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# Use of Bedaquiline as Replacement for Aminoglycosides in the Shorter Regimen for Multidrug-Resistant Tuberculosis Patients with Hearing Loss: A Report of 39 Cases in Kinshasa, Democratic Republic of the Congo

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## Abstract

**Background:** Ototoxicity remains one of the major adverse events during multidrug-resistant tuberculosis (MDR-TB) treatment. It is related to the use of aminoglycosides. Bedaquiline offers an opportunity to promote a shorter regimen without aminoglycosides.

**Methods:** This is a retrospective study. We reviewed all the MDR-TB patients with hearing losses for which a 9 month regimen has been applied in 2018 in Kinshasa, DR Congo. Kamamycin and Moxifloxacin had been replaced by Bedaquiline and levofloxacin. Treatment was given ambulatory under dot's unless the emergencies. Monthly follow-up included clinical and bacteriological features, renal and liver functions, $Q_T$ Interval.

**Results:** From 184 patients selected for 9 months shorter regimen according to WHO guidelines, 39 had hearing loss (21.2%) and were selected for the study. Mean-age was 35.7 years (Range 18-65), 21 male (54%), 8 (21%) HIV positive, 25 (64%) were under weighted; 26 patients (66.7%) had 50% or less, the 2 lungs fields affected on chest X-ray, and 20 patients (51.2%) with one or more cavities. Sputum smear conversion was respectively 82% and 97.2% at 2 and 4 months. Culture conversion was 86% and 97.2% for the same time. Cultures and Sputum smear remained negative until 9th month for 97.2% patients. Adverse events have been reported by 23 patients (58.9%), but they were severe and very severe only in 2 cases (5.1%). No QT interval over 500 millisecond (ms) noted. Treatment outcomes were: 32 patients cured (82.05%), 3 with treatment completed (7.7%), 3 (7.7%) Died, 1 (2.5%) failure. The follow-up of 6 months after treatment completion did not reveal relapse case.

**Conclusion:** The 9 months shorter regimen with bedaquiline showed a good safety and efficacy with a treatment success of 89.75%. This study shows also that the use of bedaquiline is possible even in low-income environment.

**Keywords:** Multidrug-Resistant Tuberculosis (MDR-TB) • Bedaquiline • Shorter regimen

## Introduction

The emergence of multidrug-resistant tuberculosis (MDR-TB) defined as resistance for mycobacterium Tuberculosis to at least rifampicin (RMP) and isoniazid (INH), constitute a big challenge for TB control and the goals of the WHO's End TB Strategy [1]. All the countries are concerned [2-7]. Until now aminoglycosides (AG) are the cornerstone of the treatment [8-13]. However, their adverse events are widely described and hearing loss is one of the major [14-20]. It is related to the aminoglycosides toxicity used from decades for retraitment of drug-susceptible TB and MDR-TB [8,9,12,21]. Risk factors include the dose and duration of AG, infection with human immunodeficiency virus, older age and persons exposed to a high level of noise [20]. The damage can be total and permanent. Usually, the MDR-TB patient has received one or more traitments containing AG like streptomycin [21]. In DR Congo, 75.5% of MDR-TB patients between 2014 and 2017 had TB treatment history [22] with the risk of prior AG use.

Recent studies and WHO guidelines recommend the use of new drugs, like bedaquiline, under some conditions [11-13,23-33]. This includes drug sensitivity tests to help regimen option [13]. There are interactions between resistance to bedaquiline and other drugs like clofazimin [34]. The high level of hearing loss in the observational study on 9 month short regimen in French speaking area [21] indicated this study in order to evaluate efficacy and safety of a 9 month regimen modified, where kanamycin (km) is replaced by bedaquiline.

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# Research Methodology

## Study population

This is a retrospective study, conducted in the National Tuberculosis Program (NTP) context. It concerns patients with rifampicin resistance (RR) diagnosed by genotypic method (Xpert MTB/RIF, Cepheid, USA) between 1st January to 31st December 2018 in Kinshasa. The specimen gathered in Health Centers were sent to National Referral Laboratory for Life Probe Assay (LPA-MDR, DR plus-sl) in order to test sensitivity to other drugs, mainly isoniazid, fluoro-quinolone and second line injectable drugs. So extensively and pre-extensively drug resistant TB (XDR/pre XDR) were excluded. The entire sputum specimens were also sent to Löwenstein-Jensen (LJ) culture.

## Patient eligibility criteria

Shorter regimen patients criteria have been described elsewhere [1,21]. They are: age ≤ 18 years, living in Kinshasa or involving it to stay there during the treatment, no prior use of second line TB drugs, no resistance to fluoro-quinolone and second line injectable drugs (SLID), a QT interval on ECG ≤ 500 ms, a negative pregnancy test for women, a signed consent form. QT interval was corrected by Fredericia formula (QTCF) [1]. Patient with a known any side effect against one of the regimen drugs was also excluded. The final determinant criteria to receive bed aquiline were hearing worsening with a loss over 20 decibel (dB) audiometry. Hearing loss was measured in dB by pure tone audiometry. A weighted average hearing loss (WAHL) was calculated using mean hearing loss in both ears across 500 to 4000 Hz frequencies, by the formula: WAHL= Hearing loss (better ear)* 0.7+hearing loss (worse ear)*0,3. [21]. So four grades of WAHL are defined:

1. **(Mild):** 21-40 dB,
2. **(Moderate):** 41-70 dB,
3. **(Severe):** 71-90 dB,
4. **(Very severe):** ≥ 90 dB [21].

## Treatment regimen

The regimen has 2 phases: the intensive for 4 months including bedaquiline (Bdq) (400 mg) daily for 2 weeks, followed by 200 mg three time a week for 22 weeks (9,33) and clofazimin (cfz), levofloxacin (Lfx), Ethambutol (EMB), isoniazid high dose (INHh), pyrazinamid (PZA), prothionamid (PTO) daily. The continuation phase for 5 months is composed by Lfx, Cfz, EMB, PZA given daily Dosages are those given in the WHO guidelines [1]. So the regimen is summarized as follow: **6Bdq4 (cfz, Lfx, EMB, INHh, PZA, PTO)+ 5 (Cfx, Lfx, EMB, PZA)**. All the patients not selected for the study received the standard treatment according to NTP guidelines and WHO guidelines [1].

## Patients follow-up

Treatment was daily and directly observed by a health worker throughout the entire duration. Nutritional support and money for transport were given to the patients as it is done for all drug resistant patients. Sputum smear and cultures were performed monthly until the treatment completion and at 6 months post-treatment. Other controls followed the planning (Table 1). Adverse events were reported monhly using ANRS scale (Agence Nationale de Recherche sur le Sida) [35].

**Table 1.** Patient follow-up chart.

| Variables | M0 | M1 | M2 | M3 | M4 | M5 | M6 | M7 | M8 | M9 | M12 | M15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Weight | X | X | x | x | x | x | x | x | x | x | x | X |
| Sputum smear | X | x | X | X | x | x | x | x | x | x | x | x |
| Xpert/MTB-RIF | X | | | | | | | | | | | |
| LPA | X | | | | | | | | | | | |
| Culture | X | x | X | x | x | x | x | x | x | x | | x |
| Chest Radiography | X | | | | | | | | | x | | |
| Audiogramm | X | | | | | | | | | | | |
| ECG | X | x | x | x | x | x | x | - | - | x | | |
| Serum Creatinin + Urea | X | - | X | | | | | | | | | |
| Kalaemia | X | - | X | | | | | | | | | |
| ALAT/ASAT | X | - | - | | x | | | | | | | |
| Pregnancy test | X | | | | | | | | | | | |
| HIV | x | | | | | | | | | | | |

## Definitions

Treatment outcomes was defined according to the 2013 WHO reporting framework definitions [1] except for failure and cure because of the short treatment duration [21]. Failure was defined by any positive culture after six months during treatment, except when preceded by one negative and followed by at least two negative and no other subsequent positive culture, i.e., isolated positive culture; cure was defined as treatment completed

without evidence of failure, and three or more consecutive negative cultures taken at least 30 days apart at any time during treatment, i.e., not necessarily after the intensive phase. Negative cultures obtained during post treatment follow-up were also counted to contribute to the definition of cure [21].

Body mass index (BMI) is subdivided in 3 groups: less than 18.5 = underweight, 18.5 to 24.9 = normal, equal or over 25 = overweight.

Extent of lung lesions on chest radiography is divided in two groups: ≤ 50% of the 2 fields (mild or moderate); over 50% (severe), with or without cavitation.

### Data collection and analysis

Individual data were gathered on a chart by the health workers. At the end of treatment, all the charts were collected by the research staff. Data were managed first in Microsoft Excel 2010, then analyzed using Stata SE version 13 (Stata Corp, College Station, TX, USA). Patients characteristics, follow-up and treatment outcome were recorded using the median and mean (+Standard Deviation) for continuous variables and the frequency and proportion for categorical variables.

## Results

In 2018, 236 cases of RR-TB were diagnosed in Kinshasa. From them, 184 were eligible to 9-11 months short regimen. Audiometry identified 39 cases with hearing loss that were selected to receive bedaquiline regimen.

### Baseline patients characteristics

Patient's baseline characteristics are summarized in Table 2. Mean age was 35.7 years (range 18-65). Male to female ratio is 1.2. All the patients have been tested for Human Immunodeficiency virus (HIV), 8 are positive (21%). Underweight is found in 25 cases (64%). On chest radiography, 13 patients (33,3%) had severe lesions (more than 50% of the 2 lungs fields) and 20 (51.2%) presented one or multiple cavities. Severe hearing loss (grade 3 and 4) has been observed in 14 cases (35.9%). History of previous TB treatment is reported by 28 patients (71.7%) (Table 2).

**Table 2.** Patients baseline characteristics.

| Variables | n | % |
|---|---|---|
| **Age** | | |
| Age: Mean (sd) | 35,7 (±13,3) | |
| 18- 24 | 7 | 18,0 |
| 25-44 | 24 | 62,0 |
| ≥ 45 | 8 | 21,0 |
| **Sex** | | |
| Male | 21 | 54,0 |
| Female | 18 | 46,0 |
| HIV status | | |
| Negative | 31 | 79,0 |
| Positive | 8 | 21,0 |
| **Extent of lung lesions** | | |
| ≤50% | 26 | 66,6 |
| >50% | 13 | 33,3 |
| cavities | 20 | 51,3 |
| BMI | | |
| < 18,5 | 25 | 64,0 |
| 18,5 - 24,9 | 14 | 36,0 |
| ≥ 25 | 0 | 0 |
| **WAHL** | | |
| 1 (21 - 40 dB) | 7 | 17,9 |
| 2 (41 – 70 dB) | 18 | 46,1 |
| 3 (71 – 90 dB) | 9 | 23,0 |
| 4 (> 90 dB) | 5 | 12,8 |
| **History of TB** | | |
| none | 8 | 20,5 |
| 1 | 19 | 47,7 |
| ≥ 2 | 12 | 30,8 |
| **QTcF initial** | | |
| < 400 ms | 24 | 61,5 |
| 400 – 450 ms | 13 | 33,3 |
| > 450 ms | 2 | 5,1 |

### Time from diagnosis to treatment

The mean time from diagnosis to treatment is 17,5 days (range 3 to 41). It was less than 7 days for 6 patients (15%), between 7 and 21 days for 22 patients (56.2%) and over 21 days for 11 patients (28.0%).

### Bacteriological follow-up

Sputum smear and culture on solid medium (LJ) were performed monthly. One patient died during the first month. Sputum conversion at 2 and 3 months wars respectively 32/28 (82.0%) and 36/38 (94.7%). At 4th month 2 other patients died; 35/36 results are negative (97.2%). One patient remained positive. For cultures, completion was less good, some of specimen returned contaminated. The results after 2 and 4 months showed respectively 33/38 (86.8%) and 35/36 negative culture (97.2%). Other results at 4 months were: 6 (16.6%) contaminated, 1 (2.8%) positive. Thirty-five patients remained negative on sputum smear and culture from the 4th months to 9th month and at 6 months post-treatment.

### Adverse events

Adverse events (AE) are summarized in Table 3. Twenty-three patients (58.9%) experienced one or more adverse events (or biological disorders) in whom 2 major AE cases (5.1%) of anemia (hemoglobin 6.2 and 6.5 g/dl). The others presented mild or moderate AE: gastrointestinal disorders (nausea, vomiting, gastric pain): 17 cases (43.6%), arthalgia: 6 cases (15.4%),

vertigo: 3 cases (7.7%). muscular pain: 3 cases (7.7%), peripheral neuropathy, respectively 1 cases. Electrocardiogram was performed at the beginning of treatment, after 14 days and then monthly. No patient developed a QTcF over 500 ms. At the initiation of treatment, the median QTcF was 393 ms (IQR369-422). After 24 weeks (6 months) on bedaquiline treatment, median QTcF was 424 ms (IQR 407,5-456) (Figure 1). Other biological controls (renal function, liver function, potassium) remained normal (Table 3).

**Table 3.** Adverse events.

| **Adverse events** | **n** | **%** |
|---|---|---|
| Patients number | 23 | 58,9 |
| **Grade 1-2 patients** | 21 | 53,8 |
| Gastro-intestinal distress (nausea,vomiting,gastric pain) | 17 | 43,6 |
| Arthralgia | 6 | 15,4 |
| Vertigo/ dizzness | 3 | 7,7 |
| Muscular pain | 3 | 7,7 |
| Tiredness | 3 | 7,7 |
| Pruritus | 1 | 2,5 |
| Peripheral Neuropathy | 1 | 2,5 |
| Cas avec EI grade 3-4 | | |
| Anemia (6,2 g/dl and 6,5 g/dl) | 2 | 5,1 |

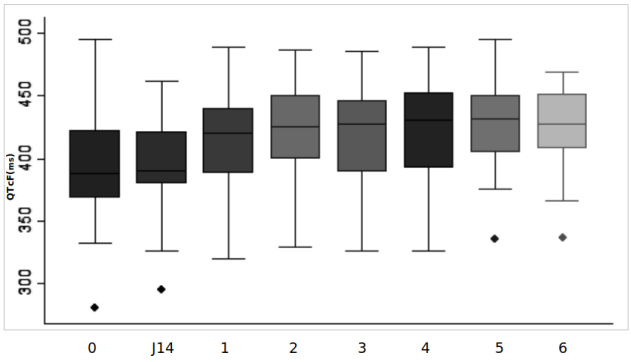


**Figure 1.** Median QTcF (in ms) and interquartile range (IQR) from the beginning, at 14th day, and monthly during BDQ treatment.

### Treatment outcome

Thirty-two patients (82.05%) were cured, 3 patients (7.7%) achieved treatment, 3 patients (7.7%) died and 1 case of failure (2.5%). Therapeutic success is 89.75%. A total of 3 deaths were reported at the first quarter (the beginning of treatment), 2 were HIV negative.

## Discussion

MDR-TB treatment requires the use of second line injectable drugs [8,10,12,15]. Their side effects are well documented [16]. In the past, without any other alternative, their use could be understood. [14]. With new drugs like bedaquiline and delamanid, and reposition of clofazimin and linezolid, there are new opportunities. In our series, 39 of 184 eligible to short regimen in Kinshasa, presented yet a hearing loss which could be worsened if an AG was given. Recent studies with short or long regimen including AG reported a high level of otoxicity [21,36-39].

Bedaquiline based regimen offer a new option. In South Africa, 2 studies reported good safety and efficacy, and a high therapeutic success [21,40]. Other studies experienced good result for MDR-TB and XDR-TB [17,23,25,29-33]. Delamanid is also recommended [41]. In our study, we noted a therapeutic success of 89.75% which is superior to those reached by the African French speaker countries study [21] and the SREAM [37].The therapeutic success can be improved by the reduction of delay between diagnosis and treatment [42-48]. Three patients died during the first quarter of treatment, this can be due to the delay before beginning the treatment. Health centers workers meetm any difficulties to access on laboratory tests and useful drugs. In this study, we have chosen to test a modified short regimen. Anterior short regimen studies highlighted their benefits in MDR-TB treatment [21,36,37,39]. They showed that it was possible, with respect of some conditions, to treat MDR-TB patients by shorter regimen than the WHO standard one implemented from 2006 [13]. We didnot associated moxiflixacine to reduce potentiality of cardiac effects [9,27].

Sputum smear and cultures conversion were very good at 2 and 4 months of treatment. This was also reported by Ying et al. [29] and Ndjeka et al. [31]. Regimen with bedaquiline improves rapid conversion of cultures and sputum smear, a feature of good prognosis [49].

Adverse events reported were mild or moderate. Major effects represented only 5.1%. As reported for other anti-tuberculosis drugs, nausea, vomiting, vertigo, headache, arthralgia, purities are common [1]. QTcF interval increment is one of the major adverse events expected [25]. In this study, the QTcF interval did not change significaly from the baseline and no patient presented increment over the limit of 500ms. Other studies reported increments that could be attributed to bedaquiline alone or to the association of other drugs like fluoro-quinolone, clofazimin, ethambutol, isoniazid [27,31,40]. Severe anemia in this study has been corrected without regimen modification. The main advantage we observed remains the good safety and efficacy [50].

## Limitations of the Study

Main limits of this study are the reduced number of cases, the retrospective and observational type. The strong point of this work is that it highlighted the first full oral experiences with bedaquiline in the shorter regimen for multidrug-resistant tuberculosis patients with hearing loss; a great hope for preventing hearing damage due to aminoglycoside. It has however the benefit of showing new options offered by bedaquiline and other new drugs. A randomized study is now undergoing.

## Conclusion

The shorter regimen with bedaquiline for the MDR-TB treatment offers an alternative to actual regimen using SLID. Therapeutic success is high and encounters the WHO recommendations to reach 75-90% of therapeutic success for drug resistant Tuberculosis. This study indicates that bedaquiline and other new drugs use is possible in a low income environment.

## Conflict of Interest

The authors declare that they do not have any financial interests pertaining to the information contained in this paper.

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