, in HIV-infected persons receiving ART, there are very little data on TB treatment outcomes, and rates of TB remain much higher than in HIV-uninfected persons [15, 16].

***Objectives.*** This systematic review and meta-analysis was originally commissioned by WHO to assess the impact on failure, relapse, and death during treatment of active TB in HIV-infected patients of (1) duration of rifampin or rifabutin and (2) dosing schedule (daily vs intermittent) in the initial intensive phase of therapy. We added the objective of assessing (3) the use of ART during anti-TB treatment.

## METHODS

***Search strategy.*** We used sensitive search strategies [17] to search OVID Medline (1950 through April 2008), EMBASE (1988 through April 2008), and the Cochrane Central Register of Controlled Trials (through first quarter 2008) for original articles and reviews (for details on search strategy see the Appendix, which appears only in the online version of the journal). Additional papers were identified from reference lists of original articles, reviews, and treatment guidelines identified. We excluded conference abstracts, conference papers or presentations, case reports, and textbook chapters.

***Study selection.*** Two reviewers (F.K. and J.M.) selected articles in the following 2 stages: titles and abstracts, and then full-text articles. Discrepancies between the 2 reviewers were resolved by consensus or through discussion with a third reviewer (D.M.). One reviewer (F.K.) performed data extraction for all articles, and a second reviewer (J.M.) independently performed data extraction for one-third of the articles to assess accuracy in data extraction.

Studies were selected if they were cohort studies or randomized, controlled trials published in English, French, or Spanish. Case-control studies were included if cases represented a consecutive cohort. Included studies reported treatment outcomes, by regimen, in patients with serologically confirmed HIV infection who were treated with standardized regimens that contained rifampin or rifabutin. Cohorts given twice-weekly therapy during the initial intensive phase were excluded, because WHO has previously recommended against use of these regimens [10]. For the primary analysis, studies were included only if all patients had microbiologically confirmed active TB (either smear positive for acid-fast bacilli or culture-positive for *Mycobacterium tuberculosis*) and if they reported failure or relapse that was also microbiologically confirmed (by smear and/or culture). In secondary analyses, we included studies in which some patients initially received a clinical diagnosis. Results of patients with pretreatment multidrug-resistant TB infection were excluded from all analyses (if identified). Some authors were contacted for additional data.

***Data extraction and quality assessment.*** A standardized form was used to extract data from full text articles (Appendix, which appears only in the online version of the journal). Following WHO definitions [1], failure was defined as a positive smear or sputum culture after $\geqslant$5 months of treatment, and relapse was defined as the occurrence of a positive smear or culture in a patient after apparently successful completion of TB treatment. If initial or pretreatment drug-sensitivity testing was not reported, we assumed that the proportion with initial drug resistance would be the same as in published drug-resistance surveillance data from the same country [18].

Indicators of study quality were the proportion of patients, during or after treatment, who were lost to follow-up, defaulted, transferred out without known outcomes, or were otherwise not accounted for. The method of randomization of randomized trials was an additional quality indicator.

***Statistical analysis.*** We used a per-protocol analysis to estimate efficacy of different regimens in preventing failure, relapse, and death during TB treatment. This excluded patients who did not complete therapy or follow-up because they developed serious adverse reactions, defaulted, dropped out, or were otherwise not accounted for during the study.

Because we found very few randomized trials with head-to-head comparisons of duration or dosing schedule of therapy in HIV-infected persons, we pooled results across all studies. This effectively treated each arm within each study as an independent cohort. We performed a random effects meta-analysis with use of Proc Nlmixed in SAS (SAS Institute) [19] to estimate the overall pooled rates and 95% confidence intervals (CIs) of cumulative failure, relapse, and death during treatment. We used the exact binomial likelihood approach [19], which accounts for study size and includes a random effect to account for interstudy heterogeneity and has been demonstrated to produce less biased estimates of the pooled effect and the between-study variability [19]. We assessed heterogeneity of outcomes of interest overall and within subgroups by estimating the $I^2$ statistic and associated 95% CIs [20]. To calculate the $I^2$, zero cells were corrected by 0.5. To minimize heterogeneity, we performed subgroup analyses stratified by duration of rifampin, receipt of ART, and dosing schedule in the initial intensive phase (defined as the initial period when more drugs were used, usually the first 1–2 months).

Meta-regression was used to estimate the effect of the treatment factors of interest, after adjustment for other treatment characteristics, mean age, and proportion with drug resistance among the study participants. We used negative binomial regression (ie, Poisson model) [21] with an offset to account for study size. In this meta-regression, each arm in each study was the unit of analysis. In this approach, residual heterogeneity between studies is accounted for in the dispersion parameter. As such, we interpreted the dispersion parameter as indicating there was no remaining unexplained heterogeneity if the value

was not significantly different from zero and as minimal heterogeneity if the value was <1.0 [22]. Effect estimates of the meta-regression model were interpreted as adjusted risk ratios (aRRs) [21]. We tested the significance of each factor in the models with use of the likelihood ratio test.

***Role of the funding source.*** The funding sources had no role in the design or conduct of the study, nor did they have any role in the decision to submit the manuscript for publication.

## RESULTS

***Study selection and assessment.*** As summarized in Figure 1, the literature search identified 5121 titles, and an additional 37 titles were identified from the references of full texts reviewed. Of these, 30 journal articles, describing 27 studies (21 cohort studies and 6 randomized trials; Table 1), were selected for inclusion in the primary analysis [7, 8, 23–50]. In secondary analysis, we examined another 7 studies with 8 arms in which some subjects received a clinical diagnosis and others had microbiologically confirmed active TB [51–57]. The excluded studies and reasons for exclusion are summarized in the Appendix, which appears only in the online version of the journal. Additional information was obtained from the authors of 8 studies [25, 29, 32, 38, 40, 42, 45, 48].

Of the 27 studies in the primary analysis, all reported data on failure and death during TB treatment, and 17 studies reported relapse rates (Table A1, which appears only in the online version of the journal). Only 1 study [43] included rifabutin, so all rifamycins were analyzed together. Prevalence of initial drug resistance was imputed for 12 studies. Only 4 studies [7, 8, 41, 45] reported acquired drug resistance, and even in these studies, drug-sensitivity testing was not performed in all cases; thus, this outcome is not described in this review. Of the 6 trials, 3 compared different durations of rifampin treatment in HIV-infected persons [7, 8, 32], and 1 each evaluated *Mycobacterium vaccae* immunotherapy [23], ciprofloxacin [37], and rifabutin [43]. All study arms from all trials, except the vaccine arm of one trial [23], were included.

Follow-up during treatment was considered to be "good quality" (<10% of enrolled patients missing outcomes) for 23 arms (58%). Eleven arms (46%) that reported relapse had <10% of patients lost to follow-up after treatment. Of the 3 trials with head-to-head comparisons of rifampin duration, 2 [7, 8] had adequate quality follow-up during treatment; only 1 described adequate randomization with regards to allocation concealment [32], and all 3 had >10% of patients lost to follow-up after treatment.

***Findings of 3 trials with internal, head-to-head comparisons.*** Findings are summarized in Table A2, which appears only in the online version of the journal. Because head-to-head comparisons are the best designs for inference, we first examined this subgroup; pooling was impossible because the 3

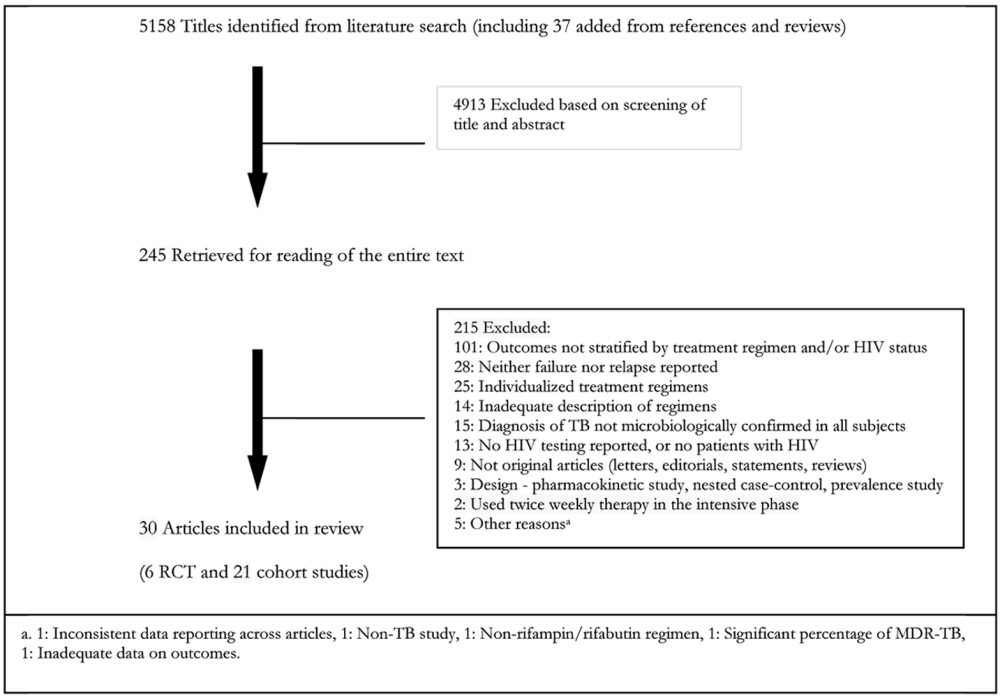


**Figure 1.** Schematic representation of study selection process. HIV, human immunodeficiency virus; MDR, multidrug resistant; RCT, randomized, controlled trial; TB, tuberculosis.

**Table 1. Characteristics of Studies Included**

| Reference | Country | Year[a] | No of arms | No of patients | TB site | Treatment history | Initial drug resistance | Rifamycin duration, months | Dose schedule, days/week | | ART use | Outcome(s) reported | Duration of follow-up, months | Lost during treatment, % | Lost after treatment, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Initial | Continuation | | | | | |
| Randomized, controlled trials | | | | | | | | | | | | | | | |
| [23] | South Africa | 1996 | 1 | 58 | P | New | PS | 6 | 7 | 3 | NS | F | 0 | 0 | NA |
| [7] | United States | 1995 | 2 | 51<br>50 | P | New | PS | 6<br>9 | 3 | 2 | Some | F, R | 18.2<br>15.2 | 3.9<br>4 | 22<br>18.9 |
| [32] | Multiple | 2001 | 3 | 44<br>44<br>36 | P | New | MS | 2<br>2<br>6 | 7<br>3<br>7 | 7<br>7<br>7 | NS | F, R | 22<br>22<br>24 | 0<br>15.9<br>13.9 | 15.6<br>33.3<br>37 |
| [37] | Tanzania | 1992 | 2 | 32<br>26 | P | New | PS | 6 | 7 | 7 | NS | F, R | 6<br>6 | 0<br>0 | 6.3<br>3.8 |
| [8] | Zaire | 1991 | 2 | 167<br>168 | P | New | MS | 12<br>6 | 7 | 2 | No | F, R | 12<br>18 | 9.3<br>9.3 | 30.3<br>39.7 |
| [43, 49] | Uganda | 1992 | 2 | 24<br>25 | P | New | PS | 6[b]<br>6 | 7 | 7 | No | F | 0 | 4<br>8 | NA |
| Cohort studies | | | | | | | | | | | | | | | |
| [24] | Cote d'Ivoire | 1993 | 1 | 180 | P | New | NS | 6 | 7 | 7 | NS | F | NA | 32.8 | NA |
| [25] | Thailand | 2004 | 1 | 62 | P | New | MS | 6 | 7 | 7 | Some | F | NA | 11.3 | NA |
| [26] | Spain | 1994 | 1 | 8 | PE | Mix | NS | 9 | 7 | 7 | NS | F, R | 3 | 12.5 | NS |
| [27] | Nigeria | 2003 | 1 | 58 | P | New | NS | 2 | 7 | NS | NS | F | NA | 22.4 | NA |
| [28] | Cote d'Ivoire | 1993 | 1 | 41 | P | New | NS | 6 | 7 | 7 | NS | F, R | 6 | 14.6 | 0 |
| [29] | Malawi | 1994 | 1 | 134 | P | New | Mix* | 2 | NS | NS | No | F, R | 20 | 19.4 | 28.6 |
| [30] | Malawi | 1995 | 1 | 255 | P | New | NS | 2 | 7 | NS | No | F | 0 | 11.4 | NA |
| [31] | Nigeria | 2002 | 1 | 88 | P | New | NS | 2 | 7 | 7 | All | F, R | 10 | 0 | 5.7 |
| [33, 50] | Uganda | 1994 | 1 | 265 | P | New | NS | 8 | 7 | 7 | NS | F, R | 9.7 | 11.7 | 0 |
| [34] | Uganda | 1997 | 1 | 14 | P | New | PS | 6 | 7 | 7 | NS | F, R | 6 | 0 | 0 |
| [35] | Cote d'Ivoire | 1992 | 1 | 553 | P | New | NS | 6 | 7 | 7 | NS | F, R | 18 | 20.3 | NS |
| [36] | Malawi | 1993 | 1 | 72 | P | Mix | NS | 2 | 7 | 7 | No | F, R | 7.4 | 6.9 | NS |
| [38] | Brazil | 2002 | 1 | 59 | PE | New | PS | 6 | NS | NS | All | F, R | 9 | 10.2 | 0 |
| [44, 47] | South Africa | 1995 | 1 | 187 | P | Mix | MS | 6 | 5 | 5 | No | F, R | 15.2 | 3.2 | 36.1 |
| [39] | Malawi | 2000 | 2 | 27<br>70 | P | New | NS | 2 | NS | NS | No | F | 0 | 3.7<br>5.7 | NA |
| [40] | Cameroon | 1998 | 4 | 22<br>75<br>4<br>10 | P | New<br>New<br>Ret<br>Ret | Res<br>PS<br>Res<br>PS | 6<br>6<br>8<br>8 | 7<br>7<br>7<br>7 | 7<br>7<br>3<br>3 | NS | F | 0 | 4.5<br>16<br>0<br>20 | NA<br>NA<br>NA<br>NA |
| [41] | Uganda | 2000 | 2 | 123<br>147 | P | New | PS<br>Mix* | 2<br>6 | 7<br>7 | 3<br>7 | No | F, R | 14<br>11 | 13<br>2.7 | 0<br>NS |
| [42] | Spain | 2003 | 2 | 18<br>13 | PE | NS | PS | 9 | 7 | 7 | All | F, R | 10.4<br>12.1 | 0<br>0 | 5.6<br>0 |
| [45] | India | 2000 | 1 | 54 | P | New | MS | 6 | 3 | 3 | No | F, R | 18 | 11.1 | 0 |
| [48] | Malawi | 2006 | 2 | 12<br>14 | P | New<br>Ret | NS | 2<br>8 | 3<br>7 | 7<br>3 | All | F | 0 | 0<br>14.3 | NA |
| [46] | Malawi | 2000 | 1 | 253 | P | New | NS | 2 | 7 | 7 | No | F | 0 | 0.8 | NA |

**NOTE.** ART, antiretroviral therapy; F, failure; MDR-NS, multidrug resistant not specified; Mix, both new and retreatment patients; MS, mixed sensitivities; NA, not applicable; NS, not specified; P, pulmonary only; PE, pulmonary and extrapulmonary; PS, pansusceptible; R, relapse; Res, only resistant isolates, multidrug resistance excluded; Ret, retreatment; TB, tuberculosis.

[a] The year in which the enrollment of patients ended.

[b] Rifabutin.

trials [7, 8, 32] compared different durations of rifampin, and only 1 distinguished between true relapse (recurrence of TB with the initial strain) and reinfection (recurrence with a new strain) [7]. In the first small trial, rates of failure and relapse were similar in patients receiving 6- or 9-month regimens [7]. In the second, relapse rates were significantly lower after 12 months, compared with 6 months, of rifampin [8]. In the most recent trial, HIV-TB–coinfected patients who received 6 months of rifampin had lower rates of failure and relapse than those receiving rifampin only for the first 2 months of an 8-month regimen [32]. In the 2 arms in the trial examining the 8-month regimen, failure and relapse rates were equally high in the arm that received thrice-weekly therapy and in the arm that received daily therapy in the first 2 months [32].

***Findings of pooled results across all 27 studies.*** Figure 2 provides a schematic representation of the rates of each outcome by study. Table 2 summarizes the distribution of potentially confounding factors in the studies analyzed. Compared with cohorts that received initially intermittent therapy, cohorts receiving daily therapy had significantly higher CD4 counts and shorter duration of post-treatment follow-up (tending to reduce relapse) but also had a higher proportion smear-positive or drug-resistant TB and reduced receipt of ART or directly observed therapy (tending to increase relapse). Cohorts receiving ART had lower CD4 counts and were older but were less likely to be smear positive.

As shown in Table 3, rates of treatment failure and relapse were lower with longer duration of rifamycin, whereas mortality was higher in groups treated with 2-month rifamycin regimens, although none of these differences were statistically significant. Failure rates were lower and relapse rates were substantially lower if initial phase therapy was daily rather than thrice weekly. However, there were few studies with small numbers of patients; thus, confidence intervals were very broad (Table 4). ART during TB treatment was associated with significantly lower rates of failure and relapse (Table 5).

***Meta-regression analysis.*** After adjustment for the major covariates of interest, as well as the proportion of subjects with initial drug resistance (any form) and age, the rates of relapse and death were significantly higher among patients who received a rifamycin for only 2 months. The rate of relapse if a rifamycin was given for 6 months was more than double the rate if given for $\geqslant$8 months, although the CIs overlapped. Interestingly, intermittent treatment during the initial intensive phase was associated with significantly higher rates of failure and relapse. Receipt of ART was associated with nonsignificantly lower rates of failure and relapse (Table 6).

After adjustment for the covariates shown in Table 6, directly observed therapy and percentage drop-out (including protocol violations, patient refusal, default, or patients not accounted for) were not significantly associated with any outcome. Duration of follow-up after treatment was not significantly associated with relapse. These variables were not included in the final models shown.

***Secondary analysis.*** Characteristics of studies in which the diagnosis of TB was not microbiologically confirmed in all patients [51–57] are summarized in Tables A3 and A4, which appear only in the only version of the journal. As seen in Table A5, which appears only in the online version of the journal, the rates of failure and relapse were somewhat lower in studies in which some patients received a clinical diagnosis, compared with studies in which all diagnoses were microbiologically confirmed (Table A5, which appears only in the online version of the journal). Failure and mortality rates were somewhat lower if ART was given (Table A6, which appears only in the online version of the journal). Because of the small numbers of patients, no differences were statistically significant.

## DISCUSSION

From this meta-analysis of 27 studies identified from a systematic review, duration of rifamycin therapy of $\geqslant$6 months and daily therapy in the initial intensive phase were associated with lower risk of failure and/or relapse in HIV-positive patients with active TB. However the most important and striking finding of this review is the paucity of well-designed and adequately powered randomized trials of HIV-TB coinfection treatment. Despite the estimated annual incidence of 1.3 million persons with HIV-TB coinfection, of whom almost half a million die [1], very basic treatment questions remain unresolved. These have important implications for patients, providers, and TB programs. These questions include the optimal dosing schedule and duration of rifamycin, as well as the use and timing of concomitant ART.

This review has a number of important limitations. First, we could find only 1 randomized trial assessing the schedule of treatment administration and only 3 trials assessing the duration of rifamycin for HIV-TB coinfection. Because of the very limited number of controlled trials, we had to incorporate results from cohort studies and pool all results across all studies. This analytic approach is subject to greater potential confounding, whereas the cohort studies may be further affected by selection bias. Second, there was substantial variability in settings, patient characteristics, interventions, and outcomes assessed, which resulted in substantial heterogeneity, even in stratified analyses. Although we used a more conservative random-effects model [19], the pooled estimates must be viewed with caution. Heterogeneity of patients and settings is not a source of weakness in itself, but the absence of randomized trials conducted within these settings certainly is. If such trials had been available, the within-trial comparisons would have balanced important differences, and the heterogeneity of study populations would then enhance the generalizability of the findings. A third limitation

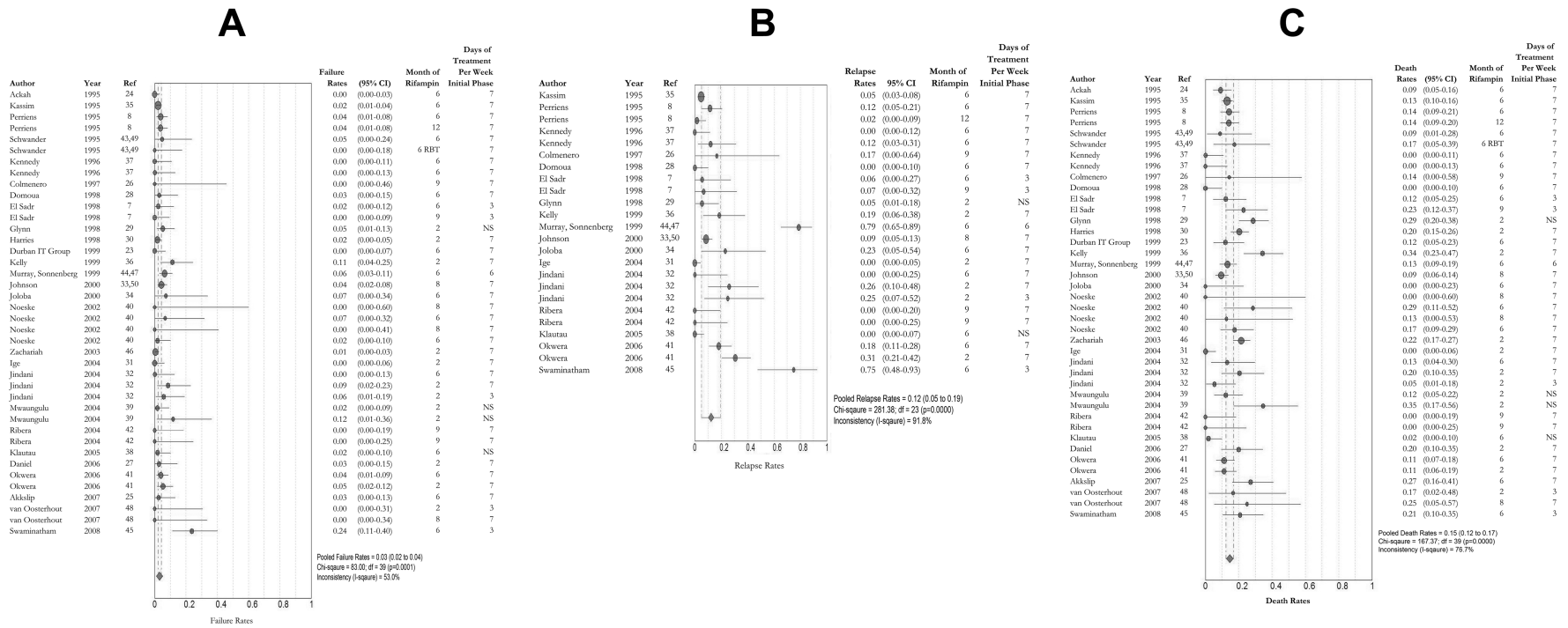


**Figure 2.** *A,* Pooled failure rates in all studies. *B,* Pooled relapse rates in studies measuring relapse. *C,* Pooled death rates in all studies.

**Table 2. Assessment of Potential Confounders, by Major Treatment Covariates Analyzed**

| Variable | Covariate reported in all studies | Duration of rifamycin | | | |
|---|---|---|---|---|---|
| | | 2 Months of treatment (no of arms)[a] | 6 Months of treatment (no of arms)[a] | ⩾8 Months of treatment (no of arms)[a] | *P* |
| No of study arms | … | 12 | 19 | 9 | |
| No of subjects | … | 1180 | 1824 | 559 | |
| Mean age, years | No | 32 (10) | 33 (18) | 33 (9) | .79 |
| Mean CD4 count,[b] cells | No | 52 (1) | 243 (7) | 175 (6) | .28 |
| Pulmonary involvement, % | Yes | 100 | 97 | 87 | .09 |
| Smear positive, % | No | 100 (11) | 90 (19) | 95 (6) | .20 |
| Drug resistance,[c] % | Yes | 7 | 13 | 17 | .66 |
| Study arms where some or all patients received ART, % | Yes | 17 | 16 | 44 | .21 |
| Study arms where full DOT was used, % | Yes | 33 | 21 | 22 | .73 |
| Study arms that used streptomycin, % | Yes | 50 | 0 | 33 | .004 |
| Patients completing therapy, % | Yes | 90 | 90 | 91 | .92 |
| Mean duration of follow-up, months | No | 16 (6) | 13 (12) | 10 (6) | .28 |

| No of study arms | Covariate reported in all studies | Schedule of administration in initial intensive phase | | |
|---|---|---|---|---|
| | | Daily treatment (no of arms)[a] | Intermittent thrice-weekly treatment (no of arms)[a] | |
| | … | 35 | 5 | |
| No of subjects | … | 3352 | 211 | |
| Mean age, years | No | 33 (32) | 34 (5) | .80 |
| Mean CD4 count,[d] cells | No | 260 (8) | 105 (4) | .02 |
| Pulmonary involvement, % | Yes | 95 | 100 | .06 |
| Smear positive, % | No | 96 (31) | 81 (5) | .04 |
| Drug resistance,[c] % | Yes | 14 | 3 | .02 |
| Study arms where some or all patients received ART, % | Yes | 17 | 60 | .03 |
| Study arms where full DOT was used, % | Yes | 20 | 60 | .05 |
| Study arms that used streptomycin, % | Yes | 26 | 0 | .20 |
| Patients completing therapy, % | Yes | 90 | 92 | .96 |
| Mean duration of follow-up, months | No | 12 (20) | 18 (4) | .05 |

| | | Use of ART | | |
|---|---|---|---|---|
| | | No ART or not reported (no of arms)[a] | ART in some/all patients (no of arms)[a] | |
| No of study arms | … | 31 | 9 | |
| No of subjects | … | 3196 | 367 | |
| Mean age, years | No | 32 (29) | 35 (8) | .02 |
| Mean CD4 count,[e] cells | No | 288 (7) | 96 (7) | .002 |
| Pulmonary involvement, % | Yes | 100 | 82 | .09 |
| Smear positive, % | No | 98 (30) | 72 (6) | .05 |
| Drug resistance,[c] % | Yes | 14 | 6 | .15 |
| Study arms where full DOT was used, % | Yes | 26 | 22 | .83 |
| Study arms that used streptomycin, % | Yes | 26 | 11 | .35 |
| Patients completing therapy, % | Yes | 89 | 94 | .13 |
| Mean duration of follow-up, months | No | 13 (18) | 12 (6) | .79 |

**NOTE.** ART, antiretroviral therapy; DOT, directly observed therapy.

[a] When values for certain parameters were not reported in all studies, the number of arms in which this parameter was reported is provided in parentheses.

[b] Mean CD4 values are based on reporting from 12 patients in 1 arm, 526 patients in 7 arms, and 537 patients in 6 arms receiving 2 months, 6 months, and ⩾8 months of rifampin, respectively.

[c] When drug resistance was not reported, published surveillance data were used to estimate resistance.

[d] Mean CD4 values are based on reporting from 167 patients in 4 arms receiving treatment 3-times weekly and 714 patients in 8 arms receiving treatment daily.

[e] Mean CD4 values are based on reporting from 903 patients in 7 arms with none receiving ART and 217 patients in 7 arms with some/all receiving ART.

**Table 3. Pooled Estimates of Major Outcomes Stratified by Duration of Rifampin**

| Outcome, duration of rifamycin | No of study arms | No of events/subjects | Pooled event rate (95% CI), % | $I^2$ (95% CI) |
|---|---|---|---|---|
| Failure | | | | |
| 2 Months | 12 | 27/872 | 2.9 (1.0–4.8) | 0.43 (0–0.71) |
| 6 Months | 19 | 45/1377 | 2.6 (1.1–4.1) | 0.22 (0–0.54) |
| ⩾8 Months | 9 | 14/441 | 1.9 (0–4.0) | 0 (0–0.62) |
| Relapse | | | | |
| 2 Months | 6 | 40/258 | 10.8 (0–25.1) | 0.77 (0.61–0.87) |
| 6 Months | 12 | 100/730 | 9.8 (0–19.8) | 0.92 (0.89–0.94) |
| ⩾8 Months | 6 | 20/314 | 3.3 (0–9.0) | 0.05 (0–0.64) |
| Death during treatment | | | | |
| 2 Months | 12 | 205/1077 | 16.6 (10.2–22.9) | 0.94 (0.91–0.96) |
| 6 Months | 19 | 196/1573 | 10.5 (6.8–14.3) | 0.76 (0.63–0.84) |
| ⩾8 Months | 9 | 60/501 | 11.7 (5.9–18.4) | 0.41 (0–0.73) |

**NOTE.** Only includes studies with high quality diagnoses. All patients and outcomes were microbiologically confirmed. CI, confidence interval.

is that the reporting of some important potential confounders, particularly CD4 counts, was incomplete. Finally, we could not adequately assess the impact of drug resistance on treatment outcomes, because drug-sensitivity testing results were not provided in 14 studies. Nevertheless, it is unlikely that the findings of high failure, relapse, and death rates were attributable to large numbers of patients with unrecognized multidrug-resistant TB. Thirteen studies either enrolled only pansensitive patients or excluded patients with multidrug-resistant TB. Of the 12 studies without drug sensitivity testing, 9 enrolled only new TB cases in countries where prevalence of initial multidrug-resistant TB is very low [18].

In our primary analysis, we included only studies with microbiological confirmation of initial diagnosis and treatment outcomes. This criterion acted to exclude certain well-known trials and cohort studies [51, 53–57], in which some patients and outcomes were clinically diagnosed. As was seen in Tables A1–A7, which appear only in the online version of the journal, the rates of failure and relapse in these studies were generally lower, and associations between treatment factors and outcomes were less strong. This is best explained by nondifferential misclassification of disease status or outcomes, which will reduce the chance of finding important treatment effects [58].

A limitation of our analysis was that we did not distinguish between true relapse and reinfection. In high TB incidence settings, reinfection can contribute importantly to recurrent disease in HIV-infected persons, as shown in 1 of the included studies [44]. Although the distinction is important, particularly in high incidence settings, it requires DNA fingerprinting, which was performed in only 4 studies [7, 33, 41, 44], and even in these 4, it was performed on <50% of recurrent episodes.

Our findings of the impact of duration of rifamycin treatment on outcome are consistent with a recent systematic review of HIV-TB treatment by Korenromp et al [2]. They also found significantly higher relapse rates with rifampin therapy of <5 months duration and nonsignificantly lower relapse rates with

**Table 4. Pooled Estimates of Outcomes Stratified by Schedule of Treatment Administration during the Initial Intensive Phase (First 8 Weeks)**

| Outcome, treatment schedule | No of study arms | No of events/subjects | Pooled event rate (95% CI), % | $I^2$ (95% CI) |
|---|---|---|---|---|
| Failure | | | | |
| Daily | 35 | 74/2531 | 2.5 (1.5–3.5) | 0.18 (0–0.46) |
| Three times weekly | 5 | 12/163 | 5.3 (0.4–10.2) | 0.43 (0–0.76) |
| Relapse | | | | |
| Daily | 20 | 142/1241 | 6.7 (0.6–12.8) | 0.87 (0.83–0.90) |
| Three times weekly | 4 | 18/65 | 28.1 (0–69.5) | 0.85 (0.71–0.92) |
| Death during treatment | | | | |
| Daily | 35 | 430/2957 | 11.9 (8.5–15.3) | 0.88 (0.84–0.91) |
| Three times weekly | 5 | 31/194 | 14.3 (4.8–23.9) | 0.48 (0–0.78) |

**NOTE.** Only includes studies with high quality diagnoses. All patients and outcomes were microbiologically confirmed. CI, confidence interval.

**Table 5. Pooled Estimates of Major Outcomes, by Receipt of Antiretroviral Therapy (ART)**

| Outcome, treatment schedule | No of study arms | No of events/subjects | Pooled event rate (95% CI), % | $I^2$ (95% CI) |
|---|---|---|---|---|
| Failure | | | | |
| No ART (or not reported) | 31 | 83/2380 | 3.2 (2.0–4.5)[a] | 0.37 (0.04–0.59) |
| Some or all patients receiving ART | 9 | 3/310 | 0.8 (0–1.8)[a] | 0 (0–0.62) |
| Relapse | | | | |
| No ART (or not reported) | 18 | 158/1108 | 15.5 (4.5–25.5)[a] | 0.88 (0.84–0.91) |
| Some or all patients receiving ART | 6 | 2/194 | 0.5 (0–1.7)[a] | 0 (0–0.62) |
| Death during treatment | | | | |
| No ART (or not reported) | 31 | 423/2803 | 13.1 (9.4–16.8) | 0.79 (0.70–0.85) |
| Some or all patients receiving ART | 9 | 38/348 | 8.4 (2.8–13.9) | 0.81 (0.66–0.90) |

**NOTE.** Only includes studies with high quality diagnoses. All patients and outcomes were microbiologically confirmed.

[a] Nonoverlapping 95% CIs, which indicate a statistically significant difference between substrata.

rifampin therapy for ⩾7 months. The Korenromp et al review included studies of patients who received individualized treatment regimens [59–62]. When therapy is individualized, clinicians are more likely to extend therapy for sicker patients, creating important confounding of disease severity with longer rifampin treatment duration. Our findings are unlikely to have been affected by this type of confounding, because we excluded all studies with individualized regimens, but we also found nonsignificantly lower relapse rates when rifamycin therapy was extended beyond 6 months. Although this finding was not statistically significant in either review, the consistency of the finding raises concerns about the optimal duration of rifamycin therapy.

Our meta-analysis has demonstrated that rates of failure and relapse are lower if therapy is given daily during the initial intensive phase. These observations are in keeping with 2 recent observational studies, which reported higher rates of relapse and acquired drug resistance among coinfected patients who received intermittent therapy during the initial intensive phase [63, 64]; these two studies were not included in our analysis because patients did not receive standardized TB treatment. However, our finding is based on 5 cohorts only, with small

**Table 6. Adjusted Risk Ratios (aRRs) of Treatment Failure, Relapse, and Death in Patients Coinfected with Human Immunodeficiency Virus and Tuberculosis (TB), from Negative Binomial Regression**

| Variable | Treatment failure, aRR[a] (95% CI) | $P$[b] | Relapse, aRR[a] (95% CI) | $P$[b] | Death during TB treatment, aRR[a] (95% CI) | $P$[b] |
|---|---|---|---|---|---|---|
| Duration of rifampin therapy[c] | | | | | | |
| 2 Months | 1.3 (0.4–4.1) | .67 | 3.6 (1.1–11.7)[d] | .14 | 1.8 (1.0–3.1)[d] | .03 |
| 6 Months | 1.0 (0.4–2.8) | | 2.4 (0.8–7.4) | | 1.0 (0.6–1.6) | |
| ⩾8 Months | 1.0 (reference) | | 1.0 (reference) | | 1.0 (reference) | |
| Intermittent therapy[c] | | | | | | |
| Initial phase daily | 1.0 (reference) | .02 | 1.0 (reference) | .002 | 1.0 (reference) | .42 |
| Initial phase thrice weekly | 4.0 (1.5–10.4)[d] | | 4.8 (1.8–12.8)[d] | | 1.3 (0.7–2.3) | |
| Receipt of ART[c] | | | | | | |
| Some or all patients | 1.0 (reference) | .10 | 1.0 (reference) | .21 | 1.0 (reference) | .39 |
| None or not stated | 3.8 (0.9–16.4) | | 3.5 (0.5–26) | | 0.8 (0.5–1.5) | |
| Dispersion parameter for model | 0.3 (−0.1 to 0.7) | | 0.22 (−0.04 to 0.53) | | 0.13 (−0.02 to 0.31) | |

**NOTE.** All patients and outcomes were microbiologically confirmed. ART, antiretroviral therapy; CI, confidence interval.

[a] For example, the aRR of 3.6 for the outcome relapse and covariate of 2 months of rifampin use (vs ⩾8 months of rifampin as the reference category) means that cohorts that received regimens with only 2 months of rifampin had 3.6-fold higher incidence of relapse than cohorts receiving ⩾8 months of rifampin.

[b] Overall significance of factor, from likelihood ratio test.

[c] Estimates of aRRs were derived from multivariate negative binomial regression. Estimates shown from final models which included these 3 factors, as well as age and proportion with initial drug resistance (any form). Duration of follow-up after treatment was not significantly associated with relapse, whereas directly observed treatment and percent drop-out (includes protocol violations, patient refusal or default, or not accounted for) were not significantly associated with any outcome. Therefore, estimates for these covariates are not shown because they were not included in final models.

[d] Nonoverlapping 95% CIs, which indicate a statistically significant difference between substrata.

number of patients in each; thus, it must be viewed with caution. Nevertheless, the very high pooled relapse rates and high adjusted incidence rate ratios for failure and relapse support the need for a well-designed and adequately powered trial to address this important question.

In our stratified analysis, receipt of ART was associated with significantly lower rates of failure and relapse, even though ART was given in only 6 studies to <350 patients. In regression analysis, the effects of ART were less important, which may have reflected confounding effects of other covariates. ART is associated with lower incidence of active TB among HIV-infected persons [13, 14, 65, 66] and lower risk of relapse following treatment [67]. As with rifamycin duration and dosing schedule, the results of our analyses should be considered to have generated important hypotheses to be addressed in future randomized trials.

In conclusion, our review raises important concerns regarding thrice-weekly treatment in the first 2 months of therapy, the optimal duration of rifamycin therapy, and the role of ART therapy in HIV-TB–coinfected patients. Our data suggest that longer duration of rifamycin therapy (at least 8 months) with daily dosing in the initial phase and that concurrent ART might be associated with better outcomes. However, these findings should be viewed with caution, because they are based mostly on observational studies. This reflects the striking paucity of adequately powered, well-designed and -executed, randomized trials on treatment of HIV-TB coinfection. Randomized trials to address the questions raised by this review regarding treatment of active TB in HIV coinfected patients are urgently needed.

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