MAJOR ARTICLE

Improving Outcomes for Multidrug-Resistant Tuberculosis: Aggressive Regimens Prevent Treatment Failure and Death

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Background. Evidence is sparse regarding the optimal construction of regimens to treat multidrug-resistant (MDR) tuberculosis disease due to strains of *Mycobacterium tuberculosis* resistant to at least both isoniazid and rifampin. Given the low potency of many second-line antituberculous drugs, we hypothesized that an aggressive regimen of at least 5 likely effective drugs during the intensive phase, including a fluoroquinolone and a parenteral agent, would be associated with a reduced risk of death or treatment failure.

Methods. We conducted a retrospective cohort study of patients initiating MDR tuberculosis treatment between 2000 and 2004 in Tomsk, Russian Federation. We used a multivariate Cox proportional hazards model to assess whether monthly exposure to an aggressive regimen was associated with the risk of death or treatment failure.

Results. Six hundred fourteen individuals with confirmed MDR tuberculosis were eligible for analysis. On multivariable analysis that adjusted for extensively drug-resistant (XDR) tuberculosis—MDR tuberculosis isolates resistant to fluoroquinolones and parenteral agents—we found that monthly exposure to an aggressive regimen was significantly associated with a lower risk of death or treatment failure (hazard ratio, 0.52 [95% confidence interval, .29–.94]; $P = .030$).

Conclusions. Receipt of an aggressive treatment regimen was a robust predictor of decreased risk of death or failure during MDR tuberculosis treatment. These findings further support the use of this regimen definition as the benchmark for the standard of care of MDR tuberculosis patients and should be used as the basis for evaluating novel therapies.

Keywords. MDR-TB; drug resistance; treatment; clinical outcomes; optimized background regimen.

Multidrug-resistant (MDR) tuberculosis—strains of *Mycobacterium tuberculosis* resistant to at least isoniazid (H) and rifampicin (R), the backbone drugs in the first-line tuberculosis regimen—is a largely curable, airborne infectious disease [1–5]. Yet, MDR tuberculosis has killed >1.5 million people since the beginning of the 21st century [1]. Only a small proportion of affected individuals are able to access treatment [2, 3]. For those who did in 2009, the average global treatment success was a dismal 48%—much lower than that known to be achievable [3–9]. The overall result continues to be high mortality and treatment failure, and ongoing airborne transmission of drug-resistant strains of tuberculosis [3, 10, 11].

Although treatment success is determined by many factors, regimen design plays a critical role. Although meta-analyses of a number of published studies have suggested that patients benefit from a minimum of 4 likely effective drugs—medicines to which their

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infecting strain is thought to be susceptible—given during the intensive phase of treatment [7, 8, 12, 13], recent studies have suggested that more drugs might be better [14–17]. In a cohort of MDR tuberculosis patients from Peru, the use of "aggressive" treatment regimens composed of at least 5 likely effective drugs during the intensive phase followed by at least 4 likely effective drugs during the continuation phase almost halved mortality [16]. When given for 18 months or longer after culture conversion, recurrence of tuberculosis after cure was more than halved as well [17].

We sought to examine the aggressive regimen definition in a cohort of patients with MDR tuberculosis in the Siberian province of Tomsk in the Russian Federation. This cohort is known to have been infected at least in part with virulent strains of *M. tuberculosis* (W-Beijing family) with broad-spectrum drug resistance, including many with extensively drug-resistant (XDR) tuberculosis [5, 18–20]. Our aim was to assess whether the use of an aggressive regimen was associated with reduced risk of death or treatment failure.

METHODS

Setting and Participants

The setting and enrollment methods for this cohort have been described previously [5, 18]. Beginning in 2000, individualized MDR tuberculosis treatment was made available in Tomsk Oblast, Russian Federation, via a public–private partnership between the Tomsk Oblast Tuberculosis Services (Tomsk, Russian Federation), the Tomsk Penitentiary Services Tuberculosis Hospital (Tomsk, Russian Federation), Partners In Health (Boston, Massachusetts and Tomsk, Russian Federation), the Massachusetts State Laboratory Institute (Boston), the Bill & Melinda Gates Foundation (Seattle, Washington), and the Open Society Institute (New York, New York) [5, 18]. The cohort consisted of all consecutive patients with suspected or confirmed MDR tuberculosis initiating treatment for MDR tuberculosis between 10 September 2000 and 1 November 2004.

Patients were diagnosed with tuberculosis via clinical, bacteriologic, and radiographic criteria; those with suspected tuberculosis were screened for tuberculosis using sputum smear microscopy and mycobacterial culture. All culture-positive isolates underwent drug susceptibility testing (DST) [18]. Patients gave written informed consent before initiation of therapy. Tuberculosis providers collected data prospectively using standardized forms, and the study team reviewed medical charts to verify and complete records. Data were entered into a dedicated electronic medical record and were exported into an Access database (Microsoft Corporation, Redmond, Washington).

Patients with baseline MDR tuberculosis were eligible for analysis. Patients were classified as having baseline MDR tuberculosis if they had a culture positive for *M. tuberculosis* and DST results showed resistance to at least both H and R in any specimen collected between 2 months before and 1 month after starting MDR tuberculosis treatment. XDR tuberculosis was defined as resistance to H, R, any fluoroquinolone, and at least 1 of 3 parenteral second-line drugs (amikacin, capreomycin, or kanamycin) [21, 22].

DST Methods and Tuberculosis Management

DSTs were performed at the Massachusetts State Laboratory Institute (MSLI) and the Tomsk Oblast tuberculosis reference laboratory (Tomsk, Russian Federation) as described previously [5, 18]. The Tomsk reference laboratory performed DSTs using the absolute concentration method on Lowenstein-Jensen media to H, R, ethambutol, and kanamycin. The MSLI performed DSTs using the proportion method on 7H10 agar plates for all first- and second-line drugs except pyrazinamide, for which the BACTEC liquid medium method was performed. Resistance to moxifloxacin was not tested.

Individualized MDR tuberculosis treatment regimens were designed according to standard algorithms described elsewhere, accounting for DST results and prior tuberculosis treatment histories [5, 18, 23]. Patients with DST results showing resistance to fluoroquinolones were treated with ofloxacin or levofloxacin. Patients with DST results showing resistance to kanamycin or amikacin with or without capreomycin resistance were treated with capreomycin. The program had limited access to "group 5" (third-line) antituberculous drugs (linezolid, meropenem, imipenem, and clofazimine were not available) [23]. All drugs were prescribed for administration under direct observation. Inpatient admission was routine for most of the intensive phase, which usually included parenteral therapy for 6–9 months. Treatment was continued until 18 months after sputum culture conversion. Patients routinely received a monthly pension as well as social and nutritional support [10, 18].

Exposure Variable Definitions

Potential predictors of the hazard of death or failure during MDR tuberculosis treatment were selected from risk factors identified in the literature and clinical experience [4, 5, 18, 24]. Low body mass index (BMI) was defined as <18.5 kg/m^2 for women and <20 kg/m^2 for men. Baseline human immunodeficiency virus (HIV) status was recorded as reported by the intake physician or confirmed by HIV enzyme-linked immunosorbent assay. The presence of a baseline comorbid condition (other than HIV) was defined as any of the following: diabetes mellitus, chronic renal insufficiency, seizure disorder, baseline hepatitis or transaminitis, or psychiatric disease. Baseline sputum samples were defined as samples obtained for acid-fast bacilli (AFB) smear or culture during the 2 months prior to MDR tuberculosis treatment initiation. Severe pulmonary disease was defined as cavernous, fibrocavernous, caseous, disseminated, or cirrhotic diagnosis on baseline chest

radiography (CXR). Severe baseline clinical status was defined as respiratory insufficiency, hemoptysis, or sputum AFB smear (+++) at baseline.

An aggressive MDR tuberculosis regimen was defined as a regimen containing at least 5 likely effective drugs during the intensive phase, followed by at least 4 likely effective drugs during the continuation phase [16, 17, 23]. This regimen definition required the use of a fluoroquinolone and an injectable agent during the intensive phase and the use of a fluoroquinolone during the continuation phase. In addition, first-line drugs and maximal dosing were included whenever possible. Each drug in a regimen was defined as likely effective if (1) all DST results prior to starting the regimen confirmed susceptibility to the drug, or (2) DST results were not available and the patient had not received the drug for >1 month prior to individualized regimen initiation [16]. If resistance data were discrepant, physicians would include the drug in question in the patient's regimen; however, that drug was not classified as likely effective. If group 5 drugs were included in the regimen, they were not considered to be likely effective.

Treatment regimens changed during the course of MDR tuberculosis therapy due to (1) adjustment of empiric MDR tuberculosis regimens to individualized DST results, (2) occurrence of adverse events, or (3) drug stock-outs. Therefore, following from Mitnick et al, we classified a patient's regimen as aggressive or not for each day of treatment [16]. A time-varying binary variable was used to classify each month of treatment as either exposed or unexposed to an aggressive regimen. A month was classified as exposed if at least 75% of regimen days in that month met the aggressive definition; otherwise, the treatment month was classified as unexposed to an aggressive regimen [16].

Outcome Variable Definition

Standard definitions for final treatment outcomes were used [25]. Favorable treatment outcome was defined as treatment completion or cure. Poor treatment outcome was defined as failure, death from any cause, or default during treatment. Patients were followed from the time of treatment initiation to the date of MDR tuberculosis treatment outcome, including death. The primary outcome was defined as the time from treatment initiation to death or treatment failure.

Statistical Methods

We conducted a univariate Cox proportional hazards analysis to assess the association between the time-varying exposure of interest (exposure to an aggressive MDR tuberculosis regimen for at least 75% of the days in any given month of treatment) and the hazard of death or treatment failure. All other covariates were also evaluated using univariate Cox proportional hazards models. Those covariates found to be independently associated with time to death or failure on univariate analysis ($P < .05$), as well as age and sex, were considered for inclusion in the time-varying multivariate Cox proportional hazards model.

The multivariate model was built using a backward selection method, retaining covariates associated with death with a P value <.20. To adjust for potential confounders, covariates were retained in the final multivariate model if they changed the effect estimate of receipt of an aggressive regimen on time to death or failure by ≥10% in either direction, or if confounding was suspected based on clinical experience. We assessed effect modification via interaction terms between receipt of an aggressive regimen and each of the following: XDR tuberculosis, previous fluoroquinolone exposure, and previous injectable exposure. We tested the proportional hazards assumption for the final multivariate model using Schoenfeld residuals fitted to rank of analysis time. A Kaplan-Meier survival curve was plotted to display exposure groups by receipt of an aggressive MDR tuberculosis regimen. Given that the exposure groups contributed differing amounts of person-time to follow-up, we performed a sensitivity analysis in which we restricted follow-up time to be <45 months. This was done to confirm that the observed effect of the exposure of interest was driven by the period of time when both exposure groups contributed person-time to follow-up.

All analyses were performed using Stata/SE version 12.1 (StataCorp LP, College Station, Texas). Continuous variables are presented as mean values with their corresponding standard deviation; categorical variables are presented as numbers with their corresponding column percentage in parentheses. The Student t test was used for the 2-sample mean-comparison test, when appropriate. The χ^2 test or Fisher exact test was used to calculate P values, when appropriate. All statistical tests were 2-sided, and significance was determined at $\alpha = .05$.

Ethical Approval

Institutional review boards at the Harvard School of Public Health (Boston, Massachusetts) and the Siberian State Medical University (Tomsk, Russian Federation) approved the study.

RESULTS

A total of 638 individuals with suspected or confirmed MDR tuberculosis were consecutively enrolled during the study period. Of these, 614 individuals had confirmed MDR tuberculosis by mycobacterial culture and DST (in any specimen obtained between 2 months before and 1 month after starting MDR tuberculosis treatment), and were included in the analysis. The mean age of the cohort was 35.9 years, 83.2% of whom were male; 56.8% were currently or previously incarcerated (Table 1). Six hundred eleven (99.5%) had previously been treated for tuberculosis; many had prior injectable (31.8%) and/or

Table 1. Baseline Characteristics and Treatment Outcomes of Patients Treated for Multidrug-Resistant Tuberculosis

Baseline Characteristic/Outcome	Total (N = 614)
Sociodemographic characteristics	
Age, y[a]	35.9 ± 11.3
Female sex	103 (16.8)
Married (n = 589)	245 (41.6)
Unemployed (n = 610)	502 (82.3)
Current or previous incarceration	349 (56.8)
Alcohol abuse/dependence	263 (42.8)
Illicit drug use	114 (18.6)
Homelessness	25 (4.1)
Comorbidities	
HIV-positive (n = 610)[b]	5 (0.8)
Diabetes mellitus (n = 613)	25 (4.1)
Comorbid condition[c]	432 (70.4)
Prior TB treatment exposure	
Previously treated for TB	611 (99.5)
History of prior injectable exposure (n = 600)	191 (31.8)
History of prior fluoroquinolone exposure (n = 600)	90 (15.0)
History of prior default	23 (3.8)
No. of previous TB treatments[a] (n = 610)	2.1 ± 1.2
>2 previous TB treatments (n = 596)	205 (34.4)
Clinical indicators of disease severity	
Bilateral and cavitary disease on baseline CXR (n = 606)	374 (61.7)
Severe pulmonary disease on baseline CXR (n = 613)[d]	266 (43.4)
Low BMI at start of treatment (n = 613)[e]	263 (42.9)
Severe baseline clinical status[f]	356 (58.0)
Extrapulmonary disease (n = 540)	46 (8.5)
Previous TB-related surgery (n = 611)	62 (10.2)
Baseline XDR-TB	32 (5.2)
Treatment outcomes	No. (%)
Favorable outcome[g]	406 (66.1)
Treatment completed	23 (3.8)
Cured	383 (62.4)
Poor outcome[h]	207 (33.7)
Failure	54 (8.8)
Death	30 (4.9)
Default	123 (20.0)
Transferred out	1 (0.2)

Data are presented as No. (%) unless otherwise specified. Because of rounding and missing data, the sum of percentages may not equal 100%.

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; CXR, chest radiography; HIV, human immunodeficiency virus; TB, tuberculosis; XDR, extensively drug resistant.

[a] Continuous variable, mean ± standard deviation presented.

[b] Baseline HIV status as reported by intake physician or confirmed by HIV enzyme-linked immunosorbent assay.

[c] Comorbid condition was defined as any of the following: diabetes mellitus, chronic renal insufficiency, seizure disorder, baseline hepatitis or transaminitis, psychiatric disease.

[d] Severe pulmonary disease was defined as cavernous, fibrocavernous, caseous, disseminated, or cirrhotic diagnosis on baseline CXR.

[e] Low BMI was defined as <18.5 kg/m^2 for women and <20 kg/m^2 for men.

[f] Severe baseline clinical status was defined as respiratory insufficiency, hemoptysis, or sputum AFB smear (+++) at baseline.

[g] Favorable treatment outcome was defined as treatment completion or cure.

[h] Poor treatment outcome was defined as failure, death from any cause, or default during treatment.

fluoroquinolone (15.0%) exposure. The mean number of previous tuberculosis treatments for the cohort was 2.1, with 34.4% having had >2 previous treatments. At least half presented with bilateral and cavitary disease on baseline CXR or with severe baseline clinical status, and 32 (5.2%) presented with baseline XDR tuberculosis.

Of the 614 individuals included in the analysis, 502 (81.8%) received an aggressive regimen at some point during MDR tuberculosis treatment, whereas 112 (18.2%) never received an aggressive regimen. The median duration of MDR tuberculosis treatment for the entire cohort was 19 months (interquartile range [IQR], 18–23 months) for a total of 14 321 person-months of observation. During the period of observation, there were 84 events: 54 treatment failures and 30 deaths (Table 1). In univariable analysis, monthly exposure to an aggressive MDR tuberculosis regimen predicted a lower hazard of death or failure during MDR tuberculosis treatment (Table 2); age, severe pulmonary disease on baseline CXR, and severe baseline clinical status predicted a higher hazard of death or failure. Among the 84 subjects who experienced treatment failure or died, the median event-free survival time was 18 months (IQR, 11–28).

In multivariable analysis, monthly exposure to an aggressive regimen, age, sex, positive HIV status, comorbid condition other than HIV, >2 previous tuberculosis treatments, low BMI at start of treatment, and severe baseline clinical status were retained in the model. Extrapulmonary disease at baseline was also retained in the model as it was found to change the effect estimate of the exposure of interest on the hazard of death or failure by ≥10%. Baseline XDR tuberculosis was also retained in the model as a potential confounder. XDR tuberculosis, previous injectable exposure, and previous fluoroquinolone exposure were not found to be significant effect modifiers, so interaction terms for these variables were not included in the final model. After adjusting for the variables retained in the final model, including baseline XDR tuberculosis, monthly exposure to an aggressive regimen was a significant predictor of a lower hazard of death or failure during MDR tuberculosis treatment (hazard ratio, 0.52 [95% confidence interval, .29–.94]; $P = .030$; Table 2). A Kaplan-Meier curve describing this relationship is shown in Figure 1. Truncation of the follow-up time to be <45 months, in our sensitivity analysis, did not change the overall interpretation of our study.

DISCUSSION

In this retrospective cohort analysis of MDR tuberculosis patients in Tomsk, we found that monthly exposure to an MDR tuberculosis treatment regimen containing at least 5 likely effective drugs during the intensive phase, and 4 likely effective drugs during the continuation phase, was a robust predictor

Table 2. Predictors Associated With Time to Death or Treatment Failure Among Patients Treated for Multidrug-Resistant Tuberculosis[a]

Variable	Study Cohort (N = 614 [85 Events])	
	Univariate HR (95% CI)	Multivariate HR (95% CI)
Monthly receipt of aggressive MDR-TB regimen	**0.46 (.27–.77)**	**0.52 (.29–.94)**
Sociodemographic characteristics		
Age, y	**1.03 (1.01–1.05)**	**1.04 (1.01–1.06)**
Female sex	1.05 (.59–1.86)	1.15 (.59–2.25)
Current or previous incarceration	0.79 (.51–1.20)	
Comorbidities		
Baseline HIV positive[b]	1.70 (.41–7.03)	3.40 (.72–16.2)
Comorbid condition other than HIV[c]	0.81 (.51–1.29)	0.60 (.35–1.02)
Prior TB treatment exposure		
>2 previous TB treatments	0.63 (.39–1.02)	**0.53 (.31–.92)**
Clinical indicators of disease severity		
Low BMI at start of treatment[d]	1.44 (.94–2.21)	1.60 (.97–2.65)
Severe pulmonary disease on baseline CXR[e]	**2.06 (1.31–3.27)**	
Severe baseline clinical status[f]	**2.27 (1.37–3.75)**	**2.68 (1.45–4.95)**
Extrapulmonary disease at baseline	1.22 (.61–2.44)	1.00 (.48–2.06)
Previous TB-related surgery	0.75 (.38–1.52)	
Baseline XDR-TB	1.63 (.85–3.10)	1.58 (.78–3.20)

Abbreviations: BMI, body mass index; CI, confidence interval; CXR, chest radiograph; HIV, human immunodeficiency virus; HR, hazard ratio; MDR, multidrug resistant; TB, tuberculosis; XDR, extensively drug resistant.

[a] Confidence intervals that do not overlap the null value of HR = 1 are shown in bold.

[b] Baseline HIV status as reported by intake physician or confirmed by HIV enzyme-linked immunosorbent assay.

[c] Comorbid condition defined as any of the following: diabetes mellitus, chronic renal insufficiency, seizure disorder, baseline hepatitis or transaminitis, psychiatric disease.

[d] Low BMI was defined as <18.5 kg/m^2 for women and <20 kg/m^2 for men.

[e] Severe pulmonary disease defined as cavernous, fibrocavernous, caseous, disseminated, or cirrhotic diagnosis on baseline CXR.

[f] Severe baseline clinical status defined as respiratory insufficiency, hemoptysis, or sputum acid-fast bacilli smear (+++) at baseline.

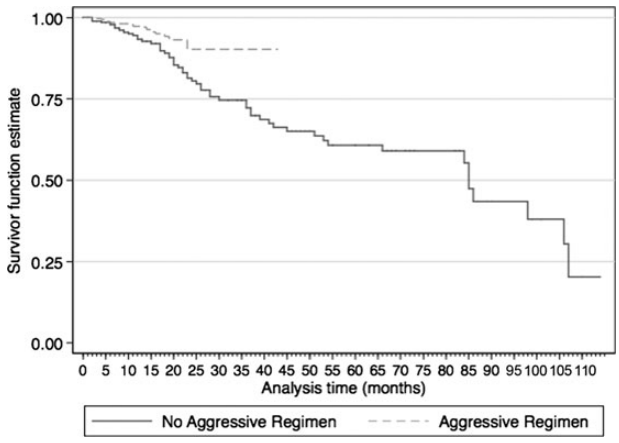

Figure 1. Death or treatment failure among patients treated for multidrug-resistant tuberculosis by time-varying monthly exposure to an aggressive regimen.

of decreased risk of death or treatment failure, reducing this risk by half. This did not change with adjustment for independent predictors of death or failure spanning categories of sociodemographic characteristics, previous tuberculosis treatment exposure, and clinical indicators of disease severity. Even after adjusting for the effect of XDR tuberculosis—extensively resistant *M. tuberculosis*, for which fluoroquinolones and parenteral agents should have limited utility—a statistically significant decrease in death and treatment failure remained. These findings support similar observations from an MDR tuberculosis treatment cohort in Peru, where an aggressive regimen, including an 18- to 24-month duration, reduced the risk of death by nearly half [16, 17]. When viewed in light of the findings from our analysis, this body of literature suggests not only that regimens containing at least 5 likely effective drugs reduce mortality and treatment failure, but that this benefit applies in patients who have had prior exposure to second-line drugs (such as those in Peru and Russia).

Although using regimens that contain a large number of second-line drugs requires more robust management of adverse events and programmatic rigor to ensure adherence to treatment, these efforts are well worth the significant mortality benefit and the prevention of transmission of drug-resistant tuberculosis strains by patients whose treatment is unsuccessful. Viewed mechanistically, regimens with at least 5 likely effective drugs may be beneficial via rapid reduction of the mycobacterial load, disrupting the bacilli's modulation of the host immune system and reducing the host inflammatory response [26–28]. Further research is needed on this question as well as on the applicability of these findings to first-line regimens and the shortening of treatment duration.

Our findings provide important insight into the treatment of patients with prior exposure to fluoroquinolones or parenteral agents. We observed a significantly reduced risk of death and treatment failure from receipt of an aggressive regimen in a cohort with 32% prior exposure to parenteral agents and 15% prior exposure to fluoroquinolones. A recent meta-analysis of MDR tuberculosis treatment outcomes from 26 centers by Falzon et al showed a stepwise worsening of outcomes with advancing resistance patterns [29]. Falzon et al noted that MDR

tuberculosis with fluoroquinolone resistance alone was associated with worse treatment outcomes than MDR tuberculosis with injectable resistance alone, suggesting that fluoroquinolones are the most important part of the MDR tuberculosis treatment backbone [29]. Given the known limitations to current DST technology for fluoroquinolones and the possibility of the presence of mixed strains in patients infected with *M. tuberculosis* [30–37], our program used fluoroquinolones and injectable agents in aggressive regimens even when these agents were classified as not likely to be effective. Although we did not have a comparator group, our data suggest a benefit even to patients thought to have resistance to fluoroquinolones and/or parenteral agents, as previously described among the XDR tuberculosis patients in this cohort [18].

The findings of the present analysis are subject to several limitations. Although we adjusted for baseline factors likely to be associated with receipt of an aggressive regimen and the hazard of death or treatment failure, given the retrospective nature of the analysis, we lacked data needed to adjust for time-varying confounders (ie, factors that may have been associated with both the hazard of death or failure and the receipt of an aggressive regimen in any given month). In a prior analysis, we reported that nearly 75% of patients experienced an adverse drug event while receiving MDR tuberculosis treatment, and that adverse events did not negatively impact treatment outcome [38]. Confounding by adverse events would therefore be unlikely to explain our findings. We acknowledge that the observed protective association of history of exposure to >2 previous tuberculosis treatments in our cohort may indicate a survival bias. We anticipate that the effect estimate of the exposure of interest would be attenuated toward the null due to survival bias in this second-line treatment–experienced cohort.

Overall, this analysis adds to a growing body of evidence that aggressive MDR tuberculosis treatment regimens including at least 5 likely effective drugs (including a fluoroquinolone and a parenteral agent) in the intensive phase of treatment, and at least 4 likely effective drugs (including a fluoroquinolone) in the continuation phase, are associated with lower risk of poor outcomes, namely, death and treatment failure. This same treatment approach should be used for patients with XDR tuberculosis or resistance to either a fluoroquinolone or parenteral agent. Insofar as this approach provides the best chance of survival for millions of patients with drug-resistant tuberculosis, it sets the benchmark for the current standard of high-quality care, and should be adopted as the "background" or comparison regimen in future clinical trials evaluating novel treatments for MDR tuberculosis [16, 17, 23].

Notes

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