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TITLE

Effectiveness and Safety of Bedaquiline-based, Modified All-oral 9-11-month Treatment Regimen for Rifampicin-Resistant Tuberculosis in Vietnam

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ABSTRACT

Background: WHO recommends a 7-drug 9-11-month rifampicin-resistant tuberculosis (RR-TB) short treatment regimen (STR). To reduce the pill burden, we assessed the safety and effectiveness of a 5-drug 9-11-month modified STR (mSTR).

Methods: Prospective cohort study of an all-oral mSTR (comprising bedaquiline, levofloxacin, linezolid, clofazimine and/or pyrazinamide) for RR-TB patients without confirmed fluoroquinolone resistance, enrolled in Vietnam between 2020-2021.

Results: One hundred eight patients were enrolled. Sixty-three of 74 (85%) achieved culture conversion at 2 months. Of 106 evaluated, 95 (90%) were successfully treated, 6 (6%) were lost-to-follow-up, 1 (1%) died and 4 (4%) had treatment failure, including 3 with permanent regimen change due to adverse events (AE) and 1 with culture reversion.

Thirty-two (30% of 108) patients encountered at least one AE. Of 45 AEs recorded, 13 (29%) were serious (hospitalization, life threatening or death). The median time to AE was 3 months (IQR:2-5). Twenty-six AEs led to regimen adaptation: either dose reduction (N=1), drug temporary interruption (N=19), or drug permanent discontinuation (N=6, 4 attributed to linezolid).

Conclusion: The high treatment success 5-drug mSTR may replace the 7-drug regimen in routine care. AEs were frequent, but manageable in most patients. Active AEs monitoring is essential, particularly when using linezolid throughout.

INTRODUCTION

Tuberculosis (TB) remains one of the most prevalent infectious diseases worldwide, causing a high mortality and morbidity. Notably, the emergence of rifampicin-resistant TB (RR-TB; resistance to the most potent TB drug) with about half a million incident cases per year threatens global efforts to control the disease (WHO, 2021). For many years, RR-TB treatment lasted 18 months or longer. Such long regimens were poorly tolerated and resulted in unsatisfactory treatment success (WHO, 2017). With the roll out of 9-11 -month regimens, global treatment success is improving, but at a slow pace, 59% of patient who started treatment in 2018 were treated successfully (WHO, 2021)

To further improve outcomes, the World Health Organization (WHO) revised its guidelines for the management of RR-TB as new evidence emerged (WHO, 2013, 2014, 2015, 2016a, 2016b, 2020, 2022; Mirzayev et al., 2021). Over the last decade, recommended RR-TB treatment regimens have rapidly evolved from long (18 months or more) injectable-containing regimens to a standardized and injectable-containing 9-11-month shorter treatment regimen ("Bangladesh regimen"), which showed similar efficacy in a randomized trial (Nunn et al., 2019). More recently, this injectable-containing regimen was replaced by a 7-drug standardized all-oral 9-11-month WHO shorter regimen (STR). The injectable agent was replaced by bedaquiline (BDQ), which was shown to be less toxic and more effective (WHO, 2018). A 6-9-month regimen composed of bedaquiline, pretomanid and linezolid (the BPaL regimen) showed high treatment success rate in highly resistant TB patients (MDR-TB with confirmed FQ resistance or intolerance to RR-TB treatment) (Conradie et al., 2020) and the regimen was recently recommended by WHO for use in the operational research conditions (WHO, 2020).

The most recent WHO rapid communication suggests using either the WHO STR (either using ethionamide or linezolid) or a novel 6-month treatment regimen, including BDQ, pretomanid, linezolid and moxifloxacin (BPaLM regimen) for patients with RR-TB and fluoroquinolone (FQ) resistance excluded. (WHO, 2022). Given that pretomanid is not yet available in most settings, the all oral 9–11-month regimen remains the preferable choice in many settings in RR-TB treatment.

At the time the Bangladesh regimen was designed and implemented, baseline drug susceptibility testing (DST) was not feasible for patients in most programme settings. Any FQ resistance, even if uncommon, would not have been identified. Therefore, a very robust 7-drug regimen was used, with back-up activity for patients with RR-TB with additional resistance. The composition of the 9-11-month injectable-containing regimen was intended to overcome low-level FQ resistance, but not high-level FQ resistance (Aung et al., 2014). However, with the advent of rapid molecular diagnostic tests, when systematic FQ DST screening can be done for all at baseline, it is reasonable to consider reducing the number of drugs used in treatment regimens for RR-TB without additional resistance to FQ. The current WHO's standardized all-oral 9-11 -month STR uses the structure of the regimen piloted in Bangladesh and contains seven drugs. It relies on FQ (levofloxacin or moxifloxacin) and bedaquiline as core-drugs; prothionamide (or ethionamide), isoniazid, ethambutol, pyrazinamide, and clofazimine are added as companion drugs to increase either bactericidal or sterilizing activity (van Deun et al., 2018b).

WHO encourages countries to conduct operational research on the effectiveness of modified STRs, with modifications in composition and duration of the regimen, to inform programmatic implementation at country level and provide important evidence for global treatment guidelines (WHO, 2020). Only few studies showed the effect of simplifying the

existing WHO STR regimen, for instance, by reducing and/or replacing a number of companion drugs to come to a 5-drug regimen. In Belarus and Georgia, compared to the WHO STR, linezolid and cycloserin replaced ethambutol, isoniazid, prothionamide and pyrazinamide. However, in Georgia, the cohort consisted only out of 25 patients (Avaliani et al., 2021). The experience from Belarus was presented as an abstract, but not yet published (Yatskevich et al., 2021). In China, 35 patients were treated with 4-5 -drug all-oral BDQ-containing 9-12 -month regimen, tailored to the patient's initial DST results. Culture conversion at 2 months was high (90%; 19/21 with culture results). However, only one patient had completed treatment (Fu et al., 2021).

In Vietnam, the 7-drug WHO recommended STR has been implemented since August 2021. Simultaneously, to address concerns with regards to the pill burden, a novel and modified all-oral STR (mSTR) containing five instead of seven drugs was piloted under operational research conditions (WHO, 2019). Compared to the WHO STR, linezolid replaced the companion drugs ethambutol, isoniazid, and prothionamide, and it was given throughout the treatment. This study, as part of WHO's ShORRT (Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis) initiative (WHO, 2020a), aimed to assess the safety and effectiveness of this mSTR to inform RR-TB treatment policy in Vietnam. This article reported the end-of-treatment safety and effectiveness outcome of the regimen while the post-treatment follow-up is still on going.

METHODS

Study design

This was a prospective cohort study that enrolled RR-TB patients between July 2020 and February 2021 in six large RR-TB treatment sites of Vietnam (National Lung hospital, and Hanoi, Nam Dinh, Hai Phong, Tay Ninh and Dong Thap lung hospitals).

Study setting and population

Vietnam is a high TB burden country. In 2019, there were an estimated 170,000 new TB and 8,400 new RR-TB cases nationally. Of 8,400 RR-TB cases, only 3.104 were enrolled on treatment (WHO, 2020b). Fluoroquinolone resistance prevalence among patients with RR-TB was 16,7% (Nhung et al., 2015). Xpert MTB/RIF (Cepheid Inc, Sunnyvale, CA, USA) was used for the diagnosis of RR-TB. Once diagnosed, RR-TB patients were screened for resistance to FQ by either genotypic (GenoType HainMTBDRsl (Nehren, Germany); second-line line probe assay [SL-LPA]) or phenotypic second-line DST (SL-DST). This study included patients with confirmed RR-TB without additional resistance to FQs. Patients were excluded if they were previously exposed for more than one month to second-line drugs, such as BDQ, FQ (levofloxacin (LFX) or moxifloxacin), clofazimine (CFZ), and linezolid (LZD), had an unknown previous exposure to second-line drugs, were at risk of cardiovascular complications (QTcF > 500ms), had extensive extra pulmonary TB, or an abnormal electrolyte index, were in an end-stage of liver or renal diseases, or were pregnant or breastfeeding.

Bedaquiline-based short treatment regimen

Eligible and consenting RR-TB patients (Figure 1) started the study regimen, which included five drugs: BDQ, LFX, CFZ, LZD, and pyrazinamide (PZA). BDQ was used during the first 24 weeks of treatment, with a loading dose of 400mg daily in the first 2 weeks, followed by maintenance dose of 200mg thrice weekly for 22 weeks, other drugs were used throughout the treatment course, LZD's dosage was 600mg per day. PZA was excluded from the regimen if

DST showed PZA resistance, even if treatment had already started. Permanent discontinuation of any drug other than PZA led to switching to an individualized longer regimen, with a composition decided upon by the National Clinical Committee. Such patients were followed in the programme until the end of treatment. Total treatment duration of the study regimen varied between 9 to 11 months. Treatment duration was extended to 11 months in case the month four sputum sample was still positive on culture or due to the National Clinical Committee's decision based on patient's clinical and chest Xray progression. Patients were hospitalised during the first 2 weeks up to 1 month of treatment, then discharged for ambulatory management at district or commune level. Adverse events (AEs) were monitored and reported monthly following the active TB drug safety monitoring (aDSM) protocol (WHO, 2015b). Monthly follow-up included clinical evaluation including neurologic examination (BPNS), sputum smear, culture, ECG, blood tests such as liver function tests, haematology, electrolytes, and chest X-ray every 3 months during follow-up. After completing treatment, patients will be scheduled for 2 follow-up consultations at month 6 and month 12 post treatment, including clinical evaluation, smear, culture and chest X-ray.

Study variables and definitions

Data were collected for the following variables: age, gender, HIV status, TB treatment history, TB type, disability status, baseline and monthly sputum smear and culture results, baseline DST, baseline and monthly para-clinical parameters (chest X-ray, ECG, blood test …). End-of-treatment outcome definitions were based on WHO and national guidelines, and they were grouped as favourable (cured or treatment completed) or unfavourable (treatment failure, died, lost-to-follow-up (LTFU)). In addition, final outcome will include the sustained treatment success assessed at 6 and 12-month post treatment (WHO, 2021). Bacteriological treatment

failure was defined by lack of culture conversion after 4 months or culture reversion after conversion. Treatment failure due to adverse events was defined by the need to permanently change the treatment regimen due to AEs. Grading of AEs was based on the "Table of Grading the Severity of Adult and Paediatric Adverse Events, version 2.0" (November 2014) of the U.S National Institute of Allergy and Infectious Disease (US Department of Health and Human Services, 2014). Severe AEs were defined as grade 3-4 adverse events, while serious AEs (SAEs) included any death, hospitalization, life-threatening AE, permanently disability or any grade 4 AE. The clinician in charge of treating RR-TB at each site determined the relation between AE and TB drugs, relying on available data of the toxicity profile of TB drugs and clinical data obtained as drugs were stopped and re-introduced. Categories showing this relationship included "definite", "probable", "possible", "unlikely", "not related", "unclassifiable".

Data collection and analyses

Paper forms were developed to collect data from the patient's medical records. aDSM reports showed data on clinical symptoms and test results. These data were entered in the REDCap database.

Proportions were used to summarise categorical variables and medians and interquartile ranges were used to summarise continuous variables. Data analyses were performed using software STATA (version 16.1).

Ethics approval

Ethical approval of this study was obtained from the National Lung hospital in Vietnam. Written informed consent was obtained from all studied patients.

RESULTS

Patients' characteristics

Between July 2020 and February 2021, 178 patients were notified with RR-TB by Xpert MTB/RIF at 6 study sites. Of those, 153 patients were screened and consulted to put on mSTR treatment as 25 (14%) patients had FQ resistance in SL-LPA. After screening process, 108 patients initiated mSTR as 45 patients were excluded from the study because of either not consent, having unknown, or previous exposure to second-line drugs in study regimen for more than 1 month, or other exclusion criteria. Then, 2 patients were excluded from the effectiveness analysis as they were enrolled in the early stage of treatment on a longer regimen on receipt of phenotypic DST results showing FQ resistance (Figure 1). A total of 106 patients were included in end-of-treatment effectiveness analysis. Table 1 shows baseline characteristics of these patients, stratified by sputum culture status at treatment initiation. Among 106 patients, 70 had a positive culture at baseline, while 36 had either a negative or no culture result at the beginning of treatment. 70,8% (N=75) were male and the median age was 41 (IQR: 29-57) years. Sixty six out of 106 patients (62,3%) were new TB cases. Of the remaining, only 1 (0,9%) had previous exposure to second-line drugs (for less than 1 month). Overall, about 40% had cavities and/or extensive lesions on chest X-ray. Seventy-one (67%) had a DST result confirming susceptibility to FQs while 35 (33%) had either an indetermined (N=3) second-line line probe assay result or were without fluoroquinolone DST result (N=32).

Treatment outcome

Bacteriological response was assessed in 74 patients: 68 patients with a positive culture at baseline and 6 patients without baseline culture result but with a positive culture in the first treatment months. Culture conversion at 2 months was achieved in 63 of 74 (85%) patients.

Thirty-two patients were excluded from conversion analysis. Of 32, 30 never had a positive culture at baseline or during follow-up. Two had a positive baseline culture but didn't have enough culture results to conclude whether conversion had occurred. Of these, 1 patient had only 1 negative culture at month 7 and several smear negative smear results (month 1, 6 and 8), and was reported as treatment completed. The other patient had a negative culture at month 1 and was lost-to-follow-up thereafter.

Regarding end of treatment outcomes, among 106 patients, 95 (90%) were successfully treated (defined as cured or treatment completed), 6 (6%) were lost-to-follow-up, 1 (1%) died and 4 (4%) had treatment failure, including 3 because of permanent regimen change due to adverse events (AE) and 1 because of reversion on culture (Table 2).

Of 35 patients without baseline FQ genotypic or phenotypic DST, 33 (94,3%) were treated successfully, 1 (2,9%) was LTFU, and 1 (2,9%) experienced treatment failure (culture reversion). Among 25 patients who stopped PZA permanently (1 due to AE and 24 due to detected PZA resistance), treatment success was achieved in 84% (N=21) patients.

Adverse events

Thirty-two (29,6% of 108 enrolled) patients were reported with at least one adverse event (AE). A total of 45 AEs were recorded, of those, 13 (29%) were serious Twelve (26,6%) AEs were grade 3 or 4. About one third of AEs recorded were mild and moderate. The most frequently reported AEs included increase of liver enzyme (N=13, 28,9%), hypokalemia (N=5, 11,1%), arthralgia (N=5, 11,1%), QT prolongation (N=4, 8,9%), peripheral neuropathy (N=3, 6,7%) and a reduced count of red blood cells and/or platelets (N=3, 6,7%). Thirty-four (75,6%) of recorded AEs had either a definite (N=5, 11,1%), probable (N=23, 51,1%) or possible (N=6, 13,3%) relationship with prescribed drugs in the treatment regimen, while for 11 (24,4%) AEs

the culprit was unclear. The median time to AE was 3 months (IQR:2-5). The time to AE was not different for different culprit drugs. Twenty-six AEs (58%) led to an adaptation of the prescribed regimen: either dose reduction (N=1), drug interruption (N=19), or drug withdrawal (N=6, of those, 4 due to LZD).

DISCUSSION

The 5-drug all oral mSTR in our study showed a high early conversion rate (85% at two months) and high treatment success (90%) among RR-TB patients in Vietnam. Fluoroquinolone resistance was excluded at baseline among the majority (67%) of patients. Treatment success of 90% compares favorably with 76% success reported in Vietnam for the 2019 RR-TB cohort treated with the injectable-containing 7-drug STR.

Our results also compare favorably with 75% success reported in South Africa for RR-TB patients treated with a 7-drug all-oral STR (using 2 months LZD instead of ethionamide as compared to WHO's STR) (Tack et al., 2020). Treatment success of our simplified mSTR was comparable with those obtained for other mSTR cohorts, also using BDQ and FQ as core drugs, and LZD and CFZ as companion drugs, but with cycloserine (CS) instead of PZA. In Georgia's cohort of 25 patients: 88% success was achieved and in Belarus 90% success was achieved among 222 patients (Avaliani et al., 2021). Comparably, the 4-drug BPaLM in TB-PRACTECAL showed 88,7 % treatment success among 62 patients (Anon, 2021). In these settings as well in our own setting, baseline screening for FQ resistance was done and patients with FQ-resistant isolates were excluded. These data confirm that a 5-drug mSTR can be highly successful in RR-TB patients without confirmed resistance to FQ. The likely reasons for the high conversion and treatment success rate of our mSTR include strong bactericidal and sterilizing

activities of the 2 core drugs, BDQ and FQ given together. Furthermore, the use of LZD is associated with improved treatment outcomes in RR-TB patients (Ahmad et al., 2018).

The Vietnam regimen did not include CS as fifth drug, but PZA, a drug with sterilizing activities (van Deun et al., 2018a). However, PZA was very frequently withdrawn during treatment due to baseline resistance on phenotypic DST reported while treatment was already ongoing. Whether 4-drug regimens, including BDQ, FQ, LZD and CFZ, can be as effective as 5-drug regimens remains to be confirmed. Phenotypic DST for PZA is not very reliable, which may result in false reports of resistance (Hoffner et al., 2013). It is possible that the optimal use of this drug is for a shorter duration, as in first-line regimens where PZA given in the initial two months allowed a shortening of treatment from 9 to 6 months (Fox, Ellard & Mitchison, 1999). In order to avoid neuropsychiatric toxicity due to CS (Court et al., 2021), this drug should be limited to a small number of RR-TB patients in need of salvage treatment after other treatment options are exhausted.

One third of our patients experienced adverse events and 13 out of 106 patients (12%) experienced SAEs, which is close to 11% SAEs reported in the first global surveillance of AEs among RR-TB patients treated with new and repurposed drugs in 26 countries (Borisov et al., 2019). According to this report, BDQ and LZD were discontinued in 0,4% and 2% of patients, respectively (Borisov et al., 2019). In our cohort, BDQ and LZD were discontinued in 1% and 4% of patients, respectively. Our study is one of the first to report safety data for a 5-drug all-oral STR (mSTR). No safety data were published for the Belarus cohort, while in small cohort of 25 patients in Georgia 3 SAEs were reported (Yatskevich et al., 2021; Avaliani et al., 2021). In South Africa, among 117 patients treated with a 7-drug all-oral STR, 62 severe AEs (grade 3-4) were reported. The drug causing most of these severe AE was LZD, 18 (17%) of 107 patients

using LZD discontinued the drug permanently (Tack et al., 2020). While adding LZD to all-oral BDQ-based regimen can contribute to treatment success, close monitoring of AEs during the whole treatment course is essential. LZD-related toxicities are mostly reversable when the drug is stopped. Unless interrupted, LZD was used throughout treatment in our 5-drug mSTR. Whether LZD can be used for a shorter duration in 5-drug regimens (eg. 2 months, as in the 7-drug regimen) requires further research.

Our cohort study had several limitations. First, results need to be verified when the regimen will be rolled out in a programmatic setting, in multiple countries. The mSTR studied in Vietnam is also studied as one of the treatment arms of the endTB trial. These results will add evidence on the safety and efficacy of this mSTR. The interpretation of the relationship relied on clinical data, including rechallenging of drugs after severe AE. We reported the relationship established by the treating clinicians. However, as some AEs may be caused by multiple drugs, it was not easy to establish this relationship with a high level of certainty. Moreover, 12-month post treatment follow-up results are not yet available to confirm the sustained treatment success. However, as most patients received about 7 months of TB treatment after conversion, we speculate that relapse will be rare. Finally, we were not able to compare the results with those obtained for the 7-drug WHO STR in Vietnam, as the latter was being used only since the end of 2021. While mild or moderate AEs may have been underreported, the emphasis on data collection for severe or life-threatening AE resulted in very complete data for this type of AE. Another strength of this study was its prospective design which led to comprehensive study monitoring and rigorous data collection and cleaning. Finally, our data from a real-life setting represent the reality of the Vietnam RR-TB programme.

CONCLUSION

In our study, interim results showing end-of-treatment outcomes showed that the shorter all-oral 9-11-month regimen, with LFX and BDQ as core drugs, and LZD, CFZ and PZA as companion drugs, was highly effective for RR-TB patients in Vietnam. This mSTR resulted in high 2-month culture-conversion and high end-of-treatment success. Adverse events were frequent, but manageable in most patients. aDSM is still essential, particularly when linezolid is used throughout treatment.

If post-treatment follow-up data show a high relapse-free cure rate, future studies are needed to assess whether it is possible to further reduce the number of drugs, eg. 4 drugs, in the regimen composition or whether it is possible to shorten the duration of LZD to increase the regimen's tolerability.

CONNFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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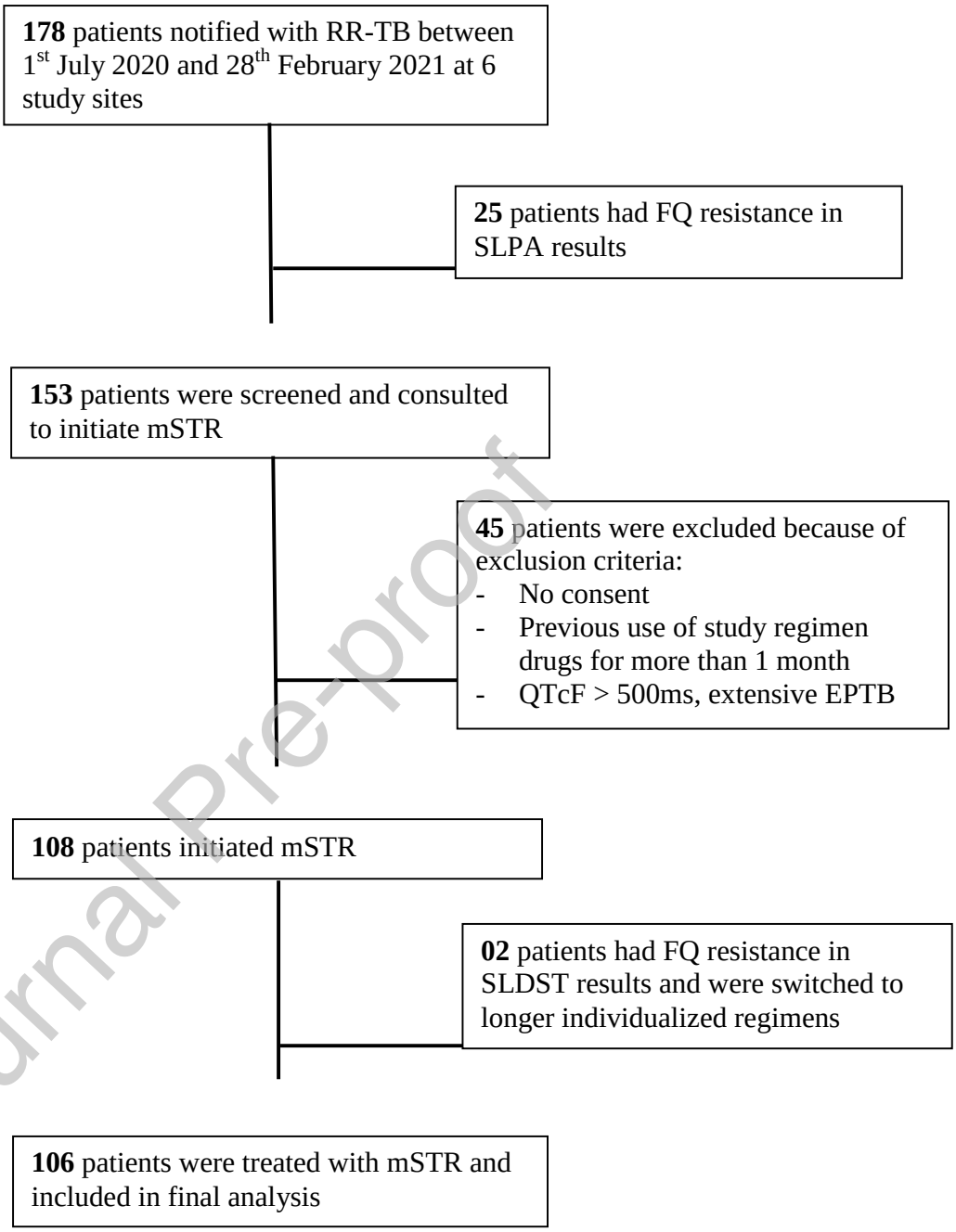

Firgue 1. Flow diagram of eligible study participants from RR-TB patients notified in 6 study sites, from July 2020 to February 2021 (RR-TB=Rifampicin resistant Tuberculosis, FQ=Flouroquinolone, SLPA=second-line line probe assay, SLDST=second-line drug susceptibility testing, EPTB=extra pulmonary TB)

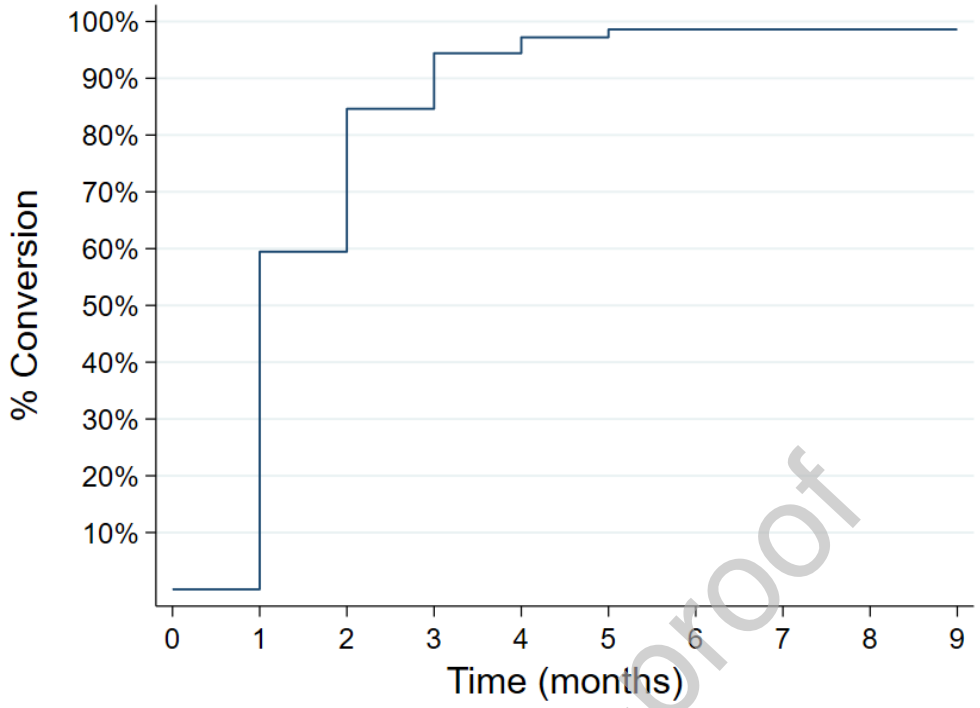

Figure 2. Time to culture conversion (N=74)

Table 1. Patients' characteristics

	Total		Culture positive at baseline		Culture negative or no result at baseline	
	N	**%**	**N**	**%**	**N**	**%**
Total	**106**		**70**		**36**	
Gender						
Male	75	70,8	51	72,9	24	66,7
Female	31	29,2	19	27,1	12	33,3
Age (median, IQR)	41	(29-57)	41	(29-57)	39	(32-56)
HIV status						
Negative	83	78,3	53	75,7	30	83,3
Positive	1	0,9	1	1,4	0	0
Unknown	22	20,8	16	22,9	6	16,7
TB treatment history						
New case	66	62,3	50	71,4	16	44,4
History of first-line drugs	39	36,8	20	28,6	19	52,8
History of second-line drugs	1	0,9	0	0	1	2,8
TB type						
New case	66	62,3	50	71,4	16	44,4
Treatment after failure	1	0,9	19	27,1	18	50
Treatment after relapse	37	34,9	0	0	1	2,8
Treatment after lost-to-follow-up	1	0,9	0	0	1	2,8
Other	1	0,9	1	1,4	0	0
FQ DST on SL LPA						
Susceptible	71	67	54	77,1	17	47,2
Indeterminate	3	2,8	1	1,4	2	5,6
No information	32	30,2	15	21,4	17	47,2
Chest X-ray						
Normal	2	1,9	2	2,9	0	0
No extensive lesions (<25%)	34	32,1	24	34,3	10	27,8
Lesions (25-49%)	25	23,6	15	21,4	10	27,8
Cavities or lesions (>50%)	42	39,6	26	37,1	16	44,4
No information	3	2,8	3	4,3	0	0
Respiratory function status						
Normal	61	57,5	44	62,9	17	47,2
Dyspnea when hurrying	25	23,6	17	24,3	8	22,2
Walks slower to avoid dyspnea	12	11,3	5	7,1	7	19,4
Dyspnea after 100m	3	2,8	0	0	3	8,3
No information	5	4,7	4	5,7	1	2,8
Culture status (at baseline OR during follow-up)						
Negative	30	28,3	0	0	30	83,3

Positive	76	71,7	70	100	6	16,7
Baseline smear microscopy						
Negative	50	47,2	29	41,4	21	58,3
Scanty	11	10,4	6	8,6	5	13,9
1+	29	27,4	22	31,4	7	19,4
2+	6	5,7	4	5,7	2	5,6
3+	7	6,6	7	10	0	0
No result	3	2,8	2	2,9	1	2,8

TB = tuberculosis; HIV = human immunodeficiency virus; FQ = flouroquinolone; DST = drug sensitivity testing; SL LPA = second-line line probe assay.

Table 2. Treatment outcome

Treatment outcomes	**N**	**%**
	106	**100**
Favourable	**95**	**89,6**
Cured	88	83,0
Treatment completed	7	6,6
Unfavourable	**11**	**10,4**
Failure/ culture reversion	1	0,9
Failure/ adverse events	3	2,8
Lost to follow up	6	5,7
Died	1	0,9

Table 3. Type of adverse events and grading among patients who experienced an adverse event, counting every adverse event once

	Total		BDQ	LFX	LZD	CFZ	PZA	Culprits (*) unclear
	N	%	N	N	N	N	N	N
Total	**45**		**2**	**4**	**11**	**3**	**15**	**10**
SAE								
Yes	13	28,9	0	2	7	0	4	0
No	32	71,1	2	2	4	3	11	10
AE diagnosed								
Blood disorders								
Hemoglobin (<10.5 g/dL)	2	4,4	0	0	2	0	0	0
Platelets (<75.000/mm3)	1	2,2	0	0	1	0	0	0
Cardiac disorders								
QT prolongation	4	8,9	0	4	0	0	0	0
Gastrointestinal disorders								
Nausea	2	4,4	1	0	1	0	0	0
Vomiting	1	2,2	1	0	0	0	0	0
Hepatobiliary disorders								
ALT increase (≥1.1xULN) $	13	28,9	0	0	0	0	11	2
Metabolism and nutrition disorders								
Hypokalemia (≤3,4 mEq/L)	5	11,1	0	0	0	0	0	5
Nervous system disorders								
Optic neuritis	1	2,2	0	0	1	0	0	0
Peripheral neuropathy	3	6,7	0	0	3	0	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	5	11,1	0	0	0	0	3	2
Myalgia	1	2,2	0	0	1	0	0	0
Skin and subcutaneous tissue disorders								
Mucocutaneous (rash …)	2	4,4	0	0	2	0	0	0
Hypo-/hyper-pigmentation	3	6,7	0	0	0	3	0	0
Other	2	4,4	0	0	0	0	1	1
Relationship with drugs (*)								
Definite	5	11,1	0	0	4	0	1	0
Probable	23	51,1	1	3	5	2	10	2
Possible	6	13,3	1	0	1	1	3	0
Unlikely	2	4,4	0	0	0	0	1	1
Unknown	9	20	0	1	1	0	0	7
Grade of AE								
1/mild	22	48,9	2	1	2	3	4	10

2/moderate	11	24,4	0	0	4	0	7	0
3/severe	10	22,2	0	3	4	0	3	0
4/life threatening	2	4,4	0	0	1	0	1	0
Treatment regimen adaptation								
No change	19	42,2	2	1	1	2	3	10
Dose reduction	1	2,2	0	0	0	1	0	0
Drug temporary discontinuation	19	42,2	0	2	6	0	11	0
Drug permanent discontinuation	6	13,3	0	1	4	0	1	0

SAE = serious adverse event; AE = adverse event; ALT = Alanine aminotransferase enzyme; BDQ = bedaquiline, LFX = levofloxacin; LZD = linezolid; CFZ = clofazimine; PZA = pyrazinamide.

$ Of 13 ALT increases, 3 were mild (1 associated with PZA, 2 culprits unclear), 6 (all associated with PZA), 3 (all associated with PZA), 1 (associated with PZA)

* The clinician in charge of treating RR-TB at each site determined the relation between AE and TB drugs, relying on available data of the toxicity profile of TB drugs and clinical data obtained as drugs were stopped and re-introduced.