SHORT REGIMEN FOR MDR-TB IN KARAKALPAKSTAN

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CURRENT TREATMENT

- **Complex**
- **Expensive**
- **Long**
- **Side-effects**
- **Limited successful treatment**
  - 64% in literature[1]
  - 54% from KK historical data
- **Default common**
  - 23% in literature[2]
  - 27% from KK historical data

1. Orenstein EW, et al, Lancet Infect Dis. 2009 Mar;9(3):153–61
2. Ahuja SD, PLoS Med. 2012;9(8):e1001300. .

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"Bangladesh Regimen"

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

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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

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

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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.

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).

- Observational cohort analysis
- Bangladesh
- Damien foundation project
- 427 MDR TB (incl 2 XDR)
- 206 on Gfx-based regimen

9+ months

88% success rate

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"Bangladesh Regimen"

Van Deun, Maug, Salim, *et al.*: Standardized MDR Treatment in Bangladesh

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

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

* Each patient may have multiple reactions.

† Percentages are proportions of patients with that episode.

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PILOT IN KARAKALPAKSTAN

- **Currently restricted to areas with low SLD use**
  - Cameroon, Benin, Niger, CAR, South Sudan
- **Limited evidence in areas with high SLD use & resistance**
- **Aim to select biased group who will benefit**
  - Exclude those with
    - History of SLD use for >1 month
    - Resistance to FQ (Ofx), Inj, or XDR-TB

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PROJECT DESIGN AND DSMB

- **Collaboration with Karakalpak and Uzbek MoH**
  - Protocols, resources, consiliums, training,
- **Prospective observational study**
- **Based on KK model of TB care in 2 rayons**
- **Ethics approved – MSF OCA and Uzbekistan ERB**

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PROJECT DESIGN AND DSMB

- **110 participants**
- **Primary outcomes:**
  - Success at end of treatment
  - Relapse/reinfection rates with 12 month follow-up
- **Excludes EPTB, renal failure, ECG criteria**
- **External monitoring of safety by WHO-assigned group**

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PILOT IN KARAKALPAKSTAN

- **Informed consent**
  - Pre-treatment counseling
  - Flipbook, general and pregnancy info leaflet
  - Consent form
- **Joint MoH and MSF consiliums**

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REGIMEN DESIGN

- **Standardised treatment regimen**
- **Intensive phase:**
  - 4-6 months
  - Duration based on sputum smear and culture results
  - 7 drugs: Z-E-H-Mfx-Km-Cfz-Pto
- **Continuation phase:**
  - 5 months
  - 5 drugs: Z-E-Mfx-Cfz-Pto

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EARLY DAYS

- **Fulfilled inclusion criteria[1]: 39**
- **Successfully recruited: 10**
- **Working up for possible recruitment: 8**
- **Excluded: 21**
  - DST-related: 9 (4 Ofx, 4 XDR or inj)
  - Consent related: 6
  - Hx of >1m SLD use: 3
- **Side-effects – limited to Grade 1-2**
- **No ECG-related side-effects or withdrawals**

1. At time of writing (November 2013)

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FURTHER STEPS

- **Enrollment**
  - Further streamline processes – field and laboratory
- **Interim analysis**
  - Planned on completion of intensive phase by 50 pts
- **Review by external DSMB**
  - Quarterly reports
  - 6 monthly teleconference

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THANK YOU & QUESTIONS

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