Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

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***Rationale*: Based on expert opinion, the global guidelines for management of multidrug-resistant tuberculosis impose lengthy and often poorly tolerated treatments.**

***Objectives*: This observational study evaluates the effectiveness of standardized regimens for patients with proven multidrug-resistant tuberculosis previously untreated with second-line drugs in low-income countries.**

***Methods*: Consenting patients were sequentially assigned to one of six standardized treatment regimens. Subsequent cohorts were treated with regimens adapted according to results in prior cohorts. The study was designed to minimize failure and default while reducing total treatment duration without increasing relapse frequency.**

***Measurements and Main Results*: We report the treatment outcome of all patients with laboratory-confirmed, multidrug-resistant tuberculosis enrolled from May 1997 to December 2007. The most effective treatment regimen required a minimum of 9 months of treatment with gatifloxacin, clofazimine, ethambutol, and pyrazinamide throughout the treatment period supplemented by prothionamide, kanamycin, and high-dose isoniazid during an intensive phase of a minimum of 4 months, giving a relapse-free cure of 87.9% (95% confidence interval, 82.7–91.6) among 206 patients. Major adverse drug reactions were infrequent and manageable. Compared with the 221 patients treated with regimens based on ofloxacin and commonly prothionamide throughout, the hazard ratio of any adverse outcome was 0.39 (95% confidence interval, 0.26–0.59).**

***Conclusions*: Serial regimen formulation guided by overall treatment effectiveness resulted in treatment outcomes comparable to those obtained with first-line treatment. Confirmatory formal trials in populations with high levels of human immunodeficiency virus coinfection and in populations with a higher initial prevalence of resistance to second-line drugs are required.**

Keywords: chemotherapy; fluoroquinolones; cohort studies; drug resistance; costs

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

In the absence of evidence from controlled clinical trials for multidrug-resistant tuberculosis (resistant to isoniazid and rifampin), the current global guidelines for its management are based on expert opinion, recommending lengthy, poorly tolerated, and expensive treatment options. As a result, implementation has been difficult, and results have remained modest.

What This Study Adds to the Field

This observational study shows that a short, standardized treatment regimen based on a fourth-generation fluoroquinolone combined with other second-line drugs and supplemented by potentially still active first-line drugs was highly effective in a setting among largely HIV-negative patients without a history of prior treatment with second-line drugs.

The World Health Organization (WHO) estimated that 0.5 million new cases of multidrug-resistant tuberculosis (i.e., resistant to isoniazid and rifampin) emerged globally in 2007 (1). Only a minority of cases is diagnosed, and, among those living in low-income countries, only a negligible proportion ever receives appropriate chemotherapy (2). This is in spite of increasing advocacy and detailed recommendations on how to treat such patients (3). The results of programmatic management of drug-resistant tuberculosis have not been impressive, with treatment success rarely exceeding 80%, even in previously untreated cases (4–7). This paradox may be due to the practical challenges in implementing the current guidelines and the less than optimal use of existing drugs. Recommended treatment regimens are very long, often poorly tolerated, and difficult to monitor (3, 8).

Standardized treatment regimens with first-line drugs are highly successful in drug-susceptible tuberculosis and fairly efficacious in isoniazid-only-resistant tuberculosis (9). Treatment standardization has also been advocated as a feasible and potentially effective approach for multidrug-resistant tuberculosis in low-income settings, where levels of resistance to second-line drugs are generally low (10), but this has not been evaluated in a clinical trial.

The report presented here is based on tuberculosis services offered by the Damien Foundation in Bangladesh, a nongovernmental organization implementing tuberculosis services in close collaboration with the government. The project serves a rural population typical for Bangladesh of over 27 million inhabitants. There are three hospitals and 163 field clinics, providing annually treatment for about 24,000 patients with tuberculosis, 75% of whom have sputum smear-positive and fewer than 1% of whom have multidrug-resistant tuberculosis (11). Among the treatment cohorts of the years 1997 to 2007, of 124,498 sputum smear-positive patients on first-line treatment, 87.5% (n = 108,877) have been cured, and fewer than 2% failed. About 5% of the patients died or defaulted during treatment (unpublished program reports, Damien Foundation, Bangladesh).

Our prospective observational study conducted over a 12-year period in this large tuberculosis control program was supported by a Supra-National Tuberculosis Reference Laboratory. We reported earlier on our experience with the first regimen for multidrug-resistant tuberculosis that followed closely the 1996

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WHO guidelines; the regimen satisfied bacteriologic efficacy but was poorly tolerated (12, 13). Careful observation of treatment outcomes and adverse drug reaction frequency among each cohort of patients receiving standardized treatment was used to guide regimen adjustments for subsequent cohorts, with the goal of developing a well-tolerated, highly effective, short, and inexpensive treatment regimen.

METHODS

Ethical Considerations

Except for the first regimen, which closely followed WHO recommendations, ethical clearance was obtained for every regimen change from the Bangladesh Medical Research Council. Before enrolment, each patient completed and signed an informed consent form in the local language.

Definition of Terms

First-line treatment is defined as treatment of tuberculosis exclusively with first-line drugs. Cases of suspected multidrug-resistant tuberculosis included patients with sputum smear-positive failure or relapse after first-line treatment with a regimen containing rifampin throughout.

The following treatment outcome definitions were adapted from WHO guidelines (3).

Cure: Completion of treatment with five or more negative cultures over at least 12 months after the last positive culture. Because of the short duration of the gatifloxacin-based regimen, the follow-up period subsequent to cessation of chemotherapy was included for assessment, and outcome was classified as having relapse-free cure for 0 (treatment completion), 6, 12, 18, or 24 months, as applicable.

Completion: Completion of treatment with documented bacteriological conversion persisting through the end of treatment but fewer than five negative cultures or less than 12 months of observation after the last positive culture.

Failure: One or more positive cultures during treatment after at least 150 days, or death or default with bacteriological evidence of active tuberculosis after the first 2 months of treatment, or a medical decision to definitively terminate treatment because of adverse drug reactions.

Relapse: Cure or treatment completion with at least one positive culture during post-treatment follow-up, unless the strain was proven to be different from the initial isolate by molecular techniques.

Reinfection Disease: Recurrent disease as defined for a relapse, but with a strain exhibiting a fingerprint pattern different from the initial isolate, provided there was clinical or microscopic evidence of recurrence.

Death: Death from any cause during treatment not meeting the criteria for failure.

Default: Interruption of treatment for at least 2 months not meeting the criteria for failure.

Unallocated Final Outcome: Not meeting the criteria of any of the above outcome definitions.

Our study used the following summary outcomes for analysis:

Successful outcome: Completion of treatment without relapse over the follow-up period.

Adverse outcome: Any death, default, or failure while on treatment, relapse of tuberculosis or inability to allocate to a defined treatment outcome.

Study Design

Calendar-defined cohorts of patients were prospectively enrolled on consecutive standard regimens without any attempt at randomization or blinding. Patients were treated strictly according to a predefined protocol. Each regimen differed from the previous one, usually only by a single change. Regimens were developed based on careful observation of treatment outcome, including ascertainment for relapse and taking newly published evidence into account. Cohort sizes were not predefined, and ethical concerns always overrode statistical power considerations.

Patient Enrollment Criteria

All patients with suspected or confirmed multidrug-resistant tuberculosis and complying with protocol-defined conditions were eligible for study enrolment if they took at least 1 day of the assigned treatment regimen and provided written consent. Enrolment exclusion criteria were nonacceptance of hospitalization during the intensive phase of treatment, being older than 65 years in the ofloxacin-treated cohorts, and having advanced liver disease or cardio-respiratory insufficiency. Advanced tuberculosis was not an exclusion criterion.

Study Exclusion Criteria

Patients who were negative on smear and culture at the start of second-line treatment were excluded from the study analysis, as were those with laboratory results proving susceptibility to rifampin or isoniazid or revealing a mycobacterium other than *Mycobacterium tuberculosis*. Patients previously treated with second-line drugs for as long as 1 month were also excluded. To allow sufficient time for ascertaining status subsequent to the end of treatment, patients who were started on treatment after December 31 2007 were excluded.

Treatment of Patients not Eligible for Study Inclusion

Patients excluded from the study may still be treated in an identical manner as study patients. Patients with laboratory-documented tuberculosis susceptible to rifampin or a mycobacterial isolate not from the *M. tuberculosis* complex could be withdrawn from the regimen for multidrug-resistant tuberculosis and prescribed more appropriate treatment. Patients with a history of 1 month or more of prior treatment with second-line drugs were given different salvage regimens not further elaborated here.

Treatment Regimens and Monitoring

Table 1 shows the six consecutive regimens, and Table 2 shows the drug dosages. More details can be found in the online supplement. All regimens were based on a fluoroquinolone (ofloxacin or, in regimen 6, gatifloxacin), kanamycin, and prothionamide as the core drugs, supplemented by other potentially active companion drugs (first-line drugs and clofazimine). A new regimen cohort was started once the outcomes of the previous one(s) seemed sufficiently clear, without striving for statistical significance.

Each treatment cohort was thus defined by a standardized regimen. The only adaptation to patient response was the duration of the intensive phase.

Nearly all patients were hospitalized for the intensive phase. Close follow-up and directly observed therapy during the decentralized continuation phase were assured by a network of project outpatient clinics and village doctors (14).

Sputum smears and solid culture were done periodically during treatment and until 2 years after cure. Drug susceptibility testing on all and fingerprinting on selected isolates were performed at the Antwerp supranational reference laboratory. From regimen 2 onward, the intensive phase duration was steered by the smear results. Details are found in the online supplement.

Data Management and Analysis

Treatment records were captured in an Epi Info 6.04d database (U.S. Centers for Disease Control and Prevention, http://www.cdc.gov/epiinfo/epi6/ei6.htm) and later in a compatible EpiData Entry database (Version 3.1, EpiData Association, http://www.epidata.dk). Analyses were performed with EpiData Analysis (Version 2.2), conforming to statistical standards recommended for biomedical publications, showing 95% confidence intervals (CI) for proportions and P values where appropriate for formal frequentist hypothesis testing. Kaplan-Meier survival statistics with 95% CI for the survival function and the hazard ratio were calculated as appropriate (15). The life table interval was set to 30 days to approximate the rhythm of bacteriological examinations,

TABLE 1. REGIMENS SEQUENTIALLY USED IN THE TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS, BANGLADESH DAMIEN FOUNDATION PROJECTS

Regimen (sequence)	Intensive Phase	Continuation Phase 1	Continuation Phase 2	Patients Enrolled	
				Number	Col %
1	3* KCOEHZP	12 OEHZP	6 EP	59	13.8
2	3(+) KCOEHZP	12 OHEZP		44	10.3
3	3(4) KCOEZP	12 OEZP		35	8.2
4	3(+) KCOEHZP	12 OHEZ		45	10.5
5	3(+) KCOEHZP	12 OHEZC		38	8.9
6	4(+) KCGEHZP	5 GEZC		206	48.2
Total number of patients enrolled				427	100.0

Definition of abbreviations: C = clofazimine; Col % = column percent; E = ethambutol; G = gatifloxacin; H = isoniazid; K = kanamycin; O = ofloxacin; P = prothionamide; Z = pyrazinamide.

* Numbers in front of phase indicate months. 3(4) indicates minimum of 3 mo, prolonged to 4 mo if no conversion by end of 3 mo. 3(+) indicates minimum of 3 mo, prolonged until conversion is achieved, if no conversion by the end of 3 mo. 4(+) indicates minimum of 4 mo, prolonged until conversion is achieved, if no conversion by the end of 4 mo. All drugs were given daily throughout under direct observation.

which could slightly vary between patients. Patients with an adverse outcome during the interval contributed observation time up to its midpoint of the interval (16).

RESULTS

Study Population

Enrolment of patients began in May 1997, and intake for the purpose of the study ended by the end of December 2007. In this period, a total of 821 proven and 363 cases suspected of multidrug-resistant tuberculosis were eligible for treatment according to program criteria. For various incompletely documented reasons, only 486 patients could be enrolled (Figure 1). Fifty-nine of the enrolled patients were excluded from analysis: 40 because multidrug resistance could not be proven and 10 because the isolated *Mycobacterium* did not belong to the *M. tuberculosis* complex. Five additional patients were excluded because of a history of prior treatment with second-line drugs for at least 1 month, three because they were negative on all smears and cultures from time of enrolment, and one because treatment was changed to a first-line regimen due to an erroneous drug susceptibility result.

Of the 427 patients available for analysis, 318 (74.5%) were male. Male patients had a mean age of 35.9 years, and female patients had a mean age of 27.5 years (Table 3). The mean body mass index (determined only in the most recent period and thus available for about half of the patients on the gatifloxacin-based regimen) was 16.1 kg/m^2 (95% CI, 15.6–16.6), indicating severe emaciation. Information on radiographic disease extent was available for 401 patients, 81.5% of whom had bilateral disease; this finding was similar among female and male patients. This proportion was identical for the ofloxacin- and gatifloxacin-cohorts, whereas weight at enrolment was lower for the latter (details not shown).

Nearly all patients enrolled on ofloxacin-based regimens and more than 90% among the gatifloxacin-treated patients had been treated repeatedly with first-line drugs (Table 4). The last cohort showed a slight decrease in the duration of suffering from tuberculosis previously, from 31 to 27 months on average, due to a significant increase of those with a history of up to 12 months (from 7% of 174 to 21% of 198).

Outcome of Treatment with Ofloxacin-based Regimens

Of 162 patients on regimens 2 to 5, 44 (27.2%) with a positive sputum smear result at the end of the third month required prolongation of the intensive phase. For regimens 1 and 2 (which were combined because they differed only in duration of the continuation phase), there were few failures (5.8%), but 14.6% defaulted from treatment (Table 5). Regimen 3 without isoniazid had a very low effectiveness (57.1% cure). Regimen 4, when neither prothionamide nor clofazimine was used in the continuation phase, resulted in 13.3% failures and one unallocated outcome (clinically declared failure), but default was reduced to 8.9%. Regimen 5 (clofazimine replacing prothionamide in the continuation phase) was the most effective, with 2.6% failing and 7.9% defaulting. There was no relapse with any of the five regimens during 2 years of follow-up (complete in 94% of 153 cured cases), but there was one case of reinfection disease (Table E1).

Outcome of Treatment with the Gatifloxacin-based Regimen

Of the 206 patients, 35 (17.0%) with a positive smear at 4 months required extension of the intensive phase. Among the 206 patients, there were one treatment failure and 12 defaults (5.8%) (Table 5). The difference in the frequency of failures (0.5%; 95% mid-P exact CI, 0.02–2.4) from that among patients on the ofloxacin-based regimens (7.2%; 95% mid-P exact CI, 4.3–11.3) was highly significant. Of the 182 patients who

TABLE 2. DAILY DRUG DOSAGES USED FOR STANDARDIZED MULTIDRUG-RESISTANT ANTITUBERCULOSIS TREATMENT, BANGLADESH DAMIEN FOUNDATION PROJECTS

Drug	Weight group		
	<33 kg	33–50 kg	>50 kg
Kanamycin*	500 mg	750 mg	1,000 mg
Ofloxacin	400 mg	600 mg	800 mg
Gatifloxacin†	400 mg	600 mg	800 mg
Prothionamide‡	250 mg	500 mg	750 mg
Clofazimine	50 mg	100 mg	100 mg
Isoniazid	200 mg	300 mg	300 mg
Isoniazid high dose‡	300 mg	400 mg	600 mg
Ethambutol	800 mg	800 mg	1,200 mg
Pyrazinamide	1,000 mg	1,500 mg	2,000 mg

* The kanamycin dosage was reduced by 25% for patients over 45 yr of age. Later, the dosage was given more precisely as 15 mg/kg body weight and was given only three times weekly rather than daily from the fourth month onward.

† Gatifloxacin was used at a lower dosage for the first 50 patients enrolled (200 mg up to 33 kg or 400 mg if over 33 kg)

‡ For prothionamide and high-dose isoniazid, the highest dosing was given only to patients weighing over 55 kg (not 50 kg). The high dose of isoniazid was used with the gatifloxacin-based regimen, whereas the normal dose was given in all ofloxacin-based regimens.

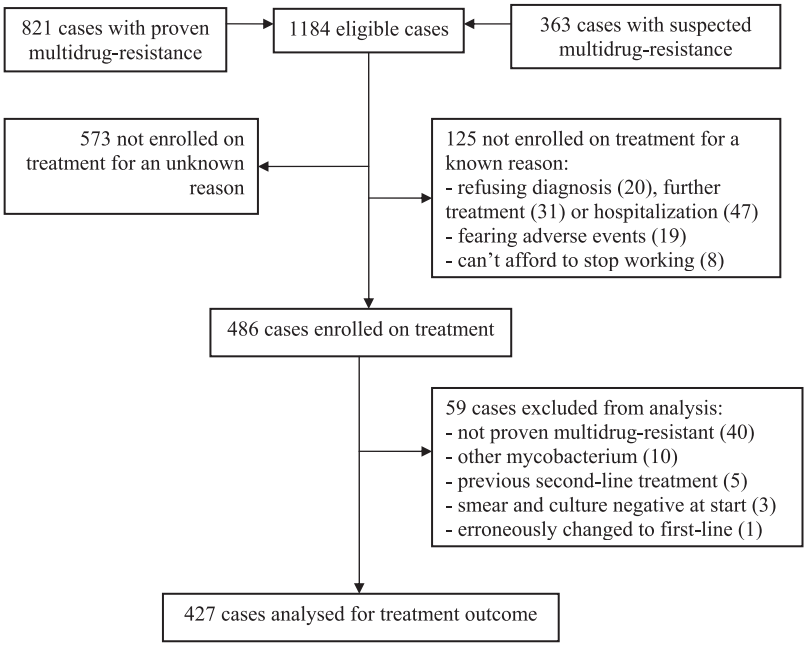

Figure 1. Flow diagram from diagnosis or suspicion of multidrug-resistant tuberculosis to inclusion in this report. Damien Foundation Bangladesh projects, enrolment period May 1997 to December 2007. Suspects were limited to failure outcome after standard first-line retreatment.

completed treatment, one had a relapse at 6 months. By the time of analysis, 163 (90%) had 1 year, 123 (68%) had 1.5 years, and 92 (51%) had 2 years of relapse-free follow-up (including one case of reinfection disease at 2 years; Table E1).

Assessing Age and Sex as Factors Influencing Treatment Outcome

Survival analyses were done by regimen group (ofloxacin-based vs. gatifloxacin-based), age group (defined by quartiles of age across all patients), and sex alone and in any combination. The analysis stratifying the patients into the 16 possible strata showed that treatment results were best among female patients (of any age) who received the gatifloxacin-based regimen and poorest among female patients (of any age) who received an ofloxacin-based regimen. However, confidence intervals were large and overlapped. The differences by age group did not show a distinct pattern or trend among either sex or regimen group (Figure E1).

Patients Who Died or Defaulted during Treatment

Among 12 of the 33 patients who died, death occurred within the first 2 months (61 d) of treatment (Table E2). Of the 21 patients who died after the first 2 months, 20 had culture conversion with the last negative culture obtained within 3 months before death. One patient who died after 75 days had no further culture available after diagnosis.

Among 21 of 41 patients who defaulted, default occurred after 2 months. All but one patient had documented conversion

TABLE 3. AGE, SEX, AND BODY MASS INDEX OF PATIENTS ON TREATMENT FOR MULTIDRUG-RESISTANT TUBERCULOSIS, BANGLADESH DAMIEN FOUNDATION PROJECTS

	Female		Male		Total	
Age and body mass index	Number	Col %	Number	Col %	Number	Col %
Age groups						
Up to 24 yr old	51	46.8	57	17.9	108	25.3
25–34 yr old	26	23.9	102	32.1	128	30.0
35–44 yr old	26	23.9	74	23.3	100	23.4
45–54 yr old	5	4.6	54	17.0	59	13.8
55 yr and older	1	0.9	31	9.7	32	7.5
Total	109	100.0	318	100.0	427	100.0
	Female		Male		Total	
Age, yr	Point	95% CI	Point	95% CI	Point	95% CI
Mean	27.5	25.8–29.3	35.9	34.6–37.2	33.8	32.7–34.9
BMI (kg/m^2)*						
Mean	16.8	14.8–18.9	16.0	15.5–16.4	16.1	15.6–16.6
First quartile	13.8		14.5		14.3	
Median	15.1		16.2		15.8	
Third quartile	21.3		17.1		17.2	
Radiographic extent	Female		Male		Total	
Bilateral disease	85	80.2	242	82.0	327	81.5
One lung	20	18.9	49	16.6	69	17.2
One lobe	1	0.9	4	1.4	5	1.2
Total	106	100.0	295	100.0	401	100.0

Definitions of abbreviations: BMI = body mass index; CI = confidence interval; Col % = column percent.
* Gatifloxacin-based regimen only, available for 109 of 206.

TABLE 4. TREATMENT ANTECEDENTS AND INITIAL DRUG RESISTANCE

	Ofloxacin Regimen		Gatifloxacin Regimen	
Treatment Antecedents	n	%	n	%
By previous treatment category and outcome				
Total classified	220		206	
Nonconversion of first treatment (category 1)	1	0.5	1	0.5
Failure of first treatment (category 1)	4	1.8	18	8.7
Failure of first-line retreatment (category 2)	193	87.7	161	78.2
Relapse of first-line retreatment (category 2)	22	10.0	26	12.6
By number of months suffering from tuberculosis				
Total known	174		198	
Range, mo	3–133		3–180	
Up to 12 mo	12	6.9	41	20.7
13–24 mo	77	44.3	93	47.0
25–60 mo	70	40.2	50	25.3
>60 mo	15	8.6	14	7.1
Mean	31		27	
Median	24		19.5	
25th percentile	18		14	
75th percentile	36		32	
Initial drug resistance				
Total multidrug resistant	221	100*	206	100*
Resistant to H and R only	24	10.9*	21	10.2*
Any resistance to E	172	77.8*	132	64.1*
Any resistance to S	159	71.9*	165	80.1*
Any resistance to O	2	1.2*	21	10.3*
Any resistance to K	3	1.8*	0	0.0*
Any resistance to P	31	26.3*	29	14.7*

Definition of abbreviations: E = ethambutol; H = isoniazid; K = kanamycin; O = ofloxacin; P = prothionamide; R = rifampin; S = streptomycin.

* Percentages have the total tested for a drug(s) as denominator. Pyrazinamide was not routinely tested; in another study on isolates from the same area, it reached about 50% after first-line retreatment.

with three or more negative cultures after diagnosis, and seven patients had the last negative culture more than 3 months before default.

Adverse Drug Reactions

Adverse drug reactions were frequent (Table 6). Of the total sample, 203 patients (47.5%) reported at least one adverse drug reaction at some time during treatment. Vomiting was the most frequent, occurring in 71% of the patients receiving regimens 1 and 2; vomiting was reduced to 21% in patients receiving regimen 6. Arthralgia, which was most likely attributable to pyrazinamide, was reported by 7% of the patients. Ataxia and diminishing hearing acuity, which were possibly kanamycin-induced, were reported with the same frequency, but far more cases were recorded for the gatifloxacin cohort. However, most of those occurred before the fourth month, and increased awareness of the hospital staff may be the explanation for this most recent cohort. Isoniazid-attributed adverse reactions, such as peripheral neuropathy or mental disturbance, were reported in 5% of patients. Dysglycemia was recorded as an adverse drug reaction for two patients on ofloxacin and eight patients on gatifloxacin regimens. This reaction occurred as glycosuria or hyperglycemia, which proved sometimes difficult to control by standard therapy, thus requiring replacement of gatifloxacin by ofloxacin. Jaundice was recorded for three cases. No patient required permanent stopping of treatment due to adverse drug reactions, but three patients had gatifloxacin replaced by ofloxacin (and treatment prolonged accordingly). The only

TABLE 5. OUTCOME OF TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS GROUPED BY REGIMEN CATEGORY, BANGLADESH DAMIEN FOUNDATION PROJECTS

	Regimens 1+2		Regimen 3		Regimen 4		Regimen 5		Regimen 6		Total	
Outcome	n	Col %	n	Col %	n	Col %	n	Col %	n	Col %	n	Col %
Completion*	0	0.0	0	0.0	0	0.0	0	0.0	11	5.3	11	2.6
Cure	71	68.9	20	57.1	30	66.7	32	84.2	170	82.5	323	75.7
Death	11	10.7	5	14.3	4	8.9	2	5.3	11	5.3	33	7.7
Default	15	14.6	7	20.0	4	8.9	3	7.9	12	5.8	41	9.6
Failure	6	5.8	3	8.6	6	13.3	1	2.6	1	0.5	17	4.0
Relapse	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.2
Not fitting any of the above†	0	0.0	0	0.0	1	2.2	0	0.0	0	0.0	1	0.2
Total	103	100.0	35	100.0	45	100.0	38	100.0	206	100.0	427	

Definition of abbreviation: Col % = column percent.

* Treatment completion is reported only for the gatifloxacin-treated cohort because cure criteria could not always be met due to the short regimen and incomplete post-treatment follow-up. However, all had converted, one patient with two and one with three negative cultures during treatment (and before moving away), and the others all had at least four negative cultures.

† One patient failed clinically but not according to the bacteriological criteria, and the treatment was changed to a salvage regimen. Although all cultures preceding the event were negative, this patient would not fit the analysis criteria. In the final analysis on effectiveness and survival, this patient was counted as an adverse outcome.

TABLE 6. REPORTED ADVERSE DRUG REACTIONS DURING TREATMENT FOR MULTIDRUG-RESISTANT TUBERCULOSIS*

	Regimens 1+2		Regimen 3		Regimen 4		Regimen 5		Regimen 6		Total	
Adverse Reaction	n	%†	n	%	n	%	n	%	n	%	n	%
Patients	103		35		45		38		206		427	
Vomiting	75	72.8	23	65.7	14	31.1	14	36.8	44	21.4	170	39.8
Dysglycemia	1	1.0	0	0.0	1	2.2	0	0.0	8	3.9	10	2.3
Neurologic	9	8.7	1	2.9	0	0.0	0	0.0	0	0.0	10	2.3
Mental	9	8.7	1	2.9	0	0.0	1	2.6	1	0.5	12	2.8
Ataxia	0	0.0	0	0.0	1	2.2	0	0.0	8	3.9	9	2.1
Hearing	5	4.9	0	0.0	1	2.2	0	0.0	13	6.3	19	4.4
Arthralgia	18	17.5	4	11.4	4	8.9	2	5.3	2	1.0	30	7.0
Jaundice	2	1.9	0	0.0	1	2.2	0	0.0	0	0.0	3	0.7

* Each patient may have multiple reactions.
† Percentages are proportions of patients with that episode.

other modification required for three gatifloxacin treatments was reduction of kanamycin dosage. One ofloxacin treatment ending in failure had been interrupted for 3 months because of severe gastric intolerance. Prothionamide had been withdrawn early from two ofloxacin treatments, and its dosage was reduced for five, while ofloxacin was replaced in continuation for three, and pyrazinamide was stopped for one. Although the staff was familiar with clofazimine from treating leprosy, not a single adverse reaction typical for this drug was recorded.

Other Drug Susceptibility Test Results

Among 49 (22%) of the 221 patients treated with an ofloxacin-based regimen, the strain was susceptible to ethambutol, compared with 74 (36%) of the 206 patients treated with gatifloxacin (Table 4). Of 163 isolates from the ofloxacin cohorts tested for these drugs, two (1.2%) and three (1.8%) were resistant to ofloxacin and kanamycin, but none was to both simultaneously, and of 118 strains tested, 31 (26.3%) were prothionamide resistant. Among the 203 isolates from the gatifloxacin cohort tested, 21 (10.3%) were ofloxacin resistant, but no kanamycin resistance was detected, while 29 (14.7%) of 197 tested were prothionamide-resistant. Detailed initial drug resistance profiles are shown in Table E3.

Post-treatment Events

Of the 427 patients, 335 (78.5%) completed treatment without a programmatically adverse outcome (death, default, failure, or clinical failure). The reasons for stopping follow-up after treatment completion are summarized in Table E1 for the two fluoroquinolone cohorts. Twelve patients moved out of the project jurisdiction, and tracing them proved impossible. Twelve patients died during follow-up; in all of these patients, preceding cultures had been negative. Three patients had recurrent tuberculosis, one of whom was classified as having a relapse and two as having reinfection disease.

Summary Outcome by Treatment Regimen

The treatment outcome categories dichotomized as successful or adverse are shown in Figure 2. The proportion with a successful outcome was largest among patients treated with the gatifloxacin-based regimen, with 87.9% having a successful outcome (95% CI, 82.7–91.6), and lowest among patients receiving the prothionamide-throughout regimen without isoniazid supplementation, with 57.1% having a successful outcome (95% CI, 40.9–72.0).

Eighty percent of the patients completed treatment within 20 months on the ofloxacin-based regimen and within 10 months on the gatifloxacin-based regimen. Virtually all (95%) patients on the gatifloxacin-based regimen had completed their treatment within 1 year.

Figure 3 shows the survival function estimates for the incidence of an adverse treatment outcome. Comparing the gatifloxacin-based cohort with all ofloxacin-based cohorts combined, the hazard ratio for an adverse outcome was 0.39 (95% CI, 0.26–0.59).

Among the ofloxacin-treated patients, one of the failure cases and the unallocated outcome (clinically considered as a failure) had strains that were initially resistant to kanamycin and prothionamide. One other patient with an initially ethionamide-resistant strain failed treatment, but neither of the two with initial ofloxacin resistance failed treatment. Five out of 11 failure cases tested had acquired ofloxacin resistance, and one had acquired kanamycin and ofloxacin resistance.

Among the gatifloxacin-treated patients, the initial isolate of the single failure case was susceptible to all second-line drugs and to ethambutol. Subculture of the failure isolate failed, making drug susceptibility testing and fingerprinting impossible.

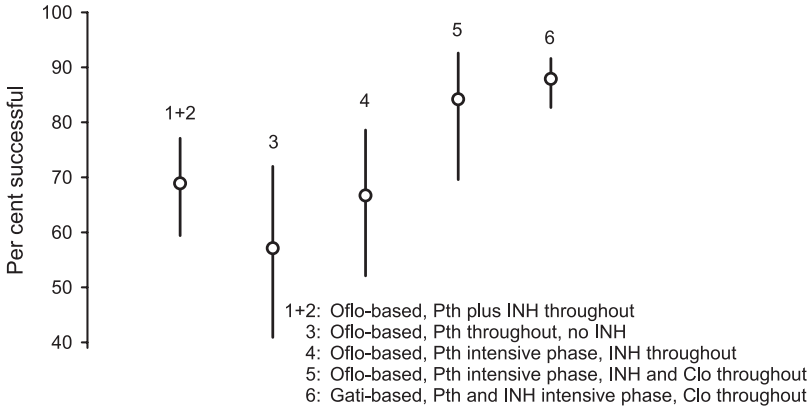

Figure 2. Proportion of patients with a successful outcome in the treatment of multidrug-resistant tuberculosis. Successful outcome was defined as treatment completion or a relapse-free cure. Death, default, failure (including one clinical failure without bacteriological evidence), and relapse were considered unsuccessful outcomes. Numbers denote regimen number. Clo = clofazimine; Gati = gatifloxacin; INH = isoniazid; Oflo = ofloxacin; Pth = prothionamide.

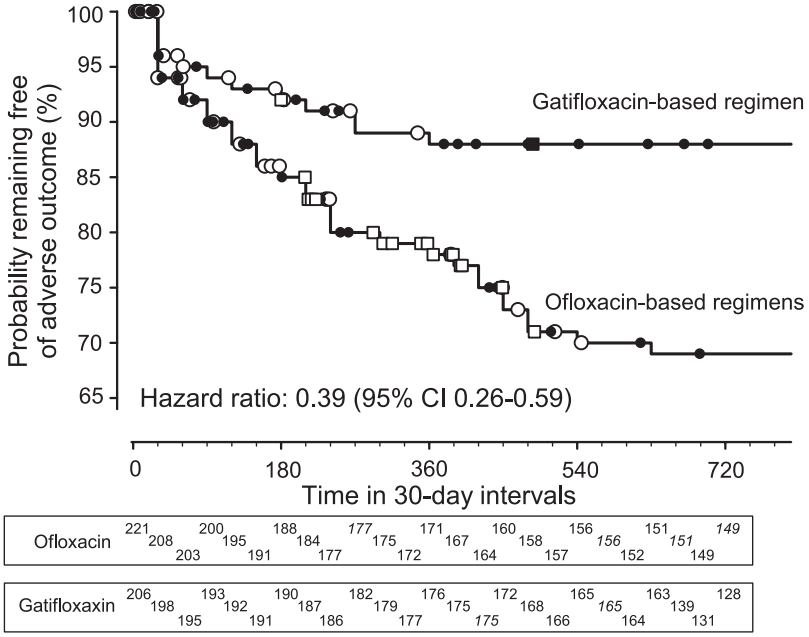

Figure 3. Kaplan-Meier survival plot of time to adverse outcome. Adverse outcomes were failure (including one clinical failure), death, and default during treatment and relapse after treatment cessation. Patients with an adverse outcome contributed observation time up to the midpoint of a 30-day interval. *Open circles* indicate default; *closed circles* indicate deaths (throughout follow-up); *open squares* indicate treatment failures; *closed squares* indicate relapse. The number of patients at risk at the beginning of each interval is shown below the abscissa label for both regimen groups (the number is in italics when no losses occurred in interval). The display is cut off at 810 days after the survival probability had stabilized, and no further instances of adverse outcomes were recorded.

The single relapse was resistant to all four first-line drugs plus ofloxacin, before and after treatment.

Cost of Gatifloxacin-based Treatment Regimen

Diagnosis, hospitalization, and all drugs were provided free of charge to the patients. Patients were given free meals during hospitalization, and transport costs were also borne by the Damien Foundation, if required, for the treatment and post-treatment follow-up, but no other incentives were provided. Using generic formulations, the drug cost of the gatifloxacin regimen was around 225 Euros.

DISCUSSION

We demonstrate, by six sequentially adapted regimens over a 12-year period, that standardized treatment of multidrug-resistant tuberculosis, when not complicated by extensive additional resistance, can be relatively short and highly successful. The first regimen followed contemporary WHO recommendations, except for the use of a combination of drugs with doubtful activity (isoniazid, pyrazinamide, and clofazimine) instead of a fourth weak, toxic, and expensive second-line drug to compensate for possible ethambutol resistance. Results from previous cohorts guided adjustment of regimens to achieve increased effectiveness through the reduced frequency of adverse drug reactions, default, and treatment failure. Regimen changes associated with improved results in all of these objectives were shorter use of the thioamide, replacing thioamide with clofazimine during continuation phase, and using a fourth-generation fluoroquinolone. The final regimen, with total treatment duration of minimum 9 months, was associated with increased success, including a substantial reduction in treatment failures. The final regimen used gatifloxacin in combination with ethambutol, pyrazinamide, and clofazimine throughout, supplemented by kanamycin, prothionamide, and isoniazid during an intensive phase of 4 months or until sputum smear conversion. This approach achieved below 1% failure and close to 90% relapse-free cure. Although not all of the patients allocated to the gatifloxacin-based regimen had completed the 24 months of post-treatment follow-up at the time of analysis, 90% had at least 1 year follow-up. The trials of the British Medical Research Council have shown that relapses occur most frequently in the first 6 months after treatment (17). Thus, we feel it is unlikely that the results would be much poorer had all patients had a full 2-year follow-up period.

Because all medications were generic preparations, the regimen cost just above 200 Euros, making it a promising approach for many low-income countries. Although adverse drug reactions were frequent even with the gatifloxacin-based regimen, they were manageable and rarely serious. In particular, gastrointestinal reactions, often leading to default, were greatly reduced in regimens with shortened thioamide administration. Gatifloxacin could probably have been replaced with moxifloxacin without losing regimen effectiveness, but in this young population uncontrollable dysglycemia during treatment was so rare that we could not justify the large costs of substituting a generic with a perhaps slightly better tolerated but patent-protected medication.

Before 1996, human immunodeficiency virus (HIV) infection prevalence in Bangladesh was less than 0.5% in groups expected to have a higher-than-average risk (18). In HIV prevalence surveys among patients with tuberculosis in the years 2000 and 2001, no patient was HIV positive among almost 1,000 outpatients, and only one patient was HIV positive among almost 900 hospitalized patients (19). Among approximately 400 hospitalized patients with tuberculosis tested in our project, only one has been found to be HIV positive (Damien Foundation, September 2009, unpublished data). The population from which this group of patients was drawn was thus most likely virtually free of HIV infection but presented late in the course of their illness with extensive disease, as indicated by their low body mass index and the finding that 80% had both lungs affected. This explains the relatively high frequency of deaths, irrespective of a favorable bacteriological response to treatment. Smear-positivity, low body mass index, and male sex predominance have been identified as risk factors for an unfavorable outcome in the treatment of multidrug-resistant tuberculosis (5).

Despite an increase in the prevalence of ofloxacin resistance over time from virtually nil to 10%, the gatifloxacin-based regimen seemed effective and, in contrast to the ofloxacin-based regimens, did not lead to additional acquired resistance.

Susceptibility of most multidrug-resistant, ofloxacin-resistant isolates to fourth-generation fluoroquinolones has been reported elsewhere (20). Our results suggest that at the high gatifloxacin dosage used, initial fluoroquinolone resistance can be overcome without *de novo* acquisition of fluoroquinolone resistance.

This study has limitations. First, it is an observational study based on programmatic patient management and sequential rather than concurrent comparisons. Secular changes in our population make interpretation of our results less straightforward. However, throughout the observation period, treatment protocols guided management and were strictly enforced. Recording of data was performed by the same trained personnel, and internal and external supervision was tight to ensure provider adherence and data quality. We based our analysis on objective, predefined, internationally recommended criteria for cure, completion, failure, and relapse. Only recorded treatment and culture and drug susceptibility testing data were used to include or exclude cases and to allocate patients to the above treatment outcomes, regardless of previous clinical decisions. Although the trend toward earlier enrolment might be partly responsible for the overall lower mortality in the gatifloxacin cohort, its lower failure rate may not be explained by secular bias in view of the increased level of initial resistance to fluoroquinolones and the very similar extent of initial disease presentation among all cohorts.

Second, laboratory services had a long tradition of external quality assurance of sputum smear microscopy, resulting early in exemplary performance (21). In contrast, culture services were introduced gradually and more recently. Long transit times and the use of solid media may have reduced the sensitivity of culture examinations. We therefore used unusually strict criteria in our analysis to compensate for the possible limitations in culture sensitivity (i.e., a single positive culture with any number of colonies defined failure or relapse) provided the strain could not be shown to differ from the initial isolate. In addition, multiple serial, consistently negative cultures over an extended period of time were required to define a patient as being bacteriologically cured.

Third, patients in poor clinical condition were included in the intention-to-treat analysis. This may explain to a large extent the frequency of death. We particularly scrutinized the bacteriological course among death and defaulter cases and were assured that none of these events was caused by hidden bacteriological failures.

Fourth, migration from the mostly poor rural to urban areas is increasing in Bangladesh, precluding follow-up of all patients after treatment completion.

Fifth, a large proportion of eligible cases never started treatment for various reasons that were not well documented. It is likely that some of those patients would have defaulted if they had started treatment because of low motivation and that the results would have been less favorable. On the other hand, no incentives were used to improve compliance, and the negative impact of adverse effects and hospitalization may not be as severe in other populations.

We used an approach to the composition of regimens that deviates in several aspects from commonly formulated expert opinion: Isoniazid and ethambutol were always prescribed despite laboratory-confirmed resistance of all or most strains, and clofazimine was added for additional coverage. Because of the large therapeutic range of isoniazid, a fraction of patients may still benefit from the drug because the high concentration achievable in tuberculosis lesions may overcome low-level resistance (found in 6% of 221 strains from our cohorts, tested at both 0.2 and 1.0 mg/L). A moderately high dose of isoniazid might have contributed beneficially in at least a few cases, particularly patients with thioamide cross-resistance (22–24). In routine practice, the inclusion of isoniazid in the intensive phase will also benefit patients suspected of harboring a multidrug-resistant strain who later turn out to have a rifampin-resistant but isoniazid-susceptible strain. The role of ethambutol remains poorly understood, and laboratory determination of susceptibility is notoriously difficult (25). Clofazimine, a drug that has never been properly evaluated but that has been recommended as a second-line agent (26), appeared to be an important companion drug, allowing us to dispense with the more toxic and poorly accepted thioamide in the continuation phase while completely compensating for the efficacy lost by its removal.

The substantially reduced treatment duration appeared justified by the sterilizing efficacy reported with fourth-generation fluoroquinolones (27, 28). Regular monitoring of blood sugar proved feasible, and the low risk of dysglycemia the drug entailed even at high dosage only rarely required a change to ofloxacin.

Current recommendations for the treatment of multidrug-resistant tuberculosis appear to emphasize the maximizing of regimen efficacy (3). Because treatment for multidrug-resistant tuberculosis is commonly the last chance for a patient, efficacy is indeed an ethically imperative argument. Nevertheless, we argue that drug efficacy is just one facet of regimen effectiveness and that equally strong emphasis must be given to whether patients tolerate these drugs and consequently are able to remain on treatment for a sufficiently long duration to ensure failure- and relapse-free cure. Where centers are specialized, it might be possible to substantially modify the treatment regimen accordingly, which was required in 30% of patients reviewed from a study in five pilot projects (29). Such an approach relies on specialists, which reduces the chance to bring the services to where the patients live. Indeed, fewer than 3% of the small subset of cases with diagnosed multidrug-resistant tuberculosis received treatment in 2007 as recommended in international guidelines (2). The treatments presented here were delivered through routine services in rural Bangladesh, with outcomes in the final cohort being very similar to outcomes achieved in the first-line drug treatment of drug-susceptible tuberculosis within the same project. Low levels of initial second-line drug resistance, particularly to the injectables, with restriction of the indications to cases not yet treated with these drugs may have been key to this success. Provided that studies in other populations (i.e., with high prevalence of HIV or with less intensive patient care) show similar results, this study opens an opportunity to truly deliver treatment throughout national tuberculosis programs in most low-income countries.

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