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Early View

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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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“Take home” message

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.

Abstract

The short treatment regimen (STR) achieves over 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 - June 2019 in Niger. Patients underwent audiometry every 2 months in 2016, and every month since 2017.

Of 195 patients, 16.9% (33/195) 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 hematologicalal toxicity was observed in 18.1% (6/33) 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% (30/33) 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.

Introduction

Rifampicin is the most powerful first-line anti-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, WHO is now encouraging the use of all-oral regimens [7]. However the efficacy of all-oral STR 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 (AE), 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 AE (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 3 health facilities: in Niamey, the capital city, in Maradi and Zinder, situated at 700km and 1000km from Niamey, respectively.

Treatment regimen and active TB drug-safety monitoring & management (aDSM)

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 10mg/kg) 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. AE monitoring has been described elsewhere [4, 12] and consisted of regular clinical and biological examinations. Patients were seen at six- and 12-month 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 AE, linezolid was temporarily stopped and reintroduced at a lower dosage of 300 mg daily once the AE was corrected. In case of severe anemia 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 AE, (grade 1: mild; grade 2: moderate; grade 3: severe; grade 4: life-threatening or permanently disabling), including ototoxicity, hematological toxicity (sign of bone marrow suppression),[15] hepatotoxicity and other AE [16]. Audiometry abnormalities were graded as mild (hearing deficit 21-40dB; grade 1), moderate (41-70dB; grade 2), severe (71-90dB; grade 3), and permanently disabling (>90dB; 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 AE (>=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% (33/195) 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% (4/16) used linezolid for 1 month, 50% (8/16) for 2 months, 18.8% (3/16) for 3 months and 6.2% (1/16) 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 (95.9%), had a history of TB (96.4%), and had an abnormal chest X-ray (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. Thirty-three patients (16.9%) were previously treated with streptomycin; of whom 4 (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 after 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 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% (161/195) of patients were cured and 12.3% (24/195) died. Among the 21 who died during treatment with the unmodified STR, 11 had converted by the second month at latest on smear, and 9 of them also on culture. The remaining 10 patients had died during the first three months of treatment before conversion on culture and smear. Among the 33 patients on a linezolid containing STR, 90.9% (30/33) were cured, 9.1% (3/33) 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 AE: one died due to severe immunosuppression (HIV-positive patient not adherent to antiretroviral therapy), one due to respiratory failure (baseline chest X-ray showed bilateral cavities), and one because of hemoptysis.

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% (8/15) and 40% (6/15) were evaluated at 6 and 12 months after cure, respectively, while 14 of the 15 cured patients (93.3%) patients that switched to linezolid during treatment completed the 6 and 12 months follow-up.

Adverse events

AEs were experienced by 90.3% (176/195) of patients (table 3). Ten severe adverse events (grade 3) were recorded in 9 (4.6% of 195) patients. Two (1.0% of 195) developed severe ototoxicity. No patient had a life-threatening or disabling AE (grade 4).

Of nineteen 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 one month after having switched to linezolid.

Hematological toxicity was observed in 6 (18.1% of 33) patients treated with linezolid, including 3 of 16 patients switched to linezolid during treatment, and 3 of 17 patients treated with linezolid from the start. The median time between initiation of linezolid and onset of hematological AE was 2 months (range: 1-4; IQR: 2-3). No grade 4 hematological toxicity was reported. In 6 patients with severe toxicity (haemoglobin level 6.5 - 6.99 g/dl, platelet count 20×10^3 - $<50 \times 10^3$ platelets/l, or leukopenia as total leukocyte count 1×10^3/l - $<2\times10^3$/l) linezolid was temporarily discontinued. Those with low haemoglobin received a blood transfusion and linezolid was reintroduced at a dosage of 300mg daily

without further problems. Severe hematological toxicity was not observed among patients treated without linezolid, but one had moderate anemia.

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 AE 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% (156/195), 28.2% (55/195), and 6.7% (27/195) of patients, respectively. Gastrointestinal toxicity and nephrotoxicity was either mild or moderate. Hepatotoxicity was severe in 2 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 AE. Less than one in 10 patients was started on the linezolid containing regimen due to baseline hearing loss. Sixteen 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% (2/178) in the entire cohort. While severe AEs (any type) were significantly more frequent in patients treated with the linezolid containing STR, AEs were manageable and no patient died due to an AE.

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 (2/178) 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-specialized health staff using simple devices that cover frequencies up to 8,000 Hz, which is feasible in countries with a similar limited access to specialized care [13].

In 33 patients treated with linezolid, the most common AE were hematotoxicity, gastrointestinal toxicity and peripheral neuropathies, similar to what was reported in a systematic review [15]. Linezolid induced AE can be severe and life-threatening [15]. In our study most AE were moderate. However, severe hematologicalal toxicity was experienced by 18.1% of 33 patients treated with linezolid. Indeed, hematologicalal 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 AE.

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% (83/95) 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% (72/109) 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 randomization are limitations of this study, as 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 AE. 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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Conflicts of interest: None to declare.

Authors' contributions: MBS, AP and TD designed the study, did the analysis, and wrote the first draft. All co-authors contributed to the interpretation of the findings, critically revised subsequent versions and approved the final version.

Table 1: Characteristics of the 195 study patients, by rifampicin-resistant TB treatment regimen

	Total		Cohort						
			STR unmodified		STR modified during treatment		STR modified from start		
	N	%	N	%	N	%	N	%	p-value #
Total, n	195		162		16	8	17	8.5	NA
Gender, n(%)									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, median (IQR)	32	(26-40)	32	(25-40)	35.5	(31-41)	40	(25-55)	0.2
HIV status, n(%)									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, n (%)									0.4
scanty	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, n (%)									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, n (%)									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 X-ray, n (%)									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	51	26.2	42	25.9	4	25	5	29.4	

cavities									
Unilateral lesions & cavities	32	16.4	22	13.6	4	25	6	35.3	
Bilateral lesions & 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, n (%)									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, n (%)									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	

NA: not applicable
Fisher's exact test was used to compare distributions for different strata; Kruskal–Wallis test to compare medians between strata

Table 2: Treatment outcomes among 195 study patients, by rifampicin-resistant TB treatment regimen

	Total		STR unmodified		STR modified during treatment		STR modified from start		
	N	%	N	%	N	%	N	%	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	

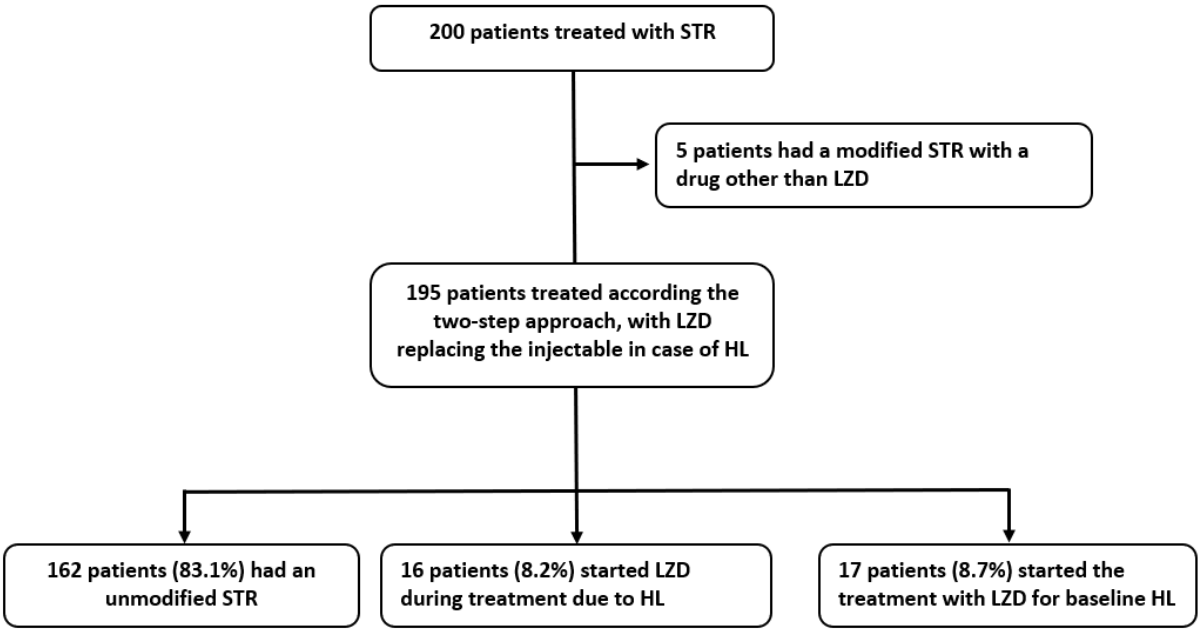
$ 37 patients not yet evaluated due to a too short post-treatment follow-up time

£ 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

Table 3: Adverse events during treatment among 195 patients, by rifampicin-resistant TB treatment regimen

	Total		Cohort					
			STR unmodified		STR modified during treatment		STR modified from start	
	N	%	N	%	N	%	N	%
Total	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



STR: shorter treatment regime; LZD: linezolid; HL: hearing loss

Figure 1: Patients diagnosed with rifampicin-resistant TB and treated with the shorter treatment regimen in Niger

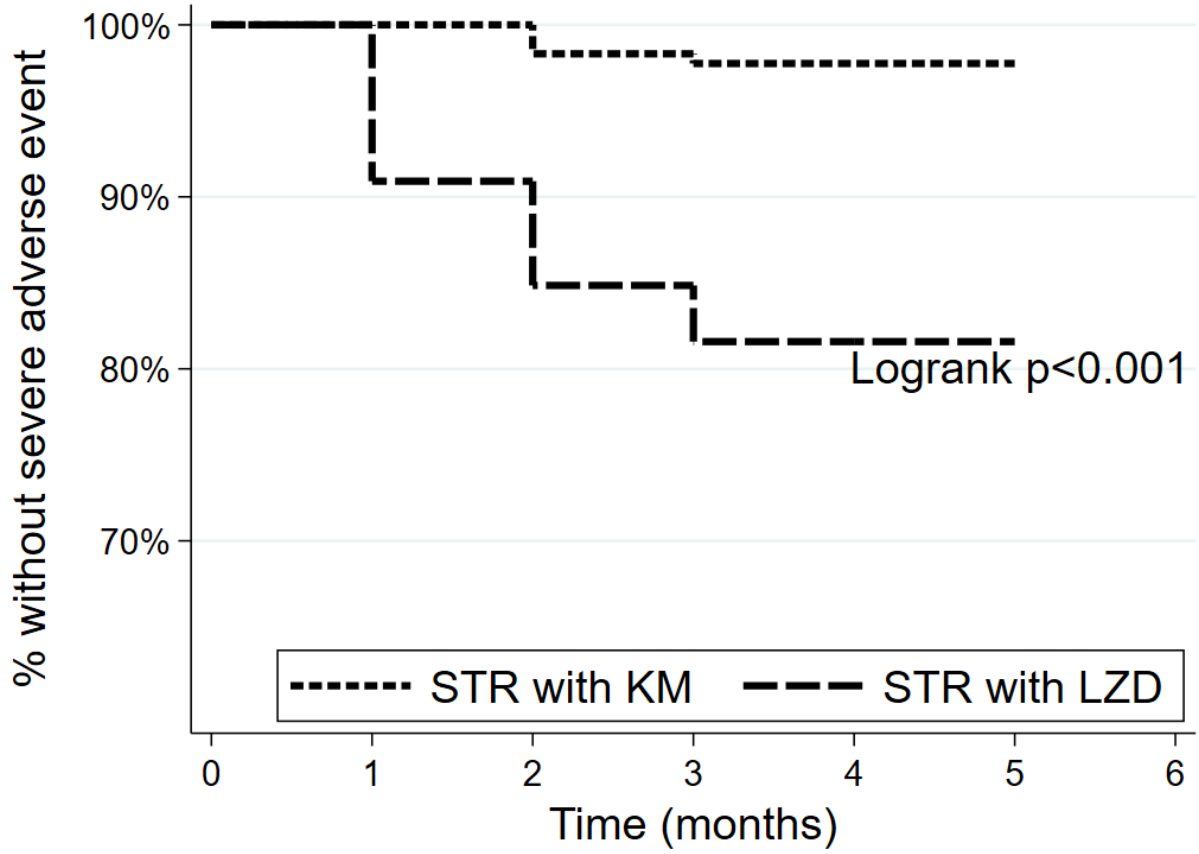


Figure 2. Time without severe adverse event on either a kanamycin or linezolid containing rifampicin-resistant TB short treatment regimen #

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.

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