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# Sensorineural Hearing Loss in Multidrug-Resistant Tuberculosis Patients in Kinshasa (Democratic Republic of Congo): Prospective Cohort Study of Therapeutic Regimen with Aminoglycoside versus Bedaquiline

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## Abstract

**Context:** Multidrug-resistant tuberculosis (MDR-TB) remains a major public health problem in developing countries such as the Democratic Republic of Congo (DRC), which continues to face the emergence of MDR-TB cases. Because of the ototoxic effects of AGs, the World Health Organization (WHO) has recommended the introduction of the bedaquiline regimen. However, very few data are available regarding the susceptibility of bedaquiline to induce hearing loss, hence the present study set out to compare the AG-based regimen and the bedaquiline-based regimen in the occurrence of hearing loss

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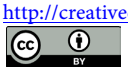



in MDR-TB patients. **Methods:** This is a prospective multicenter cohort study that included 335 MDR-TB patients, performed in Kinshasa (DRC) during the period from January 2020 to January 2021. Sociodemographic, clinical, biological and audiometric data were analyzed using Stata 17. Repeated-measures analysis of variance was used to compare changes in the degree of hearing loss over time between the two groups of patients on AG and bedaquiline regimens. The double-difference method was estimated using regression with fixed-effects. A p value < 0.05 was considered the threshold for statistical significance. **Results:** The degree of hearing loss was similar between the two groups at the first month [AGs (28 dB) vs BDQ (30 dB); p = 0.298]. At six months, the mean degree of hearing loss was significantly greater in the aminoglycoside regimen group [AGs (60.5 dB) vs BDQ (44 dB); p < 0.001]. The double difference was significant, with a greater increase in hearing loss in the AGs group (diff-in-diff 18.3; p < 0.001). After adjustment for age and serum albumin, the group receiving the AG-based regimen had a 2-point greater worsening than those with bedaquiline at the sixth month (diff-in-diff 19.8; p < 0.001). **Conclusion:** Hearing loss is frequent with both treatment regimens, but more marked with the Aminoglycoside-based regimen. Thus, bedaquiline should also benefit for audiometric monitoring in future MDR-TB patients.

## Keywords

Multidrug-Resistant Tuberculosis, Aminoglycosides, Bedaquiline, Hearing Loss

## 1. Introduction

Multidrug-resistant tuberculosis (MDR-TB) remains a major public health challenge in developing countries such as the Democratic Republic of Congo (DRC) [1] [2]. Several previous reports have demonstrated the ototoxic effects of the aminoglycoside (AGs) therapeutic regimen in the management of MDR-TB [3] [4]. In this regard, the World Health Organization (WHO) recommended the introduction of new molecules believed not to be ototoxic, notably the bedaquiline regimen [5]. Furthermore, with a view to ending tuberculosis (TB) by 2030, the WHO has adopted the "all oral" strategy since 2021, in order to reduce patient non-compliance with treatment, which is one of the causes of therapeutic failure [5].

The DRC is one of the thirty countries with the highest burden of TB in the world, and one of the ten most affected countries in Africa. Indeed, it is facing an emergence of MDR-TB cases. As a result, it has adopted the new WHO recommendations by introducing the bedaquiline regimen, which is proving more effective than the AG-based regimen with its proven ototoxic effects [6] [7] [8]. However, very few studies have assessed the susceptibility of bedaquiline to induce ototoxic Sensorineural hearing loss since its introduction in the treatment

of MDR-TB [6] [9]. The aim of the present study was therefore to compare the ototoxicity of the injectable-based therapeutic regimen (AGs) with that of the non-injectable therapeutic regimen (bedaquiline) in the management of MDR-TB, in order to determine their impact on hearing.

## 2. Methods

### 2.1. Type, Study Setting and Period of Study

This is a prospective and analytical cohort study. The University Clinics of Kinshasa and the 42 centers of screening and treatment of MDR-TB in Kinshasa (DRC) were selected as the research site. This study was carried out from January 2019 to January 2021.

### 2.2. Sampling

This is consecutive and random sampling.

### 2.3. Study Population

The study population consisted of MDR-TB patients living in the city of Kinshasa.

### 2.4. Recruitment

- Inclusion criteria: Any MDR-TB patient (diagnosed by molecular methods as Xpert MTB/RIF® or Genotype MTBR-plus®) aged at least 14 years who presented hypoacusis, without associated neurological signs, with a normal otoscopy examination, and signed the Informed Consent.
- Exclusion criteria:
- Refusal of a sample when the participant was already included;
- Incomplete collection of variables of interest;
- A current pregnancy.
- Flow Chart of MDR-TB patients (**Figure 1**).

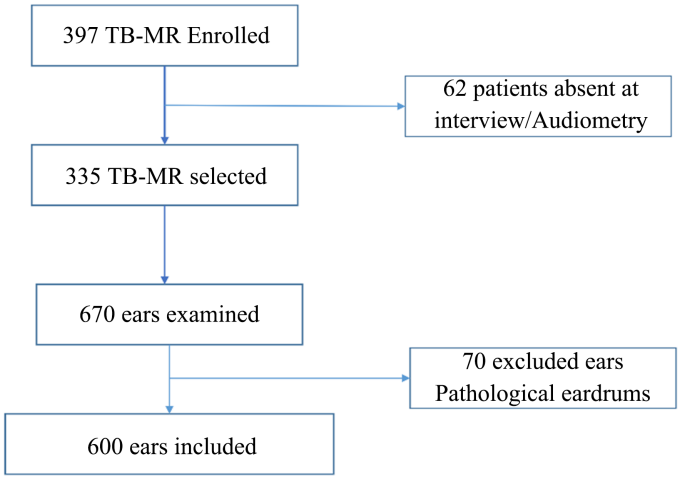


**Figure 1.** Flow chart of MDR-TB patients.

The present study enrolled a total of 397 MDR-TB patients. Sixty-two (62) were excluded because they were absent during the interview and/or the audiometry testing. Thus, there were 335 subjects for 670 ears examined, of which 600 met the inclusion criteria for the final analyses. Seventy ears (70) were excluded because of a pathological eardrum.

### 2.5. Data Collection

Three techniques were used to collect the data in this study: documentary review of patient files and registers, clinical examination of patients (interview and physical examination) and laboratory analysis. The documentary review consisted of collecting socio-demographic (age, gender, education), clinical [signs associated with hypoacusis (tinnitus, fullness of ear and dizziness), otological history, use of other ototoxic drugs], biological (serum albumin level) and therapeutic data [injectable Aminoglycosides (kanamycin or Amikacin) + clofazimine, moxifloxacin, ethambutol, isoniazid and pyrazinamide)] or [bedaquiline + (linezolid, clofazimine, isoniazid, prothionamide, pyrazinamide)] under directly observed treatment. The serum albumin was measured in all patients using an enzymatic method, with a COBAS C 111.

### 2.6. The ENT Examination

- Otoscopy using a Bistos BT-410 brand frontal light and a RIESTER brand otoscope, to visualize the external auditory canal and the external face of the eardrum.
- Anterior rhinoscopy with a nasal speculum and using a brand the Bistos BT-410 frontal light to examine the nasal cavities and describe the types of secretions if present.
- Examination of the oropharynx using the Bistos BT-410 brand frontal light with a tongue depressor to visualize the visible structures of the oropharyngeal cavity including the anterior and posterior pillars, the palatine tonsils and the pharyngeal wall posterior.

### 2.7. Audiometric Data

The Liminal Tone Audiometry determined the degree of hearing loss. It was performed using a shoebox brand audiometer. It is an Ipad in which is incorporated audiometry software that does not require a soundproof cabin. The examiner sends sounds of different frequencies (from 250 Hz to 8000 Hz) and different intensities (from −5 dB to 90 dB). At the end of the examination, an automatic tracing appears on the electronic tablet as well as the average values indicating the degree of hearing. All the subjects had undergone audiometric testing. The follow up considered audiometric data performed at 1$^{st}$ (M1), 3$^{rd}$ (M3) and 6$^{th}$ months and more (≥M6). Deafness was defined as hearing loss ≥ 21 dB [1]. The degree of hearing loss was classified according to the Pujol and Debreuil scale [10]: as mild (21 to 40 dB), moderate (41 to 60 dB), severe (61 dB to 80 dB) and deep (81 dB and more).

### 2.8. Statistical Analysis

The data were encoded using Microsoft Excel version 2013, having thus constituted the database after verification of its consistency, and were exported and analyzed using Stata 17. Descriptive statistics presented data in the form of tables and figures, with percentages for qualitative variables. Quantitative variables were expressed as mean ± standard deviation when the distribution was normal. Pearson's Chi-square or Fisher's exact test, as appropriate, was applied to compare proportions. Repeated-measures analysis of variance was used to compare changes in the degree of hearing loss over time between the two groups of patients on the A therapeutic regimen and the bedaquiline therapeutic regimen. The double-difference method was estimated using fixed-effects regression. A p value < 0.05 was considered the threshold for statistical significance.

### 2.9. Ethical Considerations

This study was approved by the Ethics Committee of the Kinshasa School of Public Health, with reference number ESP/CE/14/2020. Ethical principles relating to respect for the individual, beneficence and justice were taken into account. Before administering the questionnary, an informed consent form was presented and read to each participant. The investigator was required to obtain written approval from participants by signing this form at the start of inclusion in the study. The data collected were kept and analyzed anonymously and confidentially. All electronic or hard-copy archives were kept in a room to which only the principal investigator and members of the research team had access.

## 3. Results

### 3.1. General Characteristics of the Study Population

In total, 335 patients were included in the present study, ranging in age from 14 to 76 years. Their mean age was 34.42 ± 13.92 years. Almost half of these patients were between 20 and 34 years of age (45.7%). More than six out of ten patients (63%) were male, and the same proportion were single (62.9%). Less than half had completed secondary school (41.8%) (Table 1).

### 3.2. Clinical Data

Among the patients in the cohort, almost a quarter (24%) had at least one ENT symptom. More than one in four patients (27%) complained of hearing loss (CI 95%: 22.6 - 32.3), 30.2% of patients complained of tinnitus (CI 95%: 25.4 - 35.4) and 11.3% of patients had dizziness (CI 95%: 8.3 - 15.3) (Figure 2).

Table 2 shows the complaints of MDR-TB patients according to the AG and bedaquiline regimens. A higher proportion of tinnitus, hypoacusis and dizziness were noted with AGs compared with bedaquiline, but the difference was not significant.

The examination of the oropharynx revealed lesions in more than half the cases, the main one being atrophy of the posterior pharyngeal wall.

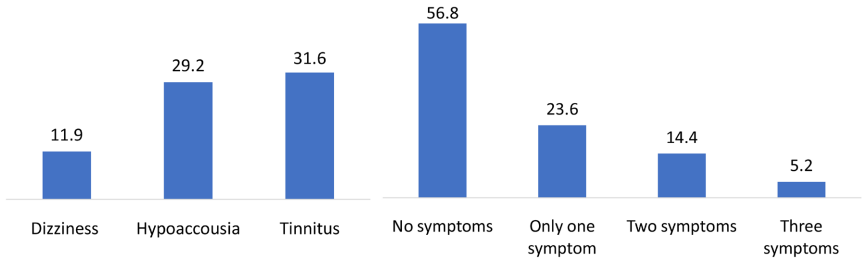


**Figure 2.** ENT symptoms.

**Table 1.** Socio-demographic characteristics.

| | n | % |
|---|---|---|
| Age (mean ± SD) | 34.42 ± 13.92 | |
| **Age** | | |
| <20 years | 35 | 10.4 |
| 20 - 34 years | 153 | 45.7 |
| 35 - 49 years | 98 | 29.3 |
| 50+ years | 49 | 14.6 |
| **Gender** | | |
| Male | 211 | 63 |
| Female | 124 | 37 |
| **Marital status** | | |
| Single | 211 | 62.9 |
| Married | 94 | 28.1 |
| Widowed/divorced | 30 | 9 |
| **Education** | | |
| None/Primary | 17 | 5.1 |
| Unfinished high school | 178 | 53.1 |
| State diploma/University | 140 | 41.8 |

**Table 2.** Complaints by therapeutic regimen.

| Complaints | All n = 335 | AGs n = 241 | BDQ n = 57 | p | OD [95% CI] |
|---|---|---|---|---|---|
| Tinnitus | 102 (30.2) | 79 (32.8) | 15 (26.3) | 0.428 | 1.37 (0.69 - 2.81) |
| Hypoacusis | 91 (27) | 72 (29.9) | 12 (21.1) | 0.195 | 1.6 (0.77 - 3.51) |
| Dizziness | 38 (11.3) | 31 (12.9) | 4 (7) | 0.260 | 1.83 (0.67 - 4.98) |

Data are expressed in absolute value (n) and proportion (%) AGs = aminoglycosides BDQ = bedaquiline OD = odd ratio CI = confidence interval.

Considering the therapeutic regimen, 241 patients (72%) had received a AG-only therapeutic regimen, 57 (17%) were on a bedaquiline-based therapeutic regimen and 37 (11%) had started on a AG-based therapeutic regimen followed by a bedaquiline-based regimen (Figure 3).

### 3.3. Audiometric Data

When comparing the AGs and bedaquiline regimens, Figure 4 shows an increase in the degree of hearing loss among MDR-TB patients in both groups over time ($p < 0.001$), and those on the AGs therapeutic regimen experienced a greater worsening of hearing loss than those on the bedaquiline regimen ($p < 0.001$). Table 3 shows the similar degree of hearing loss between the two groups at the first month's examination. At six months, the mean degree of hearing loss was significantly higher in the group receiving the AG therapeutic regimen. The double difference was significant, with a higher increase in hearing loss in the AG group. After adjustment for age and serum albumin, the group receiving the AG had a 2-point greater worsening than those receiving the bedaquiline at the sixth month (Table 3).

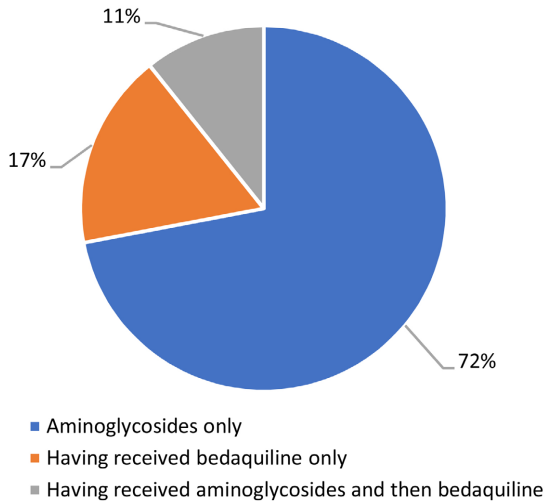


Figure 3. Distribution of patients by therapeutic regimen.

Table 3. Difference in differences of degree of hearing loss by treatment group.

| Degree of hearing loss | First month | | | p | Six month | | | p | Diff-in-Diff | p |
|---|---|---|---|---|---|---|---|---|---|---|
| | AG | BQ | Diff (AG-BQ) | | AG | BQ | Diff (AG-BQ) | | | |
| | Mean | | difference of mean | | Mean | | difference of mean | | | |
| without covariate | 28.3 | 30.1 | −1.787 | 0.298 | 60.5 | 44.0 | 16.5 | <0.001 | 18.3 | <0.001 |
| Adjusted for albumin serum only | 39.4 | 41.2 | −1.781 | 0.412 | 71.3 | 52.9 | 18.3 | <0.001 | 20.1 | <0.001 |
| Adjusted for age only | 16.1 | 18.3 | −2.223 | 0.180 | 48.3 | 32.5 | 15.8 | <0.001 | 18.0 | <0.001 |
| Adjusted for age and albumin serum | 27.3 | 29.3 | −2.02 | 0.335 | 59.1 | 41.3 | 17.8 | <0.001 | 19.8 | <0.001 |

AG: Aminoglycoside, BQ: Bedaquiline.

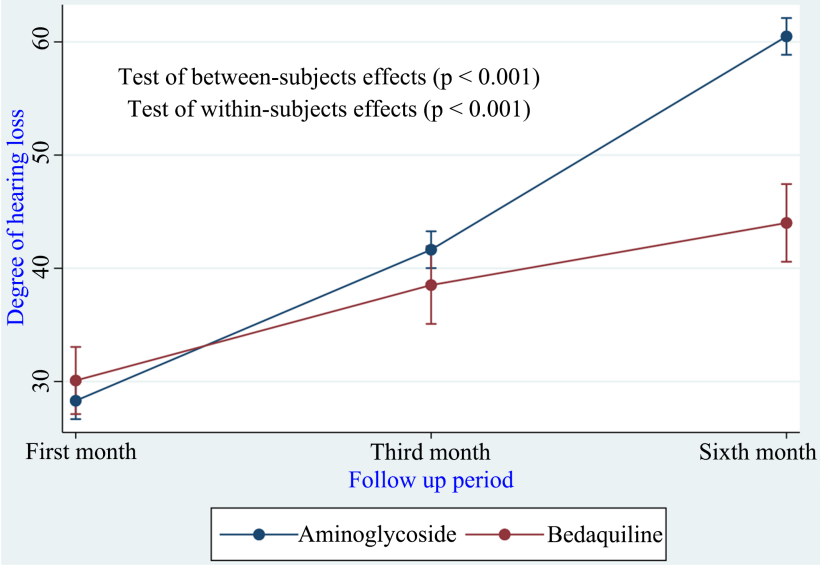


**Figure 4.** Hearing loss by treatment regimen.

## 4. Discussion

The aim of the present study was to assess the ototoxicity of the AG compared with the bedaquiline-based regimen in the management of MDR-TB patients.

### 4.1. General Characteristics of the Study Population

The present study described a relatively young age of MDR-TB patients (34.4 years) with a male predominance. This observation has also been reported in several studies in the DRC and Africa [6] [9] [11] [12]. Tinnitus was the main complaint associated with hypoacusis and dizziness, with no significant difference between the two treatment regimens. Indeed, it has been demonstrated that any process causing hearing loss is capable of triggering tinnitus [13]. Tinnitus is a warning sign of hearing loss, because if one ear is deafer than the other, tinnitus will be triggered in the worse ear [13]. Thus, since the complaints are similar in both groups, audiometric monitoring would be recommended in any patient complaining of tinnitus, even in the absence of hypoacusis.

### 4.2. Audiometric Data

In the present study, it was found that the hearing deficit worsened over time in both groups (with the AGs and bedaquiline regimens), with a significantly greater worsening of hearing loss in the group receiving the AGs-based therapeutic regimen. It should be remembered that AGs and bedaquiline are strongly bound to albumin, so hypoalbuminemia in our patients would have increased the free fraction of the drugs, exposing them more to adverse effects. Indeed, the ototoxicity of AGs is well established [3] [4], and kanamycin and amikacin are thought to be the cause of irreversible cochlear lesions, which increase with age due to the precarious vascularization and low recovery capacity of inner ear tissues in the elderly. [14] [15] [16]. In addition, AGs form a highly reactive intra-

cellular complex with iron, generating reactives oxygen species (ROS). They also inhibit anti-oxidant enzymes, notably catalase, and activate oxidative enzymes such as NO synthase and NADPH oxidase, resulting in the accumulation of ROS that induce the activation of stress-sensitive protein kinases (Mitogen-activated protein kinases and C_Jun-N terminal kinases). Activation of these enzymes results in elevation of intracellular calcium and release of cytochrome C from the mitochondria, leading to cell apoptosis [17]. Our results showed that bedaquiline also had ototoxic effects, albeit to a lesser extent than AGs. This observation is in line with the work of Kashongwe I. M. *et al.* in Kinshasa, who reported that with a too small number of patients [6].

The interpretation of our results must take into account some limitations. Acoustic photoemission was not available to detect early lesions in patients qualified as having normal hearing. The present study was observational and patients were not randomly assigned to the two groups. Factors that could influence the degree of hearing loss, but were not measured in the present study, could be distributed preferentially in one group to the detriment of another. The fact that the study did not measure the degree of hearing loss before the start of treatment is another limitation. We could have followed only patients with normal hearing and measured the proportion of AGs or bedaquiline. However, it does have the merit of demonstrating the low safety in terms of ototoxicity of the bedaquiline-based therapeutic regimen compared with the AG-based one.

## 5. Conclusion

Sensorineural hearing loss was frequent and worsened during treatment with both therapeutic regimens, although it was more marked with the AG-based regimen. Randomized controlled trials should confirm or refute the findings of this study. An audiometric follow-up plan is essential in the monitoring of MDR-TB patients, whatever the therapeutic regimen.

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## Conflicts of Interest

Authors declare no conflicts of interest.

## Authors' Contributions

Study design: Mireille A. Mpwate, Zacharie M. Kashongwe and Richard N. Ma-

tanda; data collection: Mireille A. Mpwate, Gabriel M. Lema, Eddy M. Mbambu, Christian N. Matanda, Dominique M. Mupepe, Michel K. Kaswa, Nicole M. Anshambi and Fabrice M. Matuta, Serge K. Mpwate; Analysis and interpretation of results: Pierre Z. Akilimali, Zacharie M. Kashongwe, Mireille A. Mpwate, Richard N. Matanda, Michel K. Kaswa, Nicole M. Anshambi, Luc L. Lukasu and Dominique M. Mupepe; Manuscript revision: Mireille A. Mpwate, Pierre Z. Akilimali, Zacharie M. Kashongwe, Dominique M. Mupepe and Richard N. Matanda. All authors have read and approved the final, revised version of the manuscript.

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