Treating children for drug-resistant tuberculosis in Tajikistan with Group Five medications

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Treating children for drug-resistant tuberculosis in Tajikistan with Group Five medications

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ABSTRACT

BACKGROUND: Management of extensively drug-resistant (XDR) tuberculosis (TB) and pre-XDR-TB is challenging because effective drugs are lacking. Group Five TB drugs have an unclear role in the treatment of drug-resistant TB and in children the efficacy, safety, and effects of long-term use are not well described. We present clinical outcomes and adverse effects of a cohort of children with XDR-TB or pre-XDR-TB treated with Group Five drugs in Tajikistan.

METHODS: We conducted a retrospective analysis of eight children treated with one or more of the Group Five drugs available in the Tajikistan National TB programme (linezolid, amoxicillin-clavulanate, clofazimine, and clarithromycin), which were given in addition to first- and second-line drugs. Time to sputum culture conversion, clinical outcome, and adverse effects were evaluated.

RESULTS: Two children were cured, one completed treatment, four achieved favourable interim outcomes, and one died. Adverse effects attributable to linezolid that warranted drug cessation occurred in one child; adverse effects of other Group Five drugs were insignificant or absent, requiring no regimen changes.

CONCLUSION: Group Five drugs can contribute to effective regimens in children with XDR and pre-XDR-TB. With proper monitoring and aggressive management of adverse effects, their safety profile might be acceptable, even in long-term use.

Keywords

Linezolid

Clofazimine

Amoxicillin-clavulanate

46 Neuropathy

47 MDR-TB

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INTRODUCTION

The emergence and spread of multidrug-resistant (MDR) tuberculosis (TB) threatens progress in global TB control¹. Up to 20% of TB cases occur in children and annually more than 30,000 develop MDR-TB². Once on treatment, up to 82% of children with MDR-TB achieve favourable outcomes³.

Patients with strains of MDR-TB resistant to second-line drugs, in particular the fluoroquinolones, have worse outcomes even with access to Group Five drugs⁴. Among all new and re-treatment cases of TB, the proportion of MDR-TB and XDR-TB (extensively drug-resistant TB, defined as MDR-TB with additional resistance to a fluoroquinolone and a second-line injectable drug) is highest in the World Health Organization (WHO) European Region⁵. In Tajikistan, the proportion of TB that is MDR is 13% among new patients and 56% in retreatment cases⁶. In the Médecins Sans Frontières (MSF)/Ministry of Health and Social Protection of the Republic of Tajikistan (MoH) TB programme, children with XDR-TB or pre-XDR-TB (MDR-TB with either injectable or fluoroquinolone resistance) receive regimens that include one or more of the four available Group Five drugs: linezolid (Lzd), clofazimine (Cfz), amoxicillin/clavulanate (Amx/Clv), and clarithromycin (Clr). Although Group Five TB drugs, classified by WHO as having “unclear efficacy or unclear role in drug-resistant TB treatment” are increasingly being used for the management of MDR-TB with injectable and/or fluoroquinolone resistance, efficacy and safety data in children are limited. We present the clinical outcomes and adverse effects of a cohort of children with XDR-TB or pre-XDR-TB treated with Group Five drugs in Tajikistan.

68 **METHODS**

69 We conducted a retrospective review of all patients younger than 18 years admitted to the MSF/MoH
70 programme between October 2012 and October 2014 with XDR-TB or pre-XDR-TB and started on
71 regimens that included one or more of the Group Five drugs. Programme data were analysed to the end
72 of May 2015. Interim clinical and microbiological outcomes, final treatment outcome, and adverse
73 effects of Group Five drugs were assessed.

74 Diagnosis was based on drug susceptibility testing (DST) results (National Reference Laboratory, with
75 quality control by the Supranational Reference Laboratory, Gauting, Germany). If sputum sample and
76 DST results were negative or inconclusive, DST results of close household source cases and the child's
77 previous treatment history helped determine the treatment regimen. DST against all drugs except
78 pyrazinamide was performed using standard culture on Löwenstein-Jensen media. First-line drugs were
79 assessed by the proportion method with specific concentrations: streptomycin 4µg/mL, isoniazid
80 0.2µg/mL, rifampicin 40µg/mL, and ethambutol 2µg/mL. Second-line drugs were assessed by absolute
81 concentration: ofloxacin 2µg/mL, capreomycin 40µg/mL, kanamycin 30µg/mL, and amikacin 30µg/mL.
82 DST against pyrazinamide was performed using MGIT 960 (100mg/L).

84 Patients were managed **according to** MSF-PIH⁷ (Partners in Health) protocols and other international
85 guidelines⁸, with consultation from international experts and approval by the local official body (the
86 consilium) for quality assurance in TB treatment. Regimens included ≥4 likely effective drugs, chosen
87 according to availability and registration. Lzd was given at 10mg/kg/dose twice daily for children ≤30kg
88 and 600mg once daily for those >30kg. The dose was reduced at 4 months after sputum culture
89 conversion if other effective drugs were available or in case of adverse effects. Cfz was given at 2-
90 3mg/kg/day for patients ≤30kg; those >30kg received 200mg/day for 6 weeks, followed by 100mg/day.

Amoxicillin/clavulanate was given at 80mg/kg/day (up to 3000mg/day) in two divided doses. One patient received clarithromycin at 1000mg/day.

Treatment was directly observed 6 days/week. Patients were followed up by a TB specialist at least monthly. In the intensive phase, sputum smear microscopy and culture were performed monthly; from the 4th month of treatment, DST was performed every 2 months if cultures were positive. During the continuation phase, sputum smear microscopy, culture, and DST were performed every 3 months. Patients on Lzd had complete blood counts (weekly in the first month and then monthly), were questioned on vision disturbances, and undertook Ishihara tests (monthly in children who could cooperate and communicate). Therapeutic drug monitoring was not undertaken. All data were entered in a standard database (Koch6, MSF, Paris). This retrospective review of routine programme data met the criteria of the MSF Ethics Review Board for exemption from ethics review.

RESULTS

Patient characteristics and regimens

Eight children (six girls) received treatment for XDR-TB or pre-XDR-TB. Clinical profiles are summarized in Table 1. At analysis, children had received treatment for a median of 20.5 months. Of the eight children, six had pulmonary TB and two had extra-pulmonary (EP) TB; all were HIV-negative. One had co-existent type 1 diabetes mellitus. Three had not received prior treatment with TB drugs, four had previously been treated with group 1 first-line TB drugs, and one had previously received treatment for MDR-TB. Three had XDR-TB, two had MDR-TB with resistance to fluoroquinolones, one had MDR-TB with resistance to a second-line injectable drug, and two had negative cultures but close household contact with an XDR-TB patient and pre-XDR-TB patient (injectable resistance), respectively.

Children received a median of 7 drugs (range: 6-8) during the intensive phase. Four were initiated on Group 5 drugs were included in the initial regimen for four children; for four others they were added

114 after a median of 5 months either on receipt of second-line DST results or if these suggested the
115 evolution of pre-XDR-TB or XDR-TB. One child received four Group Five drugs (Lzd, Cfz, Amx/Clv, Clr;
116 with dose adjustment of Clr due to likely interaction between Lzd and Clr), four received Lzd, Amx/Clv,
117 Cfz, two received Amx/Clv and Cfz, and one received only Lzd as part of their regimen.

118 *Outcomes*

119 Three children achieved a favourable final outcome (cured or treatment completed), four are still in
120 continuation phase, and one (with pulmonary TB) died in the intensive phase, failing to respond
121 following 5 months of treatment. Among the six children with pulmonary TB, five (including the two
122 declared cured) achieved favourable interim outcomes (sputum smear and culture conversion): one
123 before Group 5 drugs were added to the regimen; and four at a median of 2.5 months following their
124 addition. Among the two children with EP-TB, one completed treatment while the other had good
125 clinical response and is on continuation phase. None failed treatment or were lost to follow-up.

126

127 *Adverse effects*

128 Lzd: six children received Lzd for a median of 15 months (range 12-21). Haematological and neurological
129 abnormalities were noted in one patient (with co-existent type 1 diabetes) who had transient
130 thrombocytopenia in the 6th month and painful peripheral neuropathy in the 8th month, warranting Lzd
131 cessation. Symptoms of peripheral neuropathy resolved following cessation.

132 Cfz: seven children received Cfz for a median of 20 months (range 19-23). Two developed reddish brown
133 discoloration of their skin in sun exposed areas. Two developed ichthyosis in their legs after 4-6 months,
134 which resolved spontaneously after 8-10 weeks, even while continuing Cfz. One had transient gastritis,

possibly due to long-term Cfz. However, none of these side effects warranted dose reduction or
stoppage.

Amx/Clv: seven children received Amx/Clv for a median of 20 months (range 19-23). There were no
major adverse effects attributable to this drug.

Clr: one child received Clr for 20 months. No side effects were noted. The child also received Lzd, the
serum concentration of which is potentially increased by Clr-mediated inhibition of metabolism⁹;
however, no adverse effects of Lzd were noted.

DISCUSSION

Our results show that the Group Five TB drugs, when used appropriately, appear safe and effective in
the management of drug-resistant TB in children. Among the eight children in our cohort, two were
cured, one completed treatment, while four achieved favourable interim outcomes; only one child
developed serious adverse effects (Lzd). With few paediatric data available, our cohort analysis, which
includes standard protocols for treatment, follow-up, and data collection, is a useful addition to the
literature.

Reports of adults treated with Group Five TB drugs have been encouraging.¹⁰ Data on Lzd use in 16
children (from seven different reports) show that all achieved sputum culture-conversion, while 14
achieved a successful long-term outcome, **often** despite extensive disease, substantial drug resistance,
prolonged culture positivity, and **previous** failed **second-line** treatment¹¹. Peripheral neuropathy was
noted in four of these children, but resolved after dose reduction or discontinuation. A meta-analysis¹²
noted a sputum culture conversion rate of 98% with Lzd, with neuropathy and bone marrow
suppression the most common adverse effects (36% and 28%, respectively) in addition to gastro-

156 intestinal effects (diarrhoea, vomiting), myelosuppression, and lactic acidosis. Lzd has good tissue
157 penetration^{13,14}, and has been added to the WHO essential drugs list¹⁵.

158 Good outcomes have been reported for Cfz-based, short-course regimens in adults¹⁶. A meta-analysis¹⁷
159 reported an overall success rate of 62% with Cfz-based regimens with gastrointestinal disturbances and
160 skin pigmentation the most common adverse effects. In leprosy patients, long-term treatment with Cfz
161 is well tolerated, rarely requiring discontinuation; however, the dosages are often lower than used in
162 TB^{18,19}. Gastrointestinal adverse effects in children have not been well reported. Case reports on two
163 children with leprosy treated with Cfz describe severe haematemesis²⁰ and enteropathy²¹, respectively.
164 Amx/Clv has demonstrated *in-vitro* activity against MDR/XDR-TB²². Meropenem and Clv with Lzd
165 produced good results in a 14-year old with XDR-TB²³.

166 We encountered practical programmatic issues: the introduction, registration, and licensing of new TB
167 drugs in Tajikistan; training needs; establishing monitoring facilities; limited laboratory resources for
168 sputum culture and DST; and ensuring clear communication with patients and health-care providers on
169 the use of drugs of “unclear efficacy”.

170 Our study has limitations. Regimens were comprised of Group 5 and second-line drugs likely to be
171 effective and some drugs that might not have been effective or had previously been used for treatment
172 (eg pyrazinamide). Multiple drugs were used in individualized regimens, hindering definitive attribution
173 of outcomes and adverse effects to any particular drug or group. Only three children have achieved a
174 successful outcome. Follow-up is needed to monitor for relapse and to gain insight into the effectiveness
175 of the regimens in reducing mycobacterial burden and replication, and achieving sterilization. Finally,
176 there was absence of microbiological confirmation in some patients (culture-negative pulmonary TB and
177 TB pericarditis).

178 **CONCLUSION:**

Group Five TB drugs, when used appropriately, appear safe and effective in the management of drug-resistant TB in children; however, evidence remains limited. Drug choices depend on availability of drugs and paediatric-friendly formulations, efficacy, safety, co-morbidities, drug-drug interactions, and facilities for monitoring adverse effects. Lzd and Cfz are being included in many of the ongoing treatment trials in adults (either with or without the new agents: bedaquiline, delamanid, Pa-824) and are likely to be highly important in treatment regimens in the future. As there is so little known about their use in children, our cohort data are important. With the new agents increasingly being used for drug-resistant TB, there is a need for better evidence and guidance for the selection and use of these drugs in children since currently there are no pharmacokinetic, formulations, or safety data for any of these drugs in children. However, if or when these data become available, many TB programmes will not have access to these expensive drugs.

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Conflicts of interest: none declared.

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No	Age/ Sex	Prior TB treatment	Contact history	Symptom duration before sample was taken	Type of diagnostic sample used	Chest X ray findings	DST	Regimen	Adverse effect attributed to Group 5 drug	Interim outcome	Final outcome
1	16y/ F	CAT 1 and 2	No	3 months	Sputum	Infiltrate: right lung >1 lobe, left lung >1 lobe	HRZES Pto Mfx Ofx Km Cm- resistant	Lzd-Mfx- Amx/Clv-Cfz- Pto-Cs-PAS	None	Good clinical response. Achieved sputum conversion.	Cured following 25 months of treatment
2	5y/F	CAT 1	Yes	1 month	Lymph node	Normal	HRZE Mfx Ofx Pto- resistant; Cm,Km- sensitive	Z-Mfx-Am- Cs-Cfz- Amx/Clv-PAS	Transient gastritis (Cfz)	Good clinical response. Lymph node enlargement completely regressed.	Treatment completed following 24 months of treatment

3	17y/ F	CAT 1	No	6 months	Sputum	Cavities in both lungs, Infiltrate: right lung >1 lobe, left lung >1 lobe. Left sided pleural effusion	HRZES Ofx Mfx Km Am Cm Pto-resistant	Lzd-Mfx-Z-Cs-Amx/Clv-Cfz-Clr	Ichthyosis (Cfz)	Clinical improvement present. Sputum conversion achieved.	Received 27 months of XDR-TB regimen. Plan: 30 months in total.
4	14y/ F	CAT 1, CAT 4 (MDRTB regimen) for 7 months	Yes	7 months	Sputum	Cavities in both lungs. Infiltrate : right lung >1 lobe	HRZES Mfx Ofx Km Cm Am Pto-resistant	Z-Lzd-Am-Mfx-Cs-Amx/Clv-Cfz	None	Poor clinical response. Sputum conversion not achieved.	Died (after 5 months of treatment).
5	12y/ F	No	Yes	1 month	Based on contact's DST	Infiltrate: left lung (1 lobe). Nodules: left lung (1 lobe).	Not available as culture was negative. GeneXpert showed Mtb (+) and Rif resistant. (DST of contact showed HRES	Z-Am-Mfx-Pto-Cs-Amx/Clv-Cfz-PAS	None	Good clinical response. Sputum conversion achieved	Received 20 months of treatment. Plan : 24 months in total.

							OfxCm-resistant; Z Km Am-sensitive).				
6	15y/ M	No	Yes	2 weeks	Sputum	Cavity: left lung (1 lobe). Infiltrate: left lung >1 lobe	HRS Km Am Cm-resistant; ZE Ofx-sensitive	Lzd-Cm-Mfx-Z-Pto-Amx/Clv-Cfz-E	Ichthyosis and reddish skin discoloration (Cfz).Thrombocytopenia and peripheral neuropathy (Lzd stopped)	Good clinical response. Sputum conversion achieved.	Cured following 21 months of treatment.

7	15y/ F	No	Yes	1 month	Sputum	Infiltrate: right lung (1 lobe), left lung >1 lobe	HRSE Ofx-resistant; Km Am Cm-sensitive	Lzd-Mfx-Cm-Z-Pto-Cs-Cfz-Amx/Clv	Reddish skin discoloration (Cfz)	Good clinical response. Sputum conversion achieved.	Received 19 months of treatment. Plan: 24 months in total.
8	30 months/M	CAT 1 (2 months)	Yes	15 days	Based on contact's DST	Pleuritis, pericarditis. Left pleural effusion	Not available (extrapulmonary) (DST of contact showed HRS Km Am Cm-resistant; E Ofx-sensitive)	Lzd-Cm-Lfx-Pto-Cs- Z	None so far	Good clinical response (doing well following subtotal pericardiectomy).	Received 12 months of treatment. Plan: 20-24 months in total.

200 CAT: Treatment category (as per WHO classification). Category 1=initial regimen with first-line drugs. Category 2=retreatment regimen with first-
 201 line drugs. Category 4=second-line treatment regimen.

202 H: Isoniazid

203 R: Rifampicin

204 Z: Pyrazinamide

205 E: Ethambutol

206 S: Streptomycin

- 207 Cm: Capreomycin
- 208 Km: Kanamycin
- 209 Am: Amikacin
- 210 Ofx: Ofloxacin
- 211 Lfx: Levofloxacin
- 212 Mfx: Moxifloxacin
- 213 Pto: Prothionamide
- 214 Cs: Cycloserine
- 215 PAS: Para-amino salicylic acid
- 216 Lzd: Linezolid
- 217 Cfz: Clofazimine
- 218 Amx/Clv: Amoxicillin/clavulanate
- 219 Clr: Clarithromycin
- 220 DST: Drug susceptibility test
- 221
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REFERENCES:

1. Keshavjee S, Farmer PE. Time to put boots on the ground: making universal access to MDR-TB treatment a reality. *Int J Tuberc Lung Dis* 2010; 14: 1222–25.
2. Jenkins HE, Tolman AW, Yuen CM et al. Incidence of multidrug-resistant tuberculosis in children: systematic review and global estimates. *Lancet* 2014; 383: 1572–79
3. Ettehad D, Schaff HS, Seddon JA et al. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;12:449-456
4. Kwok-Chiu Chang, Wing-Wai Yiew et al. WHO Group 5 Drugs and Difficult Multidrug-Resistant Tuberculosis: a Systematic Review with Cohort Analysis and Meta-Analysis. *Antimicrobial agents and Chemotherapy* 2013; 57 (9):4097-4104.
5. Best practices in prevention, control and care for drug-resistant tuberculosis, 2013: A resource for the continued implementation of the Consolidated Action Plan to Prevent and Combat Multidrug- and Extensively Drug-Resistant Tuberculosis in the WHO European Region, 2011–2015. World Health Organization.
6. World Health Organization. Global Tuberculosis Report 2014. Copyright WHO. Geneva. 2014.
7. Varaine F, Rich ML. Tuberculosis: Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries. 2014 Edition.
8. Management of Drug-Resistant Tuberculosis in Children: A Field Guide. Boston, USA: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis; November 2012
9. Bolhuis MS, Van Altena R et al. Clarithromycin increases linezolid exposure in multi-drug resistant tuberculosis patients. *Eur Respir J*. 2013; 42: 1614-21.
10. Lee M, Lee J, Carroll MW et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med* 2012;367:1508-18.
11. GraciaPratts AJ, Donald PR, Hesseling AC, Schaff HS. Second-Line Antituberculosis Drugs in Children: A Commissioned Review for the World Health Organization 19th Expert Committee on the Selection and Use of Essential Medicines
12. Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis*. 2012; 16(4):447–454
13. Conte JE, Golden JA, Kipps J, Zurlinden E. Intrapulmonary Pharmacokinetics of Linezolid. *Antimicrobial Agents and Chemotherapy*. 2002 May 1, 2002;46(5):1475-80.
14. Yogev R, Damle B, Levy G, Nachman S. Pharmacokinetics and distribution of linezolid in cerebrospinal fluid in children and adolescents. *Pediatr Infect Dis J*. 2010 Sep;29(9):827-30.
15. http://www.who.int/selection_medicines/committees/en/
16. Van Deun A, Maug AK, Salim MA, et al. Short, highly effective and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2010;182:684-692
17. Dey T, Bridgen G et al. Outcomes of clofazimine for the treatment of drug-resistant tuberculosis: a systematic review and meta-analysis. *J Antimicrob Chemother* 2013; 68: 284–293.
18. Singh H, Nel B, Dey V, Tiwari P, Dulhani N. Adverse effects of multi-drug therapy in leprosy, a two years' experience (2006-2008) in tertiary health care centre in the tribal region of Chhattisgarh State (Bastar, Jagdalpur). *Lepr Rev*. 2011 Mar; 82(1):17-24.
19. Kroger A, Pannikar V, Htoon MT et al. International open trial of uniform multi-drug therapy regimen for 6 months for all types of leprosy patients: rationale, design and preliminary results. *Tropical Medicine and International Health*. 2008 May;13(5):594-602
20. Singh H, Nel B, Dey V, Tiwari P, Dulhani N. Adverse effects of multi-drug therapy in leprosy, a two years' experience (2006-2008) in tertiary health care centre in the tribal region of Chhattisgarh State (Bastar, Jagdalpur). *Lepr Rev*. 2011 Mar;82(1):17-24.

269 21. Parizhskaya M, Youssef NN, Di Lorenzo C, Goyal RK. Clofazimine enteropathy in a pediatric bone
270 marrow transplant recipient. J Pediatr. 2001 Apr;138(4):574-6.
271 22. Gonzalo X, Drobniewski F. Is there a place for b-lactams in the treatment of multidrug-resistant/
272 extensively drug-resistant tuberculosis? Synergy between meropenem and
273 amoxicillin/Clavulanate. J Antimicrob Chemother 2013; 68: 366–369
274 23. Dauby N, Muylle I, Mouchet F et al. Meropenem/clavulanate and linezolid treatment for
275 extensively drug resistant tuberculosis. Pediatr Infect Dis J. 2011 Sep; 30(9)
276

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