# High rifampicin-resistant TB cure rates and prevention of severe ototoxicity after replacing the injectable by linezolid in early stage of hearing loss

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**In patients with rifampicin-resistant tuberculosis and hearing loss a short treatment regimen with linezolid replacing the injectable was highly effective, adverse events were manageable, and switching early to linezolid prevented severe hearing loss.** https://bit.ly/2Oz0KMc

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ABSTRACT The short treatment regimen (STR) achieves a >80% cure in rifampicin-resistant tuberculosis (RR-TB) patients. However, ototoxicity induced by the injectable is a concern. This is the first study to evaluate the replacement of injectables by linezolid in patients with audiometry abnormalities at baseline or during the treatment.

We conducted a retrospective cohort study of all RR-TB patients started on the STR between 2016 and June, 2019, in Niger. Patients underwent audiometry every 2 months in 2016 and every month since 2017.

Of 195 patients, 16.9% (33 out of 195) received linezolid from the start (n=17), or switched from injectables to linezolid during treatment (n=16), based on audiometry abnormalities. In 2016, two patients developed severe ototoxicity despite switching to linezolid. Since 2017, no patient developed severe hearing loss or complete deafness. Severe haematological toxicity was observed in 18.1% (six out of 33) of patients on linezolid, none of which was life threatening. The use of linezolid was associated with severe but manageable adverse events (hazard ratio 8.9, 95% CI 2.5–31.5; p=0.001). A total of 90.9% (30 out of 33) of patients on a linezolid-containing STR were cured, and none experienced treatment failure. Three died, but not due to adverse events.

Baseline and monthly audiometry monitoring and using linezolid after detection of hearing abnormalities appears effective to prevent severe ototoxicity, while keeping high treatment success and manageable adverse events.

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## Introduction

Rifampicin is the most powerful first-line anti-tuberculosis (TB) drug. Therefore rifampicin-resistant tuberculosis (RR-TB) is a major public health concern. In 2018, worldwide, half a million people had RR-TB [1].

Treatment of RR-TB in patients using a short treatment regimen (STR), the so-called "Bangladesh regimen", is highly effective [2, 3]. However, severe ototoxicity induced by the second-line injectable drug used in the intensive phase is a major concern and varies between 3.1% and 22.6% [3–6]. Therefore, the World Health Organization (WHO) is now encouraging the use of all-oral regimens [7]. However, the efficacy of all-oral STRs is still uncertain.

Linezolid is an important oral TB drug [8]. It became a group A drug in the 2019 WHO classification of second-line drugs, the first-choice group of drugs to build a treatment regimen [9]. The use of linezolid is associated with severe adverse events, including bone marrow suppression and optic/peripheral neuritis [10, 11]. It is, as yet, unknown whether linezolid can safely and effectively replace the second-line injectable during the intensive phase of the STR.

In Niger, RR-TB patients are treated with the STR since 2008 [4]. To prevent severe hearing loss due to second-line injectables, systematic audiometry is implemented at baseline and during the intensive phase. Since 2016, in patients with baseline audiometry abnormalities, linezolid replaces kanamycin from the start for the entire duration of the intensive phase. In patients developing audiometry abnormalities during treatment, linezolid replaces the injectable until the end of the intensive phase.

Since the effect of this substitution has not yet been studied, we described treatment outcomes in patients treated with a linezolid-containing STR and evaluated the frequency of severe ototoxicity and any severe adverse event (SAE) since the implementation of systematic audiometry followed by the replacement of the injectable with linezolid in patients with hearing abnormalities at baseline or during the treatment.

## Methods

### *Study design and period*

This was a retrospective nationwide cohort study of all pulmonary RR-TB patients who started the STR between January, 2016, and June, 2019, in Niger. Follow-up data was collected until May, 2020.

### *Setting*

The programmatic management of RR-TB was launched in 2008 with the support of Damien Foundation, a Belgian NGO [4]. RR-TB care is provided by three health facilities: in Niamey, the capital city, in Maradi and Zinder, situated at 700 km and 1000 km from Niamey, respectively.

### *Treatment regimen and active TB drug-safety monitoring and management*

Patients diagnosed with RR-TB based on Xpert MTB/RIF were offered the 9–11 month STR, including clofazimine, ethambutol, pyrazinamide and high-dose moxifloxacin throughout, supplemented by kanamycin, prothionamide and high-dose isoniazid (around 10 $mg \cdot kg^{-1}$) during an intensive phase of 4 months, which is extended up to 6 months in case of delayed conversion on smear microscopy.

During treatment, sputum smear microscopy was performed every month and culture every 2 months. Adverse event monitoring has been described elsewhere [4, 12] and consisted of regular clinical and biological examinations. Patients were seen at six and 12 months after completing treatment for clinical examination, smear microscopy and culture.

The screening audiometry device covered speech frequencies and higher frequencies up to 8000 Hz [13]. Pure tone audiometry was systematically performed by trained nurses at baseline and during the intensive phase. In 2016, audiometry was performed bi-monthly during the intensive phase. Linezolid replaced kanamycin in a modified STR if audiometry abnormalities graded as at least moderate were detected at baseline or during treatment. From 2017 onwards, audiometry was done monthly and any abnormality justified the replacement of kanamycin with linezolid.

Linezolid was administered at a dose of 600 mg daily until the end of the intensive phase. Patients treated with linezolid had complete blood counts every month. In case of severe adverse events, linezolid was temporarily stopped and reintroduced at a lower dosage of 300 mg daily once the adverse events was corrected. In case of severe anaemia a blood transfusion was given.

### *Definitions*

The 2013 WHO definitions were used for TB treatment outcomes [14]. The National Agency for the Research on AIDS and hepatitis (ANRS) scales were used to grade adverse events, (grade 1: mild; grade 2:

moderate; grade 3: severe; grade 4: life-threatening or permanently disabling), including ototoxicity, haematological toxicity (sign of bone marrow suppression) [15], hepatotoxicity and other adverse events [16]. Audiometry abnormalities were graded as mild (hearing deficit 21–40 dB; grade 1), moderate (41–70 dB; grade 2), severe (71–90 dB; grade 3), and permanently disabling (>90 dB; grade 4).

Smear and culture conversion was defined as two consecutive negative smear and culture results, taken at least 30 days apart, respectively.

### *Data collection*

Data were retrieved from the national RR-TB individual patient database. Sources for the RR-TB database were RR-TB registers and treatment cards held at the health facility. Missing data or inconsistencies found during programme, quarterly reporting were promptly addressed by consulting the source documents.

### *Analysis*

Bivariable Cox proportional hazard regression was used to determine the correlation between the use of either kanamycin or linezolid and developing any severe adverse event (⩾grade 3). We used a time-dependent variable "bactericidal drug" (kanamycin, linezolid) as some patients switched from kanamycin to linezolid during treatment. The follow-up time was calculated as the time (in months) between starting either kanamycin or linezolid and having a severe adverse event or ending treatment with kanamycin and linezolid. Ototoxicity, a known adverse event of kanamycin, was always accounted as an adverse event of kanamycin, even if ototoxicity became severe only after switching to linezolid. Stata software (version 16.0; StataCorp LP, College Station, TX, USA) was used.

### *Ethics*

The study was approved by the Niger National Ethics Committee and the ITM Institutional Review Board, which waived the requirement to obtain informed consent.

## Results

During the study period, 200 patients were treated with the STR for pulmonary RR-TB in Niger. Five patients treated with a modified STR but with contraindications for linezolid were excluded. Of the 195 patients included in the analysis, 16.9% (33 out of 195) had audiometry abnormalities and were treated with a modified STR (figure 1), with linezolid replacing kanamycin, either from the start (n=17) or during treatment (n=16). Of the 16 patients who switched from kanamycin to linezolid during treatment, 25% (four out of 16) used linezolid for 1 month, 50% (eight out of 16) for 2 months, 18.8% (three out of 16) for 3 months and 6.2% (one out of 16) for 4 months.

No statistically significant differences were found for baseline characteristics between the different treatment groups (table 1). Overall, the vast majority of patients were male (84.1%), tested HIV negative

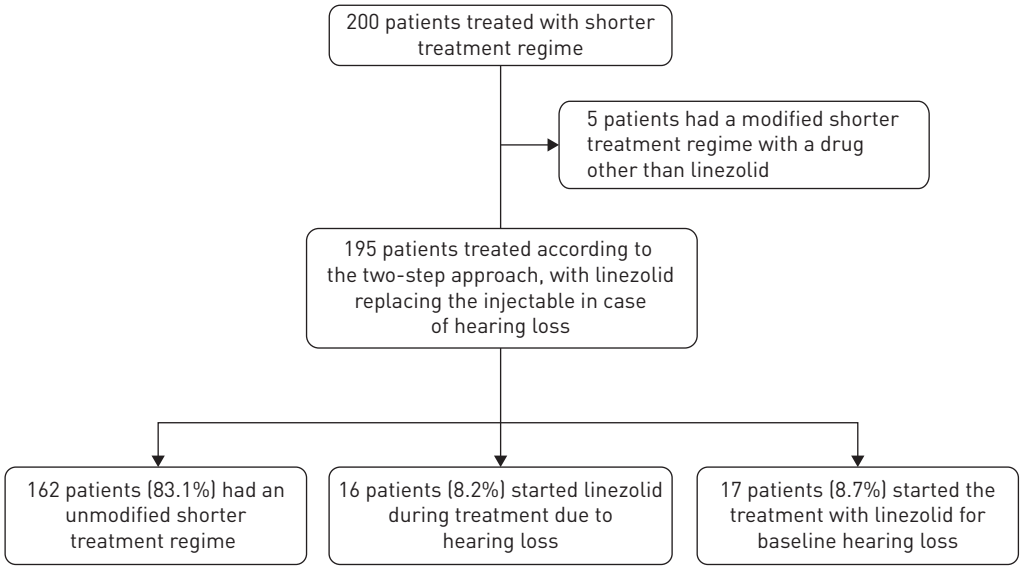


FIGURE 1 Patients diagnosed with rifampicin-resistant tuberculosis (TB) and treated with the shorter treatment regimen in Niger. STR: shorter treatment regime; LZD: linezolid; HL: hearing loss.

TABLE 1 Characteristics of the 195 study patients, by rifampicin-resistant tuberculosis (TB) treatment regimen

| | Total | Cohort | | | p-value[#] |
|---|---|---|---|---|---|
| | | STR unmodified | STR modified during treatment | STR modified from start | |
| **Total** | 195 | 162 | 16 (8) | 17 (8.5) | NA |
| **Sex** | | | | | 0.3 |
| Male | 164 (84.1) | 139 (85.8) | 12 (75) | 13 (76.5) | |
| Female | 31 (15.9) | 23 (14.2) | 4 (25) | 4 (23.5) | |
| **Age years** | 32 (26–40) | 32 (25–40) | 35.5 (31–41) | 40 (25–55) | 0.2 |
| **HIV status** | | | | | 0.4 |
| Negative | 187 (95.9) | 156 (96.3) | 15 (93.8) | 16 (94.1) | |
| Positive | 8 (4.1) | 6 (3.7) | 1 (6.3) | 1 (5.9) | |
| **Baseline sputum smear** | | | | | 0.4 |
| Scant | 9 (4.6) | 8 (4.9) | 1 (6.3) | 0 (0) | |
| 1+ | 32 (16.4) | 23 (14.2) | 4 (25) | 5 (29.4) | |
| 2+ | 49 (25.1) | 39 (24.1) | 4 (25) | 6 (35.3) | |
| 3+ | 104 (53.3) | 91 (56.2) | 7 (43.8) | 6 (35.3) | |
| Unknown | 1 (0.5) | 1 (0.6) | 0 (0) | 0 (0) | |
| **Type of TB** | | | | | 0.6 |
| New patient | 7 (3.6) | 5 (3.1) | 1 (6.3) | 1 (5.9) | |
| Treated after failure | 120 (61.5) | 100 (61.7) | 10 (62.5) | 10 (58.8) | |
| Relapse | 64 (32.8) | 54 (33.3) | 5 (31.3) | 5 (29.4) | |
| Treated after lost to follow-up | 4 (2.1) | 3 (1.9) | 0 (0) | 1 (5.9) | |
| **BMI group** | | | | | 0.97 |
| Normal | 65 (33.3) | 54 (33.3) | 6 (37.5) | 5 (29.4) | |
| Moderately underweight | 70 (35.9) | 59 (36.4) | 4 (25) | 7 (41.2) | |
| Severely underweight | 47 (24.1) | 38 (23.5) | 5 (31.3) | 4 (23.5) | |
| Unknown | 13 (6.7) | 11 (6.8) | 1 (6.3) | 1 (5.9) | |
| **Chest radiography** | | | | | 0.1 |
| Normal | 5 (2.6) | 5 (3.1) | 0 (0) | 0 (0) | |
| Unilateral lesions, no cavities | 13 (6.7) | 11 (6.8) | 2 (12.5) | 0 (0) | |
| Bilateral lesions, no cavities | 51 (26.2) | 42 (25.9) | 4 (25) | 5 (29.4) | |
| Unilateral lesions and cavities | 32 (16.4) | 22 (13.6) | 4 (25) | 6 (35.3) | |
| Bilateral lesions and cavities | 93 (47.7) | 82 (50.6) | 6 (37.5) | 5 (29.4) | |
| Unknown | 1 (0.5) | 0 (0) | 0 (0) | 1 (5.9) | |
| **Previous treatment with streptomycin** | | | | | 0.6 |
| No | 162 (83.1) | 134 (82.7) | 14 (87.5) | 14 (82.4) | |
| Yes | 33 (16.9) | 28 (17.3) | 2 (12.5) | 3 (17.6) | |
| **Initial fluoroquinolone resistance** | | | | | 0.5 |
| No | 190 (97.4) | 157 (96.9) | 16 (100) | 17 (100) | |
| Yes | 5 (2.6) | 5 (3.1) | 0 (0) | 0 (0) | |
| **Duration of intensive phase** | | | | | 0.5 |
| No prolongation | 173 (88.7) | 145 (89.5) | 13 (81.3) | 15 (88.2) | |
| Prolongation to 5 months | 17 (8.7) | 13 (8) | 2 (12.5) | 2 (11.8) | |
| Prolongation to 6 months | 5 (2.6) | 4 (2.5) | 1 (6.3) | 0 (0) | |

Data are presented n (%) or median (interquartile range), unless otherwise stated. NA: not applicable; STR: shorter treatment regime; BMI: body mass index. [#]: Fisher's exact test was used to compare distributions for different strata; Kruskal–Wallis test to compare medians between strata.

(95.9%), had a history of TB (96.4%) and had an abnormal chest radiograph (97.4%). About half of the patients had a very high bacillary load (53.3% with grade "3+" on sputum smear microscopy). Five (2.6%) patients treated throughout the intensive phase with kanamycin had initial resistance to fluoroquinolone (detected *a posteriori*). No resistance to second-line injectables was detected. Overall, 19 (9.7%) patients had baseline audiometric abnormalities. 33 (16.9%) patients were previously treated with streptomycin, of whom four (12.1%) had baseline audiometry abnormalities.

### *Treatment outcomes*

No statistically significant difference in treatment outcomes was found between treatment groups (table 2). Overall, 15 (7.7%) patients converted on smear microscopy later than 4 months of treatment. Of the 179 patients with culture follow-up, 86.1%, 96.7% and 99.4% had culture conversion after 2, 4 and 6 months

TABLE 2 Treatment outcomes among 195 study patients, by rifampicin-resistant tuberculosis treatment regimen

| | Total | STR unmodified | STR modified during treatment | STR modified from start | p-value[+] |
|---|---|---|---|---|---|
| **Total** | 195 | 162 | 16 | 17 | |
| **Outcomes at the end of treatment** | | | | | 0.99 |
| Cured | 161 (82.6) | 131 (80.9) | 15 (93.8) | 15 (88.2) | |
| Treatment failure | 7 (3.6) | 7 (4.3) | 0 (0) | 0 (0) | |
| Death | 24 (12.3) | 21 (13) | 1 (6.3) | 2 (11.8) | |
| Lost to follow-up | 3 (1.5) | 3 (1.9) | 0 (0) | 0 (0) | |
| **6-month post-treatment follow-up in cured patients[#]** | | | | | 0.9 |
| Total eligible for evaluation | 133 | 111 | 14 | 8 | |
| Relapse-free at 6 months | 124 (93.2) | 102 (91.9) | 14 (100) | 8 (100) | |
| Relapse at 6 months | 1 (0.8) | 1 (0.9) | 0 (0) | 0 (0) | |
| Died after cure | 2 (1.5) | 2 (1.8) | 0 (0) | 0 (0) | |
| Lost to follow-up after cure | 6 (4.5) | 6 (5.4) | 0 (0) | 0 (0) | |
| **12-month post-treatment follow-up in cured patients[¶]** | | | | | 0.85 |
| Total eligible for evaluation | 120 | 100 | 14 | 6 | |
| Relapse-free at 12 months | 102 (85.0) | 84 (84.0) | 12 (85.8) | 6 (100) | |
| Relapse at 12 months | 1 (0.8) | 1 (1.0) | 0 (0) | 0 (0) | |
| Died after cure | 4 (3.3) | 3 (3.0) | 1 (7.1) | 0 (0) | |
| Lost to follow-up after cure | 13 (10.8) | 12 (12.0) | 1 (7.1) | 0 (0) | |

Data are presented n (%), unless otherwise stated. STR: shorter treatment regime. [#]: 37 patients not yet evaluated due to a too short post-treatment follow-up time; [¶]: 60 patients not yet evaluated due to a too short post-treatment follow-up time; [+]: Chi-squared or Fisher's exact test to compare distributions for different strata.

of treatment, respectively. The intensive phase was prolonged for 11.3% of patients, with a similar frequency in the different treatment groups. All the 33 patients treated with the linezolid-containing STR (either switched to linezolid during treatment or on linezolid from the start) had culture conversion before the end of month 4, whereas four patients converted on smear microscopy during month 5, and another patient during month 6.

Overall, 82.6% (161 out of 195) of patients were cured and 12.3% (24 out of 195) died. Among the 21 who died during treatment with the unmodified STR, 11 had converted by the second month at latest on smear, and nine of them also on culture. The remaining 10 patients had died during the first 3 months of treatment before conversion on culture and smear. Among the 33 patients on a linezolid-containing STR, 90.9% (30 out of 33) were cured, 9.1% (three out of 33) died and no patient had treatment failure or was lost to follow-up.

Of three patients who died during treatment with linezolid, two were treated with linezolid from the start of treatment: one converted culture at 2 months, and died 4 months after starting treatment, the second patient smear converted at month 1 (no data on culture available), and died at month 2. The third patient had culture conversion at month 1, was switched to linezolid at month 2, and died at month 6. The causes of death were not related to adverse events: one died due to severe immunosuppression (HIV-positive patient not adherent to antiretroviral therapy), one due to respiratory failure (baseline chest radiograph showed bilateral cavities), and one because of haemoptysis.

Among the 161 cured patients, respectively 133 (82.6%) and 120 (74.5%) patients had 6- and 12-month post-treatment follow-up before the end of the study period. One patient treated with kanamycin throughout the intensive phase was identified with relapse. Drug susceptibility testing showed acquired resistance to fluoroquinolone (strain was found susceptible to fluoroquinolone before treatment start but resistant when relapse was diagnosed). This patient is currently being treated with a bedaquiline-containing regimen with good clinical and bacteriological treatment response. None of the 33 patients treated with linezolid-containing STR had a relapse, but some still had to be evaluated as their post-treatment follow-up was still not completed at the end of the study period. In the group that started

on linezolid, 53.3% (eight out of 15) and 40% (six out of 15) were evaluated at 6 and 12 months after cure, respectively, while 14 out of the 15 cured patients (93.3%) patients that switched to linezolid during treatment completed the 6 and 12 months follow-up.

### *Adverse events*

Adverse events were experienced by 90.3% (176 out of 195) of patients (table 3). Ten severe adverse events (grade 3) were recorded in nine (4.6% of 195) patients. Two (1.0% of 195) developed severe ototoxicity. No patient had a life-threatening or disabling adverse events (grade 4).

Of 19 patients with mild-to-moderate audiometry abnormalities at baseline, two (with mild audiometry abnormalities detected in 2016) started kanamycin and 17 started the linezolid containing regimen.

Of the 178 patients who started the kanamycin-containing STR, 52 (29.2%) developed audiometry abnormalities during treatment, among whom 36 were detected at the end of the intensive phase, and 16 before the end of the intensive phase and were switched to the linezolid containing STR. Of the 52 abnormalities, 35 (67.3%) were mild, 15 (28.8%) moderate and 2 (3.8%) severe. The two patients with severe hearing loss had started treatment in 2016 and their audiometric abnormality was detected less 1 month after having switched to linezolid.

TABLE 3 Adverse events during treatment among 195 patients, by rifampicin-resistant tuberculosis treatment regimen

| | | Cohort | | |
|---|---|---|---|---|
| | **Total** | **STR unmodified** | **STR modified during treatment** | **STR modified from start** |
| **Total n** | 195 | 162 | 16 | 17 |
| **AE during treatment (any)** | | | | |
| No AE during treatment | 19 (9.7) | 18 (11.1) | 0 (0) | 1 (5.9) |
| Grade 1 | 81 (41.5) | 75 (46.3) | 3 (18.8) | 3 (17.6) |
| Grade 2 | 86 (44.1) | 69 (42.6) | 7 (43.8) | 10 (58.8) |
| Grade 3 | 9 (4.6) | 0 (0) | 6 (37.5) | 3 (17.6) |
| Grade 4 | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| **Ototoxicity** | | | | |
| Present at baseline | 19 (9.7) | 2 (1.2) | 0 (0) | 17 (100) |
| Not during treatment | 124 (63.6) | 124 (76.5) | 0 (0) | 0 (0) |
| Grade 1 | 35 (17.9) | 31 (19.1) | 4 (25) | 0 (0) |
| Grade 2 | 15 (7.7) | 5 (3.1) | 10 (62.5) | 0 (0) |
| Grade 3 | 2 (1) | 0 (0) | 2 (12.5) | 0 (0) |
| **Nephrotoxicity** | | | | |
| Not during treatment | 182 (93.3) | 152 (93.8) | 13 (81.3) | 17 (100) |
| Grade 1 | 11 (5.6) | 8 (4.9) | 3 (18.8) | 0 (0) |
| Grade 2 | 2 (1) | 2 (1.2) | 0 (0) | 0 (0) |
| **Bone marrow suppression** | | | | |
| Not during treatment | 176 (90.3) | 161 (99.4) | 9 (56.3) | 6 (35.3) |
| Grade 1 | 4 (2.1) | 0 (0) | 3 (18.8) | 1 (5.9) |
| Grade 2 | 9 (4.6) | 1 (0.6) | 1 (6.3) | 7 (41.2) |
| Grade 3 | 6 (3.1) | 0 (0) | 3 (18.8) | 3 (17.6) |
| **Peripheral neuropathy** | | | | |
| Not during treatment | 168 (86.2) | 145 (89.5) | 12 (75) | 11 (64.7) |
| Grade 1 | 10 (5.1) | 7 (4.3) | 3 (18.8) | 0 (0) |
| Grade 2 | 17 (8.7) | 10 (6.2) | 1 (6.3) | 6 (35.3) |
| **Gastrointestinal toxicity** | | | | |
| No AE during treatment | 39 (20) | 34 (21) | 3 (18.8) | 2 (11.8) |
| Grade 1 | 99 (50.8) | 84 (51.9) | 11 (68.8) | 4 (23.5) |
| Grade 2 | 57 (29.2) | 44 (27.2) | 2 (12.5) | 11 (64.7) |
| **Hepatotoxicity** | | | | |
| No AE during treatment | 140 (71.8) | 121 (74.7) | 8 (50) | 11 (64.7) |
| Grade 1 | 39 (20) | 30 (18.5) | 5 (31.3) | 4 (23.5) |
| Grade 2 | 14 (7.2) | 11 (6.8) | 1 (6.3) | 2 (11.8) |
| Grade 3 | 2 (1) | 0 (0) | 2 (12.5) | 0 (0) |

Data are presented n (%), unless otherwise stated. AE: adverse event; STR: shorter treatment regime.

Haematological toxicity was observed in six (18.1% of 33) patients treated with linezolid, including three out of 16 patients switched to linezolid during treatment, and three out of 17 patients treated with linezolid from the start. The median time between initiation of linezolid and onset of haematological adverse events was 2 months (range: 1–4; IQR: 2–3). No grade 4 haematological toxicity was reported. In six patients with severe toxicity (haemoglobin level 6.5–6.99 $g{\cdot}dL^{-1}$, platelet count $20\times10^3$–$<50\times10^3$ $platelets{\cdot}L^{-1}$, or leukopenia as total leukocyte count $1\times10^3{\cdot}L^{-1}$–$<2\times10^3{\cdot}L^{-1}$) linezolid was temporarily discontinued. Those with low haemoglobin received a blood transfusion and linezolid was reintroduced at a dosage of 300 mg daily without further problems. Severe haematological toxicity was not observed among patients treated without linezolid, but one had moderate anaemia.

Among the 33 patients on the linezolid containing regimen, 10 (30.3%) had reversible mild-to-moderate peripheral neuropathy for which they received, anti-inflammatory drugs and/or amitriptyline as long as they were treated with linezolid. In this group, this adverse event occurred after a median time of 1.5 months (range: 1–7; IQR 1–4.25). Among the 162 patients on the unmodified STR 17 (10.5%) had reversible mild-to-moderate peripheral neuropathy with a median time occurrence of 3 months (range: 1–6; IQR 2–4). No patient had optic neuritis.

Gastrointestinal toxicity, hepatotoxicity and nephrotoxicity was recorded in 80.0% (156 out of 195), 28.2% (55 out of 195), and 6.7% (27 out of 195) of patients, respectively. Gastrointestinal toxicity and nephrotoxicity was either mild or moderate. Hepatotoxicity was severe in two patients while on kanamycin (table 3).

The cumulative follow-up time during the intensive phase with kanamycin and linezolid was 727 and 116 months, respectively. Two patients with severe hepatotoxicity during treatment with kanamycin and two patients in whom moderate ototoxicity evolved to severe ototoxicity after switching to linezolid were accounted as having had a severe adverse event as a consequence of kanamycin administrattion. The use of linezolid was significantly associated with severe adverse events (hazard ratio 8.9; 95%CI 2.5–31.5; p=0.001) (figure 2).

## Discussion

To our knowledge, this is the first study to assess the effect of systematic audiometry in RR-TB patients treated with the STR with linezolid replacing kanamycin for those having abnormal results. This approach achieved successful treatment outcomes, with a 4.6% overall frequency of severe adverse events. Fewer than one in 10 patients was started on the linezolid containing regimen due to baseline hearing loss. 16 of 178 patients started on the kanamycin containing STR were switched to the linezolid during treatment. The frequency of severe hearing loss was 1.0% (two out of 178) in the entire cohort. While severe adverse events (any type) were significantly more frequent in patients treated with the linezolid containing STR, adverse were manageable and no patient died due to an adverse event.

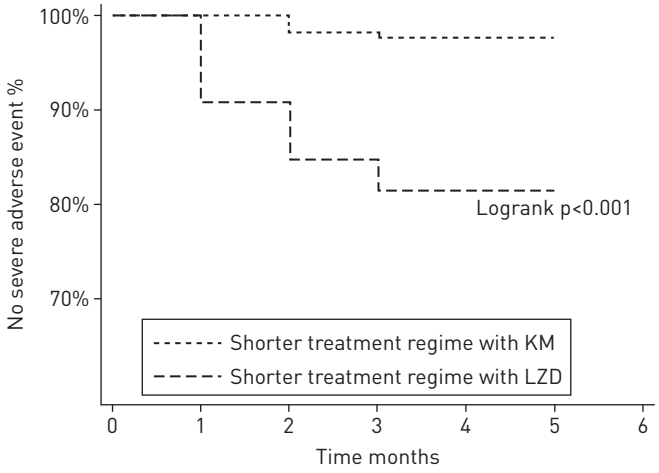


FIGURE 2 Time without severe adverse event on either a kanamycin (KM) or linezolid (LZD) containing rifampicin-resistant tuberculosis (TB) short treatment regimen. A time-dependent variable "bactericidal drug" (kanamycin; linezolid) was used, as some patients switched from kanamycin to linezolid during treatment. The follow-up time was calculated as the time (in months) between starting either kanamycin or linezolid and having a severe adverse event or ending treatment with kanamycin and linezolid. Ototoxicity, a known adverse event of kanamycin, was always accounted as an adverse event of kanamycin, even if ototoxicity became severe only after switching to linezolid.

The overall high cure rate (82.6%) among patients treated with the STR was similar to what was reported in a recent review [2]. Moreover, patients treated with a STR with linezolid replacing kanamycin had similar favourable outcomes. When replacing one anti-TB drug with another it is important to consider the specific activity of drugs. Both kanamycin and linezolid have high bactericidal activity and prevent resistance acquisition to the core drug, which probably explains a greater than 80% treatment success among those patients on a modified STR [17].

In our study, only 1.1% of all patients (two out of 178) treated with the kanamycin containing regimen developed severe (grade 3) ototoxicity, and no patient developed deafness (grade 4). We speculate that the low proportion of patients previously exposed to streptomycin and the low HIV prevalence contributed to the low frequency of ototoxicity [18]. Moreover, audiometry abnormalities were identified before starting the STR in 17 patients. In this subgroup further hearing loss was probably prevented by not starting an injectable containing STR. Our findings compare favourably with 7.1% grade 3–4 and 2.6% grade 4 (deafness) ototoxicity reported by another study on the STR in nine African countries [19].

The two patients who developed severe hearing loss had moderate hearing loss (grade 2) when they were switched from kanamycin to linezolid. Second-line injectables can still cause damage to cochlear cells months after discontinuation [20], which probably explains why severe hearing loss was only detected after switching to linezolid. Possibly evolution towards severe hearing loss could have been prevented if the switch to linezolid had occurred earlier, when hearing loss was still mild (grade 1). From 2017 onwards, it was decided to switch to linezolid patients with mild hearing loss. Moreover, as hearing loss begins with higher frequencies, which are not perceived by normal human hearing, the frequency of audiometry was increased to monthly among all patients treated with a kanamycin-containing STR. Since 2017, no severe hearing loss has been detected in the cohort. We therefore recommend monthly audiometry to early diagnose hearing impairment followed by an immediate switch to linezolid in case any audiometry abnormality is identified. Audiometry may be performed by trained non-specialised health staff using simple devices that cover frequencies up to 8000 Hz, which is feasible in countries with a similar limited access to specialised care [13].

In 33 patients treated with linezolid, the most common adverse events were haematotoxicity, gastrointestinal toxicity and peripheral neuropathies, similar to what was reported in a systematic review [15]. Linezolid-induced adverse events can be severe and life-threatening [15]. In our study most adverse events were moderate. However, severe haematologicalal toxicity was experienced by 18.1% of 33 patients treated with linezolid. Indeed, haematologicalal toxicity is known to appear early, in the first months of treatment, while neuropathies and optic neuritis usually appear later on during treatment [10]. Nevertheless, no patient had to permanently stop linezolid, which contrasts with a previous study that reported 15.8% permanent discontinuation [15]. In our study, no patient had optic neuritis or severe peripheral neuropathy. The relative short-term use of linezolid may explain the difference between our study and previous studies in terms of incidence and severity of adverse events.

Bedaquiline is less toxic than linezolid [21, 22], and has been proposed to replace the injectable second-line drug in the STR [7]. However, recent studies show that about 5% of patients may have initial resistance to bedaquiline, and that another 5% may acquire resistance to this drug during treatment [23]. As bedaquiline drug susceptibility testing (DST) is not available in most high TB burden countries, its use should probably be limited to those who need it most and to settings where DST to bedaquiline is available. In the present study, none of the patients treated with linezolid containing STR experienced failure or relapse. Bedaquiline could be preserved for those patients with contra-indications to both the second-line injectable drugs and linezolid, and those who experienced second-line TB treatment failure, thus requiring a third-line TB treatment regimen, such as one of our patients on the unmodified STR who experienced relapse, who is now responding favourably to a bedaquiline based regimen. Bedaquiline containing regimens are still being studied. A recent trial reported 90% (83 out of 95) treatment success in patients with extensively drug-resistant tuberculosis treated with bedaquiline, pretomanid and linezolid [24]. Indeed, in patients with fluoroquinolone-resistant TB and not yet exposed to these drugs this new regimen may be an option. However, due to adverse events, 66% (72 out of 109) of patients interrupted linezolid during treatment [24], leaving patients at risk of resistance acquisition (which occurred in one patient with relapse) because of the very long half-life of bedaquiline [25]. Research is recommended to assess whether this regimen could be strengthened to prevent bedaquiline resistance [17], especially if components of the regimen are poorly tolerated.

The relatively small number of patients treated with linezolid-containing STR and the absence of randomisation are limitations of this study, as is the incomplete post-treatment follow-up for some patients, particularly in the group that received linezolid (almost 50% did not yet have a follow-up at 6 or 12 months) from treatment start. Strengths of our study include the use of a prospectively updated database, including all patients treated for RR-TB in Niger during the study period as well as the proactive

and frequent monitoring of hearing loss and early discontinuation of the injectable when audiometry abnormalities were found.

In conclusion, baseline and monthly audiometry monitoring and using linezolid instead of kanamycin when hearing abnormalities are detected appears effective to prevent severe ototoxicity, while keeping high treatment success and manageable adverse events. Larger cohort studies will need to show if linezolid can safely replace the second-line injectable in the STR and protect the fluoroquinolone from acquired resistance. If this all-oral regimen STR, with linezolid (and not bedaquiline) replacing the injectable, is safe and effective, bedaquiline could be preserved for patients failing fluoroquinolone-based RR-TB treatment.

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