International Journal of Infectious Diseases 126 (2023) 148–154

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Effectiveness and safety of bedaquiline-based, modified all-oral 9–11-month treatment regimen for rifampicin-resistant tuberculosis in Vietnam

Thi Mai Phuong Nguyen[1,*], Thi Hai Minh Le[1], Corinne Simone Collette Merle[2], Debora Pedrazzoli[3], Nhat Linh Nguyen[3], Tom Decroo[4], Binh Hoa Nguyen[1], Thi Thanh Thuy Hoang[1], Viet Nhung Nguyen[1]

[1] National Lung Hospital, Hanoi, Vietnam
[2] The Special Programme for Research and Training in Tropical Diseases (TDR), World Health Organization, Geneva, Switzerland
[3] Global Tuberculosis Programme, World Health Organization, Geneva, Switzerland
[4] Institute of Tropical Medicine Antwerp, Antwerp, Belgium

ARTICLE INFO

Article history:
Received 15 August 2022
Revised 19 October 2022
Accepted 7 November 2022

Keywords:
Drug-resistant tuberculosis
All-oral regimen
Shorter regimen
Bedaquiline

ABSTRACT

Objectives: World Health Organization 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 [LZD], clofazimine, and/or pyrazinamide) for patients with RR-TB without confirmed fluoroquinolone resistance, enrolled in Vietnam between 2020-2021.

Results: A total of 108 patients were enrolled in this study. Overall, 63 of 74 (85%) achieved culture conversion at 2 months. Of 106 evaluated, 95 (90%) were successfully treated, six (6%) were lost-to-follow-up, one (1%) died, and four (4%) had treatment failure, including three with permanent regimen change owing to adverse events (AE) and one with culture reversion. Of 108, 32 (30%) 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). A total of 26 AEs led to regimen adaptation: either dose reduction (N = 1), drug temporary interruption (N = 19), or drug permanent discontinuation (N = 6, 4 attributed to LZD).

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

Introduction

Tuberculosis (TB) remains one of the most prevalent infectious diseases worldwide, causing 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, 2021a). 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 rollout of 9–11 - month regimens, global treatment success is improving, but at a slow pace. In total, 59% of patients who started treatment in 2018 were treated successfully (WHO, 2021b).

To further improve outcomes, the World Health Organization (WHO) revised its guidelines for the management of RR-TB as new evidence emerged (Mirzayev *et al.*, 2021; WHO, 2013, 2014, 2015a, 2016a, 2016b, 2020a, 2022). 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

* Corresponding author: Nguyen Thi Mai Phuong, National Lung hospital, Vietnam, 463 Hoang Hoa Tham street - Ba Dinh district, Hanoi, Vietnam, Tel: +84 949 357 999
E-mail address: phuongnguyen1186@gmail.com (T.M.P. Nguyen).

https://doi.org/10.1016/j.ijid.2022.11.007

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 BDQ, pretomanid, and linezolid (LZD) (the BPaL regimen) showed a high treatment success rate in highly resistant TB patients (multi-drug-resistant–TB with confirmed fluoroquinolone [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, 2020a. The most recent WHO rapid communication suggests using either the WHO STR (either using ethionamide or LZD) or a novel 6-month treatment regimen, including BDQ, pretomanid, LZD, and moxifloxacin (BPaLM regimen) for patients with RR-TB and FQ resistance excluded. (WHO, 2022). As 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 program 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 [LFX] or moxifloxacin) and BDQ as core drugs; prothionamide (or ethionamide), isoniazid, ethambutol, pyrazinamide (PZA), and clofazimine (CFZ) are added as companion drugs to increase either bactericidal or sterilizing activity (van Deun *et al.*, 2018).

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, LZD, and cycloserin (CS) replaced ethambutol, isoniazid, prothionamide and PZA. However, in Georgia, the cohort consisted only 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, LZD 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 RR-TB) initiative (WHO, 2020b), 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 ongoing.

Methods

Study design

This was a prospective cohort study that enrolled patients with RR-TB 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 8400 new RR-TB cases nationally. Of 8400 RR-TB cases, only 3104 were enrolled in treatment (WHO, 2020c). FQ 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, patients with RR-TB 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 1 month to second-line drugs, such as BDQ, FQ (LFX or moxifloxacin), CFZ, and LZD, had an unknown previous exposure to second-line drugs, were at risk of cardiovascular complications (QTcF > 500 ms), had extensive extrapulmonary TB, or an abnormal electrolyte index, were in an end-stage of liver or renal diseases, or were pregnant or breast-feeding.

Bedaquiline-based short treatment regimen

Eligible and consenting patients with RR-TB (Figure 1) started the study regimen, which included five drugs: BDQ, LFX, CFZ, LZD, and PZA. BDQ was used during the first 24 weeks of treatment, with a loading dose of 400 mg daily in the first 2 weeks, followed by a maintenance dose of 200 mg thrice weekly for 22 weeks, other drugs were used throughout the treatment course, LZD's dosage was 600 mg 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 program until the end-of-treatment. The 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 the patient's clinical and chest X-ray progression. Patients were hospitalized during the first 2 weeks up to 1 month of treatment, then discharged for ambulatory management at the 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, sputum smear, culture, electrocardiogram, blood tests such as liver function tests, hematology, electrolytes, and chest X-ray every 3 months during follow-up. After completing treatment, patients will be scheduled for two follow-up consultations at month 6 and month 12 post treatment, including clinical evaluation, smear, culture, and chest X-ray.

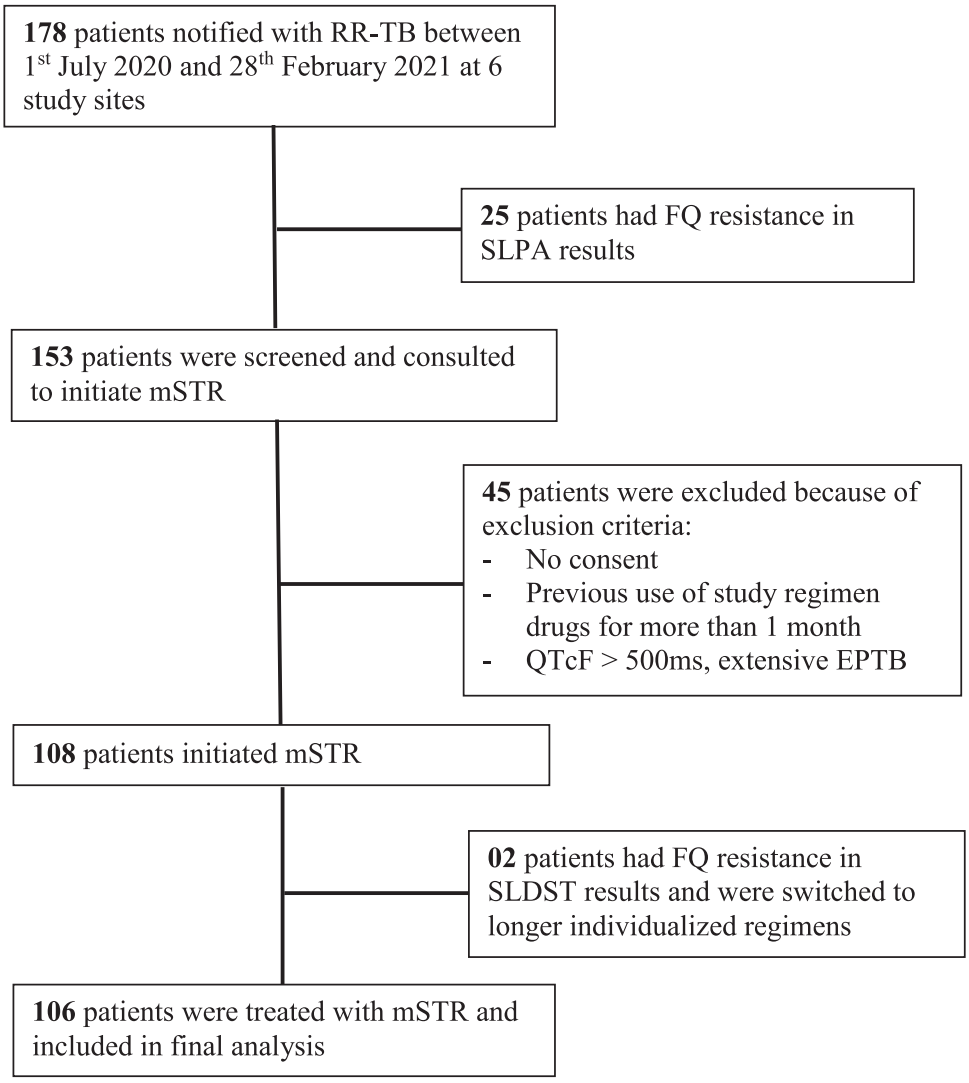

Figure 1. Flow diagram of eligible study participants from RR-TB patients notified in six study sites, from July 2020 to February 2021
FQ, Flouroquinolone; EPTB, extra pulmonary tuberculosis; mSTR, modified short treatment regimen; RR-TB, rifampicin-resistant TB; SLDST, second-line drug susceptibility testing; SLPA, second-line line probe assay.

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, electrocardiogram, blood test). End-of-treatment outcome definitions were based on WHO and national guidelines, and they were grouped as favorable (cured or treatment completed) or unfavorable (treatment failure, died, lost-to-follow-up [LTFU]). In addition, the final outcome will include the sustained treatment success assessed at 6 and 12-month post treatment (WHO, 2021a). Bacteriological treatment failure was defined by lack of culture conversion after 4 months or culture reversion after conversion. Treatment failure due to AEs 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 US National Institute of Allergy and Infectious Disease (US Department of Health and Human Services, 2014). Severe AEs were defined as grade 3-4 AEs, 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 into the Research Electronic Data Capture database.

Proportions were used to summarize categorical variables, and medians and interquartile ranges were used to summarize continuous variables. Data analyses were performed using the 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.

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
Tuberculosis 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
Tuberculosis 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
Flouroquinolone drug sensitivity testing on second-line line probe assay						
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 100 m	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

Results

Patients' characteristics

Between July 2020 and February 2021, 178 patients were notified with RR-TB by Xpert MTB/RIF at six 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 the 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, two 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 the 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 one (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 FQ DST result (N = 32).

Treatment outcome

Bacteriological response was assessed in 74 patients: 68 patients with a positive culture at baseline and six patients without baseline culture results but with a positive culture in the first treatment months. Culture conversion at 2 months was achieved in 63 of 74 (85%) patients (Figure 2). A total of 32 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 did not have enough culture results to conclude whether conversion had occurred. Of these, one patient had only one negative culture at month 7 and several smear negative smear results (month 1, 6 and 8), and was reported as treatment com-

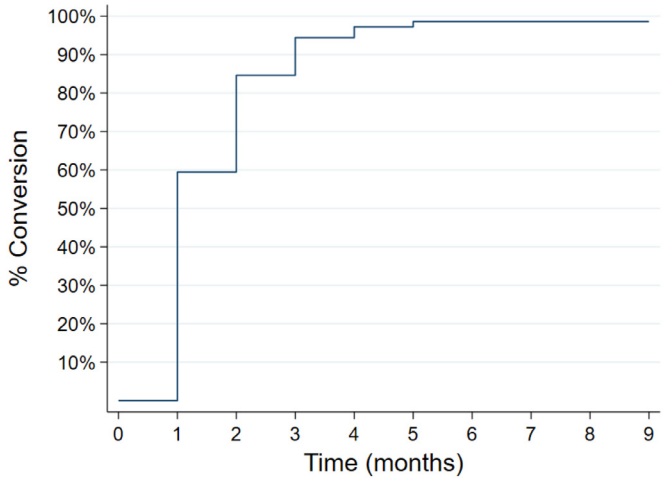

Figure 2. Time to culture conversion (N = 74)

Table 2
Treatment outcome

Treatment outcomes	N106	%100
Favorable	**95**	**89.6**
Cured	88	83.0
Treatment completed	7	6.6
Unfavorable	**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

pleted. The other patient had a negative culture at month 1 and was LTFU thereafter.

Regarding end-of-treatment outcomes, among 106 patients, 95 (90%) were successfully treated (defined as cured or treatment completed), six (6%) were LTFU, one (1%) died and four (4%) had treatment failure, including three because of permanent regimen change due to AEs and one because of reversion on culture (Table 2).

Of 35 patients without baseline FQ genotypic or phenotypic DST, 33 (94.3%) were treated successfully, one (2.9%) was LTFU, and one (2.9%) experienced treatment failure (culture reversion). Among 25 patients who stopped PZA permanently (one because of AE and 24 due to detected PZA resistance), treatment success was achieved in 84% (N = 21) patients.

Adverse events

Of 108, 32 (29.6%) patients were reported with at least one AE. A total of 45 AEs were recorded, of those, 13 (29%) were serious and 12 (26.6%) AEs were grade 3 or 4 (Table 3). About two thirds 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%). Overall, 34 (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. A total of 26 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, four due to LZD).

Discussion

The 5-drug all-oral mSTR in our study showed a high early conversion rate (85% at 2 months) and high treatment success (90%) among patients with RR-TB in Vietnam. FQ 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 patients with RR-TB treated with a 7-drug all-oral STR (using 2 months LZD instead of ethionamide as compared to WHO's STR) (Tack *et al.*, 2021). 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 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 (Migliori and Leung, 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 patients with RR-TB 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 two core drugs, BDQ and FQ, given together. Furthermore, the use of LZD is associated with improved treatment outcomes in patients with RR-TB.

The Vietnam regimen did not include CS as fifth drug, but PZA, a drug with sterilizing activities (van Deun *et al.*, 2018). 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 2 months allowed a shortening of treatment from 9 to 6 months (Fox *et al.*, 1999). In order to avoid neuropsychiatric toxicity due to CS (Court *et al.*, 2021), this drug should be limited to a small number of patients with RR-TB in need of salvage treatment after other treatment options are exhausted.

One third of our patients experienced AEs, and 13 out of 106 patients (12%) experienced SAEs, which is close to 11% SAEs reported in the first global surveillance of AEs among patients with RR-TB 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 a small cohort of 25 patients in Georgia, three 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.*, 2021). While adding LZD to an 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 reversible 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 regi-

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

	Total		Bedaquiline	Levofloxacin	Linezolid	Clofazimine	PZA	Culprits[b] unclear
	N	%	N	N	N	N	N	N
Total	**45**		**2**	**4**	**11**	**3**	**15**	**10**
Serious AE								
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/mm^3)	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								
Alanine aminotransferase enzyme increase (≥1.1 x upper limits of normal)[a]	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[b]								
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

AE, adverse event; PZA, pyrazinamide.
[a] Of 13 alanine aminotransferase enzyme increases, three were mild (one associated with PZA, two culprits unclear), six (all associated with PZA), three (all associated with PZA), one (associated with PZA)
[b] 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.

mens (e.g., 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 has being used only since the end of 2021. Although 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 program.

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 patients with RR-TB in Vietnam. This mSTR resulted in a high 2-month culture conversion and high end-of-treatment success. AEs 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, e.g., four drugs, in the regimen composition or whether it is possible to shorten the duration of LZD to increase the regimen's tolerability.

Declaration of Competing Interest

The authors have no competing interests to declare.

Disclaimer: NNL, DP and CSCM are staff members of the World Health Organization; the authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy or views of the WHO.

CRediT authorship contribution statement

Thi Mai Phuong Nguyen: Conceptualization, Methodology, Investigation, Validation, Project administration, Data curation, Writing – original draft, Writing – review & editing. **Thi Hai Minh Le:** Conceptualization, Methodology, Investigation, Validation, Project administration, Data curation, Writing – review & editing. **Corinne Simone Collette Merle:** Conceptualization, Methodology, Project administration, Writing – review & editing. **Debora Pedrazzoli:** Conceptualization, Methodology, Project administration, Writing – review & editing. **Nhat Linh Nguyen:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Tom Decroo:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Binh Hoa Nguyen:** Conceptualization, Methodology, Investigation, Validation, Supervision, Writing – review & editing. **Thi Thanh Thuy Hoang:** Conceptualization, Methodology, Investigation, Validation, Supervision, Writing – review & editing. **Viet Nhung Nguyen:** Conceptualization, Methodology, Investigation, Validation, Supervision, Writing – review & editing.

Acknowledgments

We would like to acknowledge the great contribution of:

- WHO's Vietnam country office, ShORRT initiative (Short, all-Oral Regimens for Rifampicin-resistant Tuberculosis) of the Special Programme for research and training in Tropical Diseases (TDR) of the WHO for technical and financial support to conduct this study.

The Global Fund for their financial support through the National TB control programme (NTP) to provide diagnosis and treatment service to all rifampicin-resistant tuberculosis patients in Vietnam.

REFERENCES

Aung KJM, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis 2014;18:1180–7.

Avaliani T, et al. Effectiveness and safety of fully oral modified shorter treatment regimen for multidrug-resistant tuberculosis in Georgia, 2019–2020. Monaldi Arch Chest Dis 2021;91:1679.

Borisov S, et al. Surveillance of adverse events in the treatment of drug-resistant tuberculosis: first global report. Eur Respir J 2019;54.

Conradie F, et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med 2020;382:893–902.

Court R, et al. Neuropsychiatric toxicity and cycloserine concentrations during treatment for multidrug-resistant tuberculosis. Int J Infect Dis 2021;105:688–94.

Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. Int J Tuberc Lung Dis 1999;3:S231–79.

Fu L, et al. Insignificant difference in culture conversion between bedaquiline-containing and bedaquiline-free all-oral short regimens for multidrug-resistant tuberculosis. Int J Infect Dis 2021;111:138–47.

Hoffner S, et al. Proficiency of drug susceptibility testing of Mycobacterium tuberculosis against pyrazinamide: the Swedish experience. Int J Tuberc Lung Dis 2013;17:1486–90.

Nhung NV, Hoa NB, Sy DN, et al. 2014 The fourth national anti-tuberculosis drug resistance survey in Viet Nam. Int J Tuberc Lung Dis 2015;19:670–5.

Migliori GB, Leung CC, et al. Abstract book, 52nd World Conference on Lung Health of the International Union against Tuberculosis and Lung Disease (The Union). Int J Tuberc Lung Dis 2021;25:S1–S452.

Mirzayev F, et al. World health organization recommendations on the treatment of drug-resistant tuberculosis, 2020 update. Eur Respir J 2021;57.

Nunn AJ, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. N Engl J Med 2019;380:1201–13.

Tack I, et al. Safety and effectiveness of an all-oral, bedaquiline-based, shorter treatment regimen for rifampicin-resistant tuberculosis in high human immunodeficiency virus (HIV) burden rural South Africa: a retrospective cohort analysis. Clin Infect Dis 2021;73:e3563–71.

van Deun A, et al. Principles for constructing a tuberculosis treatment regimen: the role and definition of core and companion drugs. Int J Tuberc Lung Dis 2018;22:239–45.

World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis, Interim policy guidance. Geneva: World Health Organization; 2013.

World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis: Interim policy guidance. Geneva: World Health Organization; 2014. p. 1–65.

World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2015a.

World Health Organization. Framework for implementation Active tuberculosis drug-safety monitoring and management (aDSM). https://www.who.int/publications/i/item/WHO-HTM-TB-2015.28, 2015b (accessed 17 August 2022).

World Health Organization. WHO Treatment guidelines for drug-resistant tuberculosis 2016 update. https://www.who.int/publications/i/item/9789241549639, 2016a (accessed 17 June 2022).

World Health Organization. Interim Policy - the use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents. Geneva: World Health Organization; 2016b.

World Health Organization. Global tuberculosis report 2017. Geneva: World Health Organization; 2017.

World Health Organization. Rapid Communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis. Geneva: World Health Organisation; 2018.

World Health Organization. Consolidated guidelines on tuberculosis treatment. Geneva: World Health Organisation 2019.

World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020a https://www.who.int/publications/i/item/9789240007048 (Accessed 28 June 2022).

World Health Organization. The ShORRT research package. https://www.who.int/tdr/research/tb_hiv/en/, 2020b (accessed 28 November 2022).

World Health Organization. Global tuberculosis report 2020. Geneva: World Health Organization; 2020c.

World Health Organization. Meeting report of the WHO expert consultation on drug-resistant tuberculosis treatment outcome definitions. Geneva: World Health Organization; 2021a https://www.who.int/publications/i/item/9789240022195 (accessed 17 June 2022).

World Health Organization. Global tuberculosis report 2021b https://www.who.int/publications/i/item/9789240037021 (Accessed 17 June 2022), 2021

World Health Organization. Rapid communication: key changes to the treatment of drug-resistant tuberculosis. https://www.who.int/publications/i/item/WHO-UCN-TB-2022-2, 2022 (Accessed 18 June 2022).

Yatskevich N, et al. Outcomes of modified all-oral 9-month treatment regimen for rifampicin-resistant tuberculosis in Belarus. Eur Resp J 2021;58:OA1600.