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LETTER

Family directly observed therapy for children with drug-resistant TB

Dear Editor,

A major evolution in managing TB is person-centred care, which returns autonomy and agency to patients, while reducing personal and economic hardship and stigma.[1] Family directly observed therapy (F-DOT) is a model that trains family caregivers to provide in-home TB treatment, reducing risk of exposure to infections, such as COVID-19, at health facilities.[2,3] In April 2017, the Tajikistan National TB Programme (NTP) supported by Médecins Sans Frontières (MSF) began piloting F-DOT for paediatric drug-resistant TB (DR-TB) patients in Dushanbe, Tajikistan. We hypothesised that F-DOT would result in non-inferior rates of cured or completed DR-TB treatment outcomes, be acceptable to patients and families, and be feasible to deliver. Here we describe the implementation of this pilot programme.

This descriptive analysis used routine programmatic data on DR-TB paediatric patients aged 0–17 years managed with F-DOT from April 2017 to December 2021. Because F-DOT is included in WHO and Tajikistan TB Guidelines, this study was exempt from institutional review board approval. However, eligible families could decline to participate. We delivered patient/family education and training on F-DOT and DR-TB, ensured families were ready and capable, and conducted in-home follow-up visits weekly (progressing to monthly). We conducted this pilot in Dushanbe and four surrounding districts (population: 1,769,464). We screened and recruited eligible patients/families using a checklist that required a basic understanding of TB treatment, good treatment adherence to TB treatment for $\geq$1m, one literate and committed family member, and telephone availability. Severe disease, malnutrition, HIV co-infection and treatment with injectables were not exclusion criteria. F-DOT decliners and those ineligible were managed with standard DOT. We followed participants until a DR-TB treatment outcome, reversion to standard DOT or F-DOT cessation for non-medical reasons. We monitored patients for relapse until 24 months after successful treatment. All patients received comprehensive care from a team of doctors, nurses, counsellors and social workers. Those who declined or were ineligible received the same quality of care.

A total of 122 eligible DR-TB paediatric patients and families agreed to use F-DOT. Their baseline characteristics are shown in the Table. Of these, 12 transferred out because of administrative changes. Of the remaining 110 F-DOT participants, we observed the following:

- 5/110 (4.5%) reverted to standard DOT because of adherence difficulties;
- 105/110 (95.5%) remained on F-DOT, 7 were still on treatment at the time of writing;
- 97/98 (99.0%) achieved a cured or completed treatment outcome;
- 1 failed treatment;
- none were treated with injectables, and;
- there were no deaths, lost-to-follow-up, or relapse cases.

The median duration of DR-TB treatment for those completing F-DOT was 13 months (interquartile range [IQR] 11–19) and the median duration of F-DOT management was 6 months (IQR 4–7). The median delay between treatment onset and F-DOT onset was 5 months (IQR 3–7). DR-TB paediatric care in Tajikistan involves hospitalisation after diagnosis (often for months), followed by standard DOT before the healthcare team is comfortable offering F-DOT. Musonda et al. have previously documented long periods of hospitalisation in children with DR-TB.[4] DR-TB treatment regimens followed the current WHO and national guidelines. We administered 102 satisfaction questionnaires after 1 month (average satisfaction score 14.96/15 points, 99.7%) and 101 questionnaires at the end (average satisfaction score 19.12/21 points, 91.0%). Comments were universally positive and encouraging. Partial F-DOT was successful in 97/103 (94%) children with DR-TB. Prior to F-DOT in the same population, the overall success rate was 85%. F-DOT was feasible and successful across genders, TB types, DR-TB resistance patterns and age groups. In a systematic review and meta-analysis conducted for WHO,[5] DR-TB treatment outcome success for paediatric cases was 78% overall. We observed the following challenges for standard DOT: no reimbursement for NTP staff travel, lack of counsellors or social workers, TB stigma, non-child-friendly services and long hospitalisation risking developmental regression. Standard DOT with regular attendance at DOT corners was difficult because of distance, bad weather, cost, family and employment disruptions,

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Table Baseline characteristics and outcomes of all 122 children with drug-resistant TB receiving family DOT

Characteristic	*n*	%
Sex		
Male	54	44.3
Female	68	55.7
Age, years		
<5	21	17.2
5–<10	58	47.5
10–<15	20	16.4
15–17	23	18.9
Site of TB		
Extrapulmonary TB	75	61.5
Pulmonary TB	47	38.5
Type of TB diagnosis		
TB confirmed*	50	41.0
TB non-confirmed	72	59.0
Drug resistance pattern†		
MDR-TB‡	54	44.3
Pre-extensively drug-resistant TB§	27	22.1
Extensively drug-resistant TB¶	39	32.0
Polydrug-resistant TB#	2	1.6
Treatment outcome		
Completed or cured	97	79.5
Failed	1	0.8
Unknown (transferred out/reverted to standard DOT)	17	13.9
Still on treatment	7	5.7

* TB signs and symptoms plus microbiologic confirmation.
† Drug resistance pattern for non-confirmed TB is the pattern of the likely source of infection.
‡ TB caused by *Mycobacterium tuberculosis* strains that are resistant to at least both rifampicin and isoniazid.
§ TB caused by *M. tuberculosis* strains that fulfil the definition of MDR-TB and are also resistant to a fluoroquinolone or an SLID.
¶ TB caused by *M. tuberculosis* strains that fulfil the definition of MDR-TB and are also resistant to both a fluoroquinolone and an SLID.
# TB caused by *M. tuberculosis* strains that are resistant to more than one first-line anti-TB drug other than both rifampicin and isoniazid.
DOT = directly observed therapy; MDR-TB = multidrug-resistant TB; SLID = second-line injectable drug.

and multiple children and elderly needing attention. Typically, DR-TB patient families were very poor. With F-DOT, we observed that patients/families could manage daily routines helping them to adhere and complete treatment: they felt empowered and better informed. Positive reinforcement and self-monitoring helped children and adolescents feel more in control. Drug side effects, negative psychosocial responses, avoidance behaviours, and stress were detected early. Travel cost, stigma and problems at school were reduced. These observations were often mentioned in the satisfaction questionnaires. The selection, education and support of the family caregiver was critical to F-DOT success. Pillboxes, medication management plans, and positive reinforcement charts and stickers are valuable aids to adherence and correct dosing. F-DOT can be especially appropriate and cost-effective when other family members are simultaneously receiving TB treatment. One disadvantage was the potential for children to blame caregivers for drug side effects.

We found three recent reviews of F-DOT[6–8] and several articles, but none from Central Asia and none involving paediatric DR-TB patients. A Cochrane review of randomised controlled trials (RCTs) and quasi-RCTs, primarily for adult drug-susceptible TB (DS-TB), found no significant difference in treatment success comparing home-based and facility–based DOT, and family-delivered vs. health worker-delivered DOT.[6] In 2016, a systematic review and meta-analysis on DOT for DR-TB examined retrospective and prospective cohort studies (CSs) plus one cross-sectional study.[7] They found no significant difference comparing DOT provided by healthcare workers, family members and private providers. They also found no difference between health facility-based DOT and home-based DOT. Paediatric-only studies were excluded. Finally, a 2018 systematic review and meta-analysis examined DS-TB and DR-TB, in adults and children, and RCTs and CSs.[8] Two studies included children. They found that healthcare worker-delivered DOT resulted in better adherence than family member-delivered DOT, and that community-delivered DOT had higher treatment success and 2-month sputum conversion rates than clinic-delivered DOT.

Patients in our cohort receiving partial F-DOT did well if patients and caregivers were carefully selected. The introduction of bedaquiline and delamanid during this pilot may have improved treatment success rates overall. Tajikistan is a low-income country ranking 125th of 189 countries in economic terms[9] and 154th of 191 countries in healthcare system efficiency.[10] Even when motivated, the high poverty rate makes it more difficult for patients and families to comply with standard DOT compared to F-DOT. Lower healthcare system efficiency would impede the implementation of standard DOT, making F-DOT more successful in comparison.

This report demonstrates that F-DOT is acceptable to patient and families, and scalable for paediatric DR-TB in the Dushanbe Region of Tajikistan. We did not measure cost-effectiveness, but F-DOT is now standard of care in NTP/MSF clinics. We believe that with further advocacy and capacity building F-DOT can become standard of care nationwide. We suggest that F-DOT should be the preferred option for paediatric DR-TB patients in low-income countries with significant healthcare delivery challenges.

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