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Challenge to treat pre-extensively drug-resistant tuberculosis in a low-income country: A report of 12 cases

Innocent Murhula Kashongwe [a,b,c,*], Fina Mawete [c], Nicole Anshambi [d], Nadine Maingowa [d], Murielle Aloni [e], Luc Lukaso L'osenga [b], Michel Kaswa [c,e], Zacharie Munogolo Kashongwe [a]

[a] Internal Medicine, Pulmonology Unit, Kinshasa University Hospital, Kinshasa, Democratic Republic of the Congo
[b] Drug-Resistant Tuberculosis Unit 'Centre d'excellence Damien', Damian Foundation, Kinshasa, Democratic Republic of the Congo
[c] National Tuberculosis Program of the Democratic Republic of the Congo, Democratic Republic of the Congo
[d] Provincial Coordination for Tuberculosis Control, Kinshasa, Democratic Republic of the Congo
[e] National Laboratory of Mycobacteria, Kinshasa, Democratic Republic of the Congo

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ABSTRACT

Setting: Democratic Republic of the Congo is a high-burden TB country. Its capital, Kinshasa, reports annually about one-third of all MDR-TB cases in the country; thus, pre-XDRTB management is warranted.
Objectives: To describe the main challenges in treating pre- XDR TB in this low resources setting and possible solutions.
Method: This is a retrospective study of all pre-XDR TB patients diagnosed in Kinshasa in 2018. A personalized regimen was applied according to the clinical profile, drug availability, and the Drug susceptibility testing (DST). Treatment was administered by hospitalization during the intensive phase and in ambulatory care in the continuation phase except in emergencies. Monthly follow up included evaluating clinical and bacteriological features, renal and liver functions, QT interval on ECG, and audiometry for those under aminoglycosides.
Results: Among the 236 MDR-TB patients identified in 2018, 14 had pre-XDR. Two died before treatment initiation. Of the remaining 12. 75% were male, 50% were aged 25–44 years, 66.7% had previous anti-tuberculosis treatment, 75% had a body mass index < 18.5 kg/m^2, and 1 patient was HIV positive. On radiography, all the patients had cavities. The median time from the diagnosis to treatment initiation was 48.5 days (range: 14–105). A favorable outcome occurred in 10 cases (83.3%), one patient died, and anotherwas lost to follow up. Nine (75%) patients reported adverse reactions, which were mild or moderate in 6 cases and severe in 2 cases. The severe reactions were psychosis (1 case) and ototoxicity (1 case).
Conclusion:: Successful pre-XDRTB treatment using the new strategy is possible even in a low-income country. The main challenges are diagnosis access, drug availability and follow-up laboratory facilities. These can be included in a global policy review by the NTP to ensure the sustainability of the strategies implemented.

1. Introduction

The continuing spread of drug-resistant tuberculosis (TB) represents a considerable challenge to the End TB strategy [1–5]. Multidrug-resistant tuberculosis (MDR-TB, defined as TB resistant to at least Isoniazid [H] and Rifampicin [R]) is a major concern for TB control programs worldwide [2,6–12]. Extensively drug-resistant tuberculosis (XDR) refers to MDR-TB with additional resistance to second-line injectable drugs (e.g., amikacin, kanamycin, and capreomycin) and any fluoroquinolone (FQ); but in case of additional resitance only second line injectable drug (SLID) or FQ, it is called pre XDR [13–15]. Until now, patients with pre XDR or XDR tuberculosis had few treatment options and no standard treatment regimen. The published treatment success rates remains low around 56% [2,3,15,16]. Some studies using new drugs have achieved better results [17–22]. The second-line drugs are expensive with many adverse effects [2,3,23] and require well-trained medical staff, laboratory facilities and drug availability. These conditions are very difficult to achieve in low-income countries [2]. The Democratic Republic of Congo (DRC) is one of 30 countries worldwide that bears the load of the TB epidemic (sensitive and drug-resistant TB)

* Corresponding author at: Internal Medicine, Pulmonology Unit, Kinshasa University Hospital, Kinshasa, Democratic Republic of the Congo.
E-mail address: innocent.kashongwe@unikin.ac.cd (I. Murhula Kashongwe).

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Table 1
Definitions of treatment outcomes for drug-resistant patients [13].

Treatment outcome	Definitions
Cured	Treatment completed as recommended by the national policy without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment failed	Treatment terminated or need for permanent regimen change in at least two anti-TB drugs because of: • The lack of conversion by the end of the intensive phase; or • Bacteriological reversion in the continuation phase after conversion to negative; or • Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or • Adverse drug reactions
Died	A patient who dies for any reason during treatment
Lost to follow up (LTFU)	A patient whose treatment was interrupted for two consecutive months or more
Treatment success	The sum of Cured and Treatment Completed

[23]. The country is currently ranked 179th in the Human Development Index [24]. This study was aimed to describe the challenges in treating pre- XDR patients in a low-resource setting and possible solutions.

2. Methods

2.1. Patient selection

This retrospective study analyzed all patients identified with Rifampicin resistance (RR) using a genotypic method (Xpert® MTB/RIF testing, Cepheid, Sunnyvale, CA, USA) at different health centers of Kinshasa from January to December 2018. At the national referral laboratory, samples from the health centers were subjected to the line probe assay (LPA: Geno Type® MTB DR plus and MTB DR sl assay; Hain Life Science, Gmbh, Germany) to control Rifampicin (R), isoniazid (H), second-line injectable drugs (SLIDs) and fluoroquinolone (FQ) sensitivity and to perform Löwenstein–Jensen (LJ) culture. It was not possible to perform drug-sensitivity tests (DSTs) for all the anti-tuberculosis drugs. The included patients had to have a laboratory-confirmed diagnosis of pulmonary pre-XDRTB or XDR TB.

2.2. Drugs available in the NTP and regimen

The drugs available in the NTP regimen were as follows: kanamycin (Km), PAS, linezolid (Lzd), isoniazid (H), clofazimine (Cfz), pyrazinamide (Z), bedaquiline (Bdq), delamanid (Dlm), levofloxacin (Lfx), meropenem-clavulanate (Mpm-Clv), amikacin (Am), imipenem-clavulanate acid (Ipm-clv), and cycloserine (Cs). The regimen was discussed for each patient according tohistory of TB , DSTs and drugs availability. The NTP adopted a 20-month treatment with 2 phases: a 6-month intensive phase and a 14-month continuation phase. The dosages followed the WHO guidelines [13].

2.3. Patient management

During the intensive phase, the patients were hospitalized at the Kinshasa Damian Excellency Center, which specialized in MDR/TB management. For the continuation phase, ambulatory treatment occurred daily and was directly observed by a nurse or a community member except in emergencies where hospitalization was indicated. Specifically prepared cards facilitated the recording of patient characteristics, clinical and laboratory controls, follow up of drug intake, adverse events including biological abnormalities. Adverse events were recorded monthly and graded using the ANRS (Agence Nationale de Recherche sur le SIDA) score, which includes 4 grades ranked from 1 (mild) to 4 (very severe, life threatening) [25]. Bacteriological controls (sputum smear and culture) were planned monthly. After treatment completion, the patients were asked to return for a quarterly clinical and sputum control and in the case of problems. Other tests performed at the onset and during treatment according to planning included the following: hemoglobin, blood white cell count, glycemia, potassium, serum creatinine, liver enzymes (aspartate and alanine aminotransferases), human immunodeficiency virus (HIV) test, pregnancy test for child-bearing women, and ECG to follow QT interval corrected according the Fridericia formula [13]. Audiometry was performed for all patients at the treatment onset; for those under aminoglycosides, it was repeated after 4 months and whenever required; abnormality was reported as the weighted average hearing loss (WAHL) in decibels. Chest radiography was performed at the onset and end of treatment.

2.4. Definitions

For the outcomes, we used the definitions given in the WHO guidelines [13], as shown in Table 1.

The body mass index (BMI) is subdivided into 3 groups: <18.5 kg/m^2 = underweight, 18.5 to 24.9 kg/m^2 = normal, equal to or greater than 25 kg/m^2 = overweight.

The extent of lung lesions on chest radiography is divided into two groups: $< 50\%$ of the 2 fields (mild or moderate); $\geq 50\%$ (severe), with or without cavitation.

2.5. Data collection and analysis

Individual data were collected on a chart by health workers. At the end of treatment, all the charts were collected by research staff. The data were managed in Microsoft Excel 2010. The patient characteristics, laboratory results, follow up and treatment outcomes were recorded using medians and means ($\pm$standard deviation) for continuous variables; frequencies and proportions were used for categorical variables.

2.6. Ethical considerations

The study protocol was approved by the Kinshasa Public Health School Ethics Committee. The study was organized within the framework of the NTP, and treatment was provided free of charge. The patients had to sign an informed consent form. The data for analysis were collected anonymously.

3. Results

3.1. Patient enrollment

In 2018, 236 RR-TB cases were diagnosed in Kinshasa; 38 did not undergo LPA or culture tests. Among the others, 14 were MDR-TB with additional resistance to either SLID or fluoroquinolone. None presented additional resistance to the 2 drugs at the same time. In this group, 2 patients died before starting treatment. Thus, the report concerned 12 patients.

Table 2
Patients baseline characteristics.

Characteristics	n	%
Total	12	100
Sex		
Male	9	75
Female	3	25
Age, years		
< 25	2	16.4
25–44	6	50.0
≥ 50	4	33.3
BMI		
< 18,5	9	75
18,5–24,5	3	25
>25	0	0
HIV		
Positive	1	8.3
Negative	11	91.7
Previous TB History		
None	4	33.3
≥ 1	8	66.7
Delay to treatment (days)		
< 30	1	8.3
30–60	9	75
>60	2	16.7
Extent of lung lesions		
< 50%	5	41.7
≥ 50%	7	58.3
Cavities	12	100

3.2. Patient baseline characteristics

The patient baseline characteristics are shown in Table 2. Nine (75%) patients were male. The mean age was 35.83 years (±11.55); six (50%) were aged between 25 and 44 years. Eight (66.7%) had received previous anti-tuberculosis treatment; 9 (75%) were underweight with a body mass index (BMI) < 18.5 kg/m^2. The mean BMI was 17.71 kg/m^2 (±17.65). Only one patient was HIV positive. Seven (58.3%) had severe lung lesions on chest radiography, and all the patients presented with cavities.

3.3. Time from diagnosis to treatment initiation

Nine (75%) patients had to wait between 1 and 2 months, and 2 patients had to wait longer before starting treatment (66 and 105 days). The cause was due to drug unavailability. The median time from the diagnosis to treatment initiation was 48.5 days (range: 14–105).

3.4. Microbiological patterns

Among the 12 patients, 3 (23%) were resistant to SLID and 9 (75%) were resistant to fluoroquinolone, as shown in Table 3.

3.5. Evolution under treatment

3.5.1. Sputum smear and culture conversion

Sputum smear and culture were performed monthly, but some valid culture results lacked controls. One patient died before the 2nd-month control. The sputum smear was negative at 2 and 3 months in 8/11 (72.7%) and 11/11 (100%) cases, respectively. At the 6-month control, 11 samples remained negative; this trend persisted until the 13th-month control, where one patient was lost to follow up. The remaining patient achieved control until 20th months. For cultures, some controls produced non-valid results ("contaminated"). However, 8/11 (72.7%) and 9/11 (81.8%) patients showed negative results after 2 and 3 months, respectively. At the 6-month control, 11/11 (100%) patients were negative. Because one patientwas lost to follow up, only 10 achieved controls until 20 months, and none reverted. The sputum smear and culture control performed 6 months after treatment completion remained negative (Fig. 1).

3.6. Treatment outcomes:

Overall treatment success (Curated + Treatment completed) was attained in 10/12 (83.3%) patients with 8/12 (66.6%) cured and 2/12 (16.7%) completing treatment. Of the 2 patients with unfavorable treatment outcomes, one died during the second month of treatment; she was HIV positive. The second was lost to follow up after 12 months of treatment. During that period, his smear was negative.

3.7. Adverse events

3.7.1. Clinical manifestations

Nine (75%) patients reported adverse reactions that were mild in most cases: gastrointestinal disturbances, arthralgia, nausea, anorexia, pruritis and rush (grade 1 or 2). Three patients had aminoglycosides (AG) in their therapeutic regimen; among two of them AG have been replaced by delamanid following a hearing loss of more than 20 db. A patient developed psychosis that was related to cycloserine; the drug was withdrawn and replaced by PAS/pyrazinamide. The regimens used and outcomes are summarized in Table 3.

3.7.2. Others laboratory test: Biology, audiometry and fundus examination

Globally, the different tests were in the normal range except in one case of mild anemia (Hb: 9.8 g/dl) and two cases with audiometry abnormality (WAHL = 93 dB). All the patients had received linezolid in theirs therapeutics regimens; 3/12 (40%) had major adverse effects requiring treatment modification: linezolid was stopped following optic neuritis in the 17th month of treatment in one patient (1/12) and for the two others , the dose was reduced from 600 mg to 300 mg and pregabaline was added in the treatment following Grade 3 peripheral neuropathy in the 9th and 13th months of treatment. Thereafter, the three patients had a good therapeutic evolution.

4. Discussion

In this study, the number of pre-extensively drug-resistant TB cases seemed low: only 14 patients (5.9%) among 236 MDR-TB cases were identified and no XDR TB patients. It is estimated that 9.6% of MDR-TB cases worldwide have XDR-TB [3,26]. The first limit encountered was diagnosis access. Some patients were excluded because of a lack of DST. As in many developing countries, specialized laboratories are not sufficient [2]. In DR Congo, only one laboratory can perform LPA and cultures in solid medium. Thus, missed cases must be numerous.

Drug availability constitutes the second challenge [2,11,16,18]. The delay before treatment start was long, likely due to drug unavailability. For decades, drugs have been supplied by different partners; thus, there is less room to maneuver. This explains why the treatment regimen was discussed according to the drugs available.

The third challenge is the laboratory facilities for the diagnosis and controls during treatment [2,3,9,13]. Indeed, if the genotype methods can lead to a quick diagnosis, they are not largely distributed; a regular supply is needed. For the treatment follow up, cultures are required [14,15]. Additionally, specific tests are indicated to manage some adverse events, such as renal and liver functions, hematology, and ionograms [20,27,28]. These are not available everywhere.

The favorable outcomes recorded in this short report were better than those reported previously [3,6,29]. Recent studies conducted in South Africa [20] and Germany [18,29] have shown high rates of cured patients. The role of new drugs (delamanid, bedaquiline, and pretonamid) is emphasized [2,14–19,30]. In this study, 58,3% (7/12) of patients had received fully oral TB treatment with good results. Novel therapeutic TB drugs like delamanid and bedaquiline are promising for the management of pre-XDR and XDR TB patients. However, presently, these drugs remain expensive for low-resource settings and are hard to

Table 3
DST, regimen, outcomes, adverse events (degree).

Patient	DST				Regimen	Outcomes	Adverse events(degree)
	R	H	Am/Km	O			
1	R	R	S	R	6 Km, Bdq, Hhd, PAS, Lzd, Cfz, Z 14 Lzd, PAS, Cfz, Z	Died	Anorexia(1), epigastric pain(2)
2	R	R	S	R	6 Bdq, Mpm-clv, PAS, Lzd, Cfz, Z 14 PAS, Lzd, Cfz, Z	Cured	Pruritus(2)
3	R	R	S	R	4 Am, 6 Bdq, PAS, LZd, Cfz, Z 14 PAS, Lzd, Cfz	Cured	Nausea(1)
4	R	R	S	R	4 Am, 6 Bdq, PAS, Lzd, Cfz, Z 14 PAS, Lzd, Cfz	Cured	Hb: 9.8 g/dl(1) Asthenia(1) arthralgia(2)
5	R	R	S	R	6 Bdq, Mpm-Clv, PAS, Lzd, Cfz,Z 14 PAS, Lzd, Cfz, Z	Cured	Anorexia(1)epigastric pain(2)
6	R	R	R	S	6 Bdq, Imp-Clv, PAS, Lfx, Lzd, Cfz, Z 14 Lfx, Lzd, Cfz, Z	Cured	Abdominal disconfort(1)
7	R	S	S	R	4 Am, 6 Bdq, PAS, Lzd, Cfz, Z 14 PAS, Lzd, Cfz	Cured	Hearing loss(3)
8	R	R	S	R	6 Dlm, Bdq, Lzd, Cfz, Cs 14 Lzd, Cfz, Cs	Cured	Psychosis(3)
9	R	R	R	S	6 Lfx, Bdq, Lzd, Cfz, Cs 14 Lfx, Cfz, Cs	Treatment completed	
10	R	S	S	R	6 Dlm, Bdq, Lzd, Cfz, Cs 14 Lzd, Cfz, Cs	Cured	Arthralgia(2)
11	R	R	S	R	6 Dlm, Bdq, Lzd, Cfz, Cs 14 Lzd, Cfz, Cs	Treatment Completed	
12	R	R	R	S	6 Bdq, Lfx, Lzd, Cfz, Pas, Z 14 Lfx, Cfz, PAS, Z	LTFU	

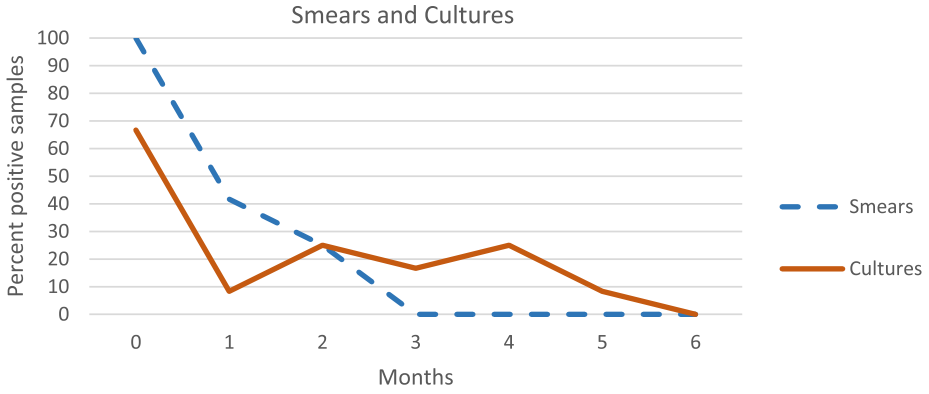

Fig. 1. Sputum smear and culture conversion.

manage. Their use in Kinshasa has been facilitated by building a specialized structure involved in drug-resistant TB management. Adverse drug reactions were reported by almost all the patients; however, they were mostly mild or moderate with gastrointestinal disturbance, arthralgia, anorexia, anemia. This finding was consistent with that in other recent reports [2,20,30]. No abnormal QTc interval had been reported concerning the drugs used [1,31]. More severe adverse events included hearing loss with aminoglycosides, psychosis with cycloserine, allergic reaction with meropenem and severe linezolid adverse events (peripheral neuropathy and optic neuritis). Hearing loss with aminoglycosides has been largely described [32,33]. Aminoglycosides must be replaced by novel therapeutic tuberculosis drugs. The latest World Health Organization (WHO) treatment guidelines recommend drug-resistant tuberculosis (DR-TB) must be treated with oral drugs only, including newer, more potent drugs with fewer side effects [34,35]. It would be better to avoid the drugs concerned when other options are available. This study showed the benefit and favorable result of the management of pre- XDR TB patients in a low-income country and the good contribution of full oral treatment. Further studies with large cohorts may better determine the benefit of those new treatments.

5. Limitations

The main limitations of this study are the reduced patient number and its retrospective design. However, the important merit of the study is that pre-XDRTB can be successfully managed in a low-resource setting.

6. Conclusion

Successful pre-XDR-TB treatment is possible even in a low-income country setting. We observed a therapeutic success of 83.3%. The main challenges were diagnosis access, drug availability and follow-up laboratory facilities. These can be included in a global policy review by the NTP to ensure the sustainability of the strategies implemented.

7. Ethics Statement

Ethical approval for the retrospective collection of clinical data was obtained by the National Tuberculosis Program of the DR Congo (PNLT/01/JTN/MKK/525/2019). Data for analysis were collected anonymously; all patient records were coded by a number designated based on the date of treatment initiation; the number one was the first patient to be treated with bedaquiline containing treatment.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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