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Treatment of multidrug-resistant tuberculosis in a remote, conflict-affected area of the Democratic Republic of Congo

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SUMMARY

The Democratic Republic of Congo is a high-burden country for multidrug-resistant tuberculosis. Médecins Sans Frontières has supported the Ministry of Health in the conflict-affected region of Shabunda since 1997. In 2006, three patients were diagnosed with drug-resistant TB (DR-TB) and had no options for further treatment. An innovative model was developed to treat these patients despite the remote setting. Key innovations were the devolving of responsibility for treatment to non-TB clinicians remotely supported by a TB specialist, use of simplified monitoring protocols, and a strong focus on addressing stigma to support adherence. Treatment was successfully completed after a median of 24 months. This pilot programme demonstrates that successful treatment for DR-TB is possible on a small scale in remote settings.

KEY WORDS: tuberculosis; multidrug-resistant tuberculosis; Democratic Republic of Congo; resource-limited

THE DEMOCRATIC REPUBLIC of Congo (DRC) is considered a high-burden country for multidrug-resistant tuberculosis (MDR-TB),[1] but the capacity to diagnose and treat MDR patients is severely limited. Conflict has fuelled the disease outbreak by disrupting health care and drug supplies and causing forced displacements.[2,3] Treatment for MDR-TB is highly specialised, complex and expensive, and whether it can be safely implemented in remote settings is uncertain. We describe a pilot programme implemented in Shabunda, an isolated conflict-affected region of DRC, where treatment for drug-resistant TB (DR-TB) was integrated into the National TB Programme (NTP) on a small scale.

Shabunda is located 340 km from the provincial capital of South Kivu, Bukavu, and the main channel of communication is by air. The roads are impassable and in an advanced state of disrepair, making trade difficult and discouraging agricultural initiatives. The region has been affected by conflict since 1996,[3] and Médecins Sans Frontières (MSF) intervened in 1997 to restart health services in a destroyed hospital. Only one centre in the region, located in the general hospital, had the capacity to diagnosis and treat TB, and patients often had to walk up to 90 km to seek treatment. In 2004, the DRC Ministry of Health (MoH) asked MSF to become involved in their NTP. Cohort results for the first year showed a treatment success rate of 79.7%, a death rate of 7.8%, a defaulter rate of 3.6% and a failure rate of 1.3%.

Despite these positive results, the health of three patients diagnosed in April 2006 did not improve despite good adherence and human immunodeficiency virus negative status. All had received inadequate treatment regimens at the time of their first diagnosis, and two had experienced treatment disruptions directly due to conflict. Standard treatment protocols at the time dictated that these patients be sent home in the absence of second-line drugs. However, two of the patients had already been turned out of their homes due to their illness; one patient was the sole care giver of two young children. The TB treatment team, unable to accept defeat, enrolled them once again on a Category II regimen, again without result. Sputum samples were eventually exported to a regional laboratory for drug susceptibility testing (DST), and resistance to 3–5 first-line drugs was confirmed for each patient.

TREATMENT MODEL

MSF operated out of a busy district hospital, supporting general medical and surgical care. Neither the MSF nor the MoH doctors were TB specialists, and none had experience in treating MDR-TB. They received support from an expert TB clinician based in Europe with whom they communicated by mobile phone. The advisor was responsible for making all regimen choices and guiding the management of severe side effects. A simplified protocol for monitoring was developed (Table 1). A key simplification was to reduce the frequency of culture monitoring in the continuation stage of treatment from monthly to quarterly samples. Treatment regimen changes were to be made only in response to the second-line DST results or in

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Table 1 Simplified protocol for treatment and monitoring*

Baseline patient examination
1 Thorough history and clinical examination
2 Psychosocial assessment with a focus on factors affecting adherence (e.g., living situation, substance use/abuse, psychosocial supports)
3 Sputum smear, culture and drug susceptibility testing
4 Blood tests:
i Full blood count
ii Liver function (ALAT)
iii Renal function (creatinine)
iv HIV test
5 Hearing assessment (clinical)
6 Vision testing
7 Weight
8 Pregnancy test

Clinical follow-up
First month of treatment
1 Daily physician review: clinical follow-up—cough, fever, weight, sputum production, side effects
Remainder of intensive phase
1 Twice weekly physician review
2 Daily nursing review
Continuation phase
1 Daily review with DOT worker
2 Monthly physician review
Monitoring during treatment
1 Sputum smear every month during treatment
2 Culture monthly during intensive phase, starting at end of month 2 and then 3-monthly in the continuation phase
3 Blood tests as required and
i Monthly creatinine and potassium during phase with injectable drug
ii Liver function test (ALAT) every 3 months if receiving pyrazinamide or if at risk of hepatitis
4 Monthly weight

*Chest X-ray was not available and was not used in the clinical follow up.
ALAT = alanine aminotransferase; HIV = human immunodeficiency virus; DOT = directly observed treatment.

case of severe side effects. Simple tools were used for clinicians to triage potentially serious adverse effects that required consultation with headquarters.

To ensure reliable culture results, sputum samples were exported to a reference laboratory in Antwerp, Belgium. Sputum smears were performed locally. Biochemical tests were performed in Bukavu, 2 days' travel from Shabunda by plane, boat and car. Radiology was not available in Shabunda.

The initial treatment regimen was based on first-line DST for two patients, and consisted of five second-line drugs in the intensive phase of treatment, followed by four in the continuation phase. However, the NTP did not allow para-aminosalicylic acid (PAS) due to concerns regarding maintenance of the cold chain, and preferred a regimen with four second-line drugs, together with pyrazinamide (PZA) and ethambutol (EMB); at the time, generic PAS that did not require cold chain was not available. The final accepted regimen consisted of kanamycin, levofloxacin, prothionamide, cycloserine, PZA and EMB in the intensive phase, which were continued for 4 months past culture conversion. The continuation phase was 18 months and consisted of the same drugs without the injectable agent (kanamycin).

Treatment during the intensive phase took place in a hospital isolation ward. As all patients lived outside Shabunda, host families were needed to provide housing during the ambulatory phase of treatment. All drugs were delivered under directly observed treatment (DOT) by a nurse. Intensive health education and adherence support, including food supplements, were provided.

The patients' treatment was further challenged by MSF's decision to hand over the Shabunda project to the MoH 7 months after treatment initiation, as the security situation in the region had improved. The hospital director took over responsibility for treating minor-to-moderate side effects. One mobile MSF doctor visited the project once a month until September 2008 to follow up on patients and provide supervisory support. This doctor had previously been based in Shabunda and had the respect of patients and MoH staff. During his visits, he reviewed all patients together with the MoH doctor and treatment nurse, provided on-the-job training and assessed other programmatic aspects such as adherence, stigma, nutrition needs, equipment and staff issues. In the final year of the programme, flight restrictions meant that he could only visit every 3 months.

In the MoH pharmacy MSF left a complete stock of all of the drugs needed to treat the three patients, including cimetidine, ibuprofen, promethazine, metoclopramide, oral potassium, loperamide, pyridoxine and amitriptyline, to complete treatment and manage side effects. There were no drug stock-outs; however, an extra delivery of PZA was organised when the NTP ran out of stock and had to borrow from the MDR-TB patients.

RESULTS

All patients had persistent negative culture results after culture conversion in the intensive phase and at least 2–4 culture-negative results in the continuation phase (Table 2). Second-line DST determined that one patient was on a regimen consisting of three second-line drugs during the intensive phase due to resistance to ethionamide, but no history of second-line drug use was recorded. Despite this suboptimal regimen, culture conversion occurred at month 2 and remained negative. One patient had delayed results from his initial DST, and was therefore started on an empiric regimen. The results, when returned, suggested that he was resistant to all first-line drugs except rifampicin; however, this was not identified until he was late into the continuation phase. He therefore continued on the empiric MDR-TB regimen. Conversion took place at 4 months; however, delay in receiving the sample at the reference laboratory in Antwerp meant that the patient remained on the intensive phase for 10 months instead of 8. This patient, although improved, retained a chronic cough. The treatment outcome for all patients was 'treatment completed', as the frequency of

Table 2 Treatment results

	Age	Sex	TB treatment history	Baseline DST	Culture conversion	Treatment duration	Smear and culture results in the last 12 months of treatment	Clinical improvement	Outcome
Patient 1	29	Female	Treated with first-line drugs in 2001 and 2005, 2006	First-line drugs: resistant to INH, RMP, EMB; susceptible to SM, PZA Second-line drugs: susceptible to KM, CPM, OFX, ETH, PAS	Month 2	24 months	Smear: continuously negative Culture: 3 negative and 1 contaminated	No TB signs or symptoms	Completed
Patient 2	22	Female	Treated with first-line drugs in 2003, 2004 and 2005	First-line drugs: resistant to INH, RMP, EMB, SM; susceptible to PZA Second-line drugs: resistant to ETH; susceptible to KM, CPM, OFX, PAS	Month 2	24 months	Smear: continuously negative Culture: 2 negative, 1 contaminated, 1 unable to produce sputum	Occasional non-productive cough, no other TB signs or symptoms	Completed
Patient 3	30	Male	Treated with first-line drugs in 2003, 2004, 2005 and 2006	First-line drugs: resistant to INH, EMB, PZA, SM; susceptible to RMP Second-line drugs: results not available due to contamination	Month 4	28 months	Smear: continuously negative Culture: 2 contaminated, 1 negative	Frequent productive cough, no other TB signs or symptoms	Completed

TB = tuberculosis; DST = drug susceptibility testing; INH = isoniazid; RMP = rifampicin; EMB = ethambutol; SM = streptomycin; PZA = pyrazinamide; KM = kanamycin; CPM = capreomycin; OFX = ofloxacin; ETH = ethionamide; PAS = para-aminosalicylic acid.

culture monitoring was not sufficient to meet the defined criteria for 'cure'.[4]

Side effects experienced with treatment were mild to moderate. One patient had hypokalaemia during the intensive phase, which resolved with oral potassium. Another experienced jaundice in the intensive phase, which resolved without having to stop treatment. Three months before treatment completion, one patient experienced psychological symptoms, which resolved with antidepressants. Stigmatisation of patients by members of the host families and neighbours was a major issue throughout the course of illness; prompt educational interventions from the DOT nurse and a supportive head of family were instrumental in resolving these issues.

A major challenge in the model was communication between the treating staff and headquarters. Standardised forms proved useful in maintaining an overview of treatment despite the frequent changeover of staff during the long treatment period. The forms, however, proved vulnerable to transcription errors. Direct communication from the reference laboratory to headquarters helped reduce the risk of miscommunication on critical culture results. The availability of rapid DST and simplified methods to monitor response would improve the feasibility of the model.

CONCLUSION

We were able to demonstrate in a small pilot programme that successful treatment of MDR-TB is possible even in isolated low-resource settings using a simplified treatment protocol. Such integrated models of care will be needed as DRC and other countries introduce new World Health Organization TB guidelines, which recommend early access to diagnosis and treatment of drug-resistant TB for high-risk Category II patients. Key aspects of our programme included remote advice to non-specialist clinicians by a TB specialist, the support of a respected MSF doctor throughout treatment, simplified monitoring protocols and strong emphasis on addressing stigma. The long delay in starting the programme and delayed receipt of DST results likely contributed to the less than complete clinical recovery of one patient despite the successful outcome.

References

1 World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. WHO/HTM/TB/2010.3. Geneva, Switzerland: WHO, 2010.

2 Coninx R. Tuberculosis in complex emergencies. Bull World Health Organ 2007; 85: 637–643.

3 Markandya P, Lloyd-Davis F. DRC: a plaster on a gaping wound. New York, NY, USA: Reliefweb, 2012. http://reliefweb.int/node/99546 Accessed March 2012.

4 World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008. WHO/HTM/TB/2008.402. Geneva, Switzerland: WHO, 2008.

RÉSUMÉ

La République Démocratique du Congo est un pays à fardeau élevé de tuberculose à germes multirésistants aux médicaments. Médecins Sans Frontières a apporté son soutien au Ministère de la Santé dans la région de Shabunda atteinte par les conflits depuis 1997. En 2006, le diagnostic de tuberculose à germes résistants (TB-DR) a été porté chez trois patients qui n'avaient aucune possibilité de traitement ultérieur. On a élaboré un modèle innovateur pour traiter ces patients en dépit de leur situation éloignée. Les innovations-clé ont été de déplacer la responsabilité du traitement vers des cliniciens non-TB qui ont été soutenus à distance par un spécialiste TB, l'utilisation de protocoles simplifiés pour le suivi ainsi qu'une forte focalisation pour éviter la stigmatisation afin de renforcer l'adhésion thérapeutique. Le traitement a été achevé avec succès après une durée médiane de 24 mois. Ce programme pilote démontre qu'un traitement couronné de succès est possible pour la TB-DR à une petite échelle dans des contextes éloignés.

RESUMEN

La República Democrática del Congo es un país con alta carga de morbilidad por tuberculosis multidrogorresistente. Médicos Sin Fronteras ha apoyado al Ministerio de Salud desde 1997 en la región de Shabunda, afectada por el conflicto. En el 2006, se estableció el diagnóstico de TB farmacorresistente (TB-DR) en tres pacientes y no existía para ellos otra opción de tratamiento. Pese a su situación apartada, se concibió un modelo innovador con el propósito de ofrecer tratamiento a estos pacientes. Los aspectos más notorios del modelo consistieron en la transferencia de la responsabilidad del tratamiento a médicos que no eran expertos en TB que contaban con el apoyo distante de un especialista, el uso de protocolos simplificados de seguimiento y un interés esencial en resolver el problema del estigma a fin de reforzar el cumplimiento terapéutico. Tras un lapso mediano de 24 meses se completó exitosamente el tratamiento. Este programa piloto demuestra que es posible tratar eficazmente la TB-DR en pequeña escala en los entornos remotos.