International Journal of Infectious Diseases 124 (2022) 81–88

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Programmatic management of rifampicin-resistant tuberculosis with standard regimen in Cameroon: a retrospective cohort study

Christelle Géneviève Jouego[a,b,c,d,*], Tinne Gils[b], Alberto Piubello[e], Vincent Mbassa[a], Albert Kuate[a], Annie Ngono[a], Edwige Belinga[a], Antoine Etoundi[a], Alphonse Tollo[a], Danielle Makondi[a], Emmanuel André[d], Palmer Masumbe[c], Lutgarde Lynen[b], Jürgen Noeske[f], Tom Decroo[b,g]

[a] *Cameroon National Tuberculosis Program (NTP), Mballa 2, BP 15 656 Yaoundé, Cameroun*
[b] *Institute of Tropical Medicine, Department of Clinical Sciences, Unit of HIV and Tuberculosis, Nationalestraat 155, 2000 Antwerp, Belgium*
[c] *University of Yaoundé 1, Biotechnology centre, Molecular Diagnostic and Research Group, 11864 Yaoundé, Cameroon*
[d] *Catholic University of Leuven, Laboratory of Clinical Microbiology, Department of Microbiology, Immunology and Transplantation, UZ Herestraat 49, 3000 Leuven, Belgium*
[e] *Damien Foundation, Boulevard Leopold II 263, 1081 Koekelberg, Brussels, Belgium*
[f] *Independent Consultant, Yaoundé, Cameroon*
[g] *Research Foundation Flanders, Egmontstraat 5, 1000 Brussels, Belgium*

ARTICLE INFO

Article history:
Received 21 April 2022
Revised 19 August 2022
Accepted 9 September 2022

Keywords:
Rr-TB
Fluoroquinolone and second-line injectable resistance
Standard regimen
Cameroon

ABSTRACT

Objectives: To describe treatment outcomes for rifampicin-resistant tuberculosis (Rr-TB) started on standard regimen and the frequency of acquired drug resistance in patients treated using the standard treatment regimen (STR) in Cameroon between 2015-2019.

Methods: This is a retrospective cohort study. Rr-TB patients were initiated on the STR, including a fluoroquinolone (FQ), a second-line injectable drug (SLI), and companion drugs. In case of resistance to fluoroquinolones (FQr) at baseline, FQ, SLI and ethionamide were replaced by bedaquiline, delamanid, and linezolid in a modified treatment regimen (mTR), FQr-mTR. In case of resistance to SLI (SLIr) at baseline, SLI was replaced by linezolid (LZD), SLIr-mTR. Logistic regression and competing risk regression were used to estimate predictors of early (first eight weeks) mortality and overall mortality, respectively.

Results: Of 709 patients started on a standard regimen, treatment success occurred in 84.7% (587/693), 72.7% (8/11) and 100% (10/10) of patients treated with STR, FQr-mTR and SLIr-mTR as final regimens, respectively. Three (0.6%) patients acquired FQr during treatment. Early mortality occurred in 4.1% (29/709) and was associated with being HIV positive, male sex and being underweight. Overall mortality was associated with missing drug-susceptibility testing results at baseline, being HIV positive, age>40 and male sex.

Conclusion: Programmatic management of Rr-TB, with additional second-line drug resistance treated with mTR, resulted in excellent treatment outcomes.

Introduction

Tuberculosis (TB) remains among the top 13 causes of death worldwide. An estimated 10 million people developed TB in 2019. Among those, about half a million people had rifampicin-resistant TB (Rr-TB). Only 38% of those with Rr-TB were enrolled on adequate treatment. Globally, treatment success was 58% for the 2018 Rr-TB cohort (World Health Organization (WHO), 2020).

* Corresponding author: Christelle Géneviève Jouego, National Tuberculosis Program, and Molecular Diagnostic and Research Group, University of Yaoundé 1, B.P. 15 656 Yaoundé, Cameroon.
E-mail addresses: jouego.christelle@gmail.com (C.G. Jouego), tgils@itg.be (T. Gils), anniebissongono@pnlt.cm (A. Ngono), abengmvondo@pnlt.cm (E. Belinga), antoineetoundi@pnlt.cm (A. Etoundi), albertkuate@pnlt.cm (A. Tollo), danieltollo@pnlt.cm (D. Makondi), emmanuel.andre@uzleuven.be (E. André), masumbe.palmer@facsciences-uy1.cm (P. Masumbe), llynen@itg.be (L. Lynen), tdecroo@itg.be (T. Decroo).

https://doi.org/10.1016/j.ijid.2022.09.012

Table 1
Treatment regimens used between 2015-2019 in Cameroon.

Regimen	Indication	Core drug	Companion drug used to protect the core drug	Other companion drugs	Duration
Standard treatment regimen (STR)	Rr-TB without proof of FQr or SLIr	moxifloxacin (400 mg)	kanamycin (1g)	clofazimine (100mg), ethambutol (400mg), pyrazinamide (400mg), protionamide (250mg) isoniazid (300 mg)	9-11 month
FQr-mTR	Rr-TB with FQr, regardless of SLIr	bedaquiline (100mg),	linezolid (600mg)	clofazimine (100mg), pyrazinamide (400mg), isoniazid (300mg) delamanid (50mg)	12-14 month
SLIr-mTR	Rr-TB with SLIr and susceptible to FQ	moxifloxacin (400 mg),	linezolid (600mg)	clofazimine (100mg), ethambutol (400mg), pyrazinamide (400mg), protionamide (250mg), isoniazid (300 mg)	9-11 month

FQ = fluoroquinolone, FQr = fluoroquinolone resistant, FQr-mTR = fluoroquinolone-resistant modified treatment regimen, Rr-TB = rifampicin-resistant tuberculosis, SLIr = second-line injectable resistant, SLIr-mTR = second-line injectable resistant modified treatment regimen, STR = standard treatment regimen.

In Bangladesh a 9–11-month fluoroquinolone (FQ) and second-line injectable (SLI)-based standard treatment regimen (STR) was piloted and resulted in 89% relapse-free treatment success (Van Deun et al., 2010). The regimen relied on a high-dose FQ as core drug, thus with high bactericidal and sterilizing activity, and a SLI to prevent acquired FQ resistance (Decroo et al., 2020b). Ethionamide, ethambutol, isoniazid, clofazimine and pyrazinamide provided either additional bactericidal or sterilizing activity. These findings were much better than those obtained with long Rr-TB treatment regimens, which treated about half of patients successfully (World Health Organization (WHO), 2014a). Nine West and Central African countries, including Cameroon, showed similar results for the 9–11-month STR, also among HIV-positive patients (Trebucq et al., 2018). In other low- and middle-income settings similar outcomes were obtained (Trébucq et al., 2020). A randomized controlled trial concluded that the 9–11-month STR was non-inferior to the long treatment regimen in second-line drug-naive Rr-TB patients (Nunn et al., 2019).

Patients with TB resistant to important components of the 9–11-month STR, such as the FQ and the SLI, should not be treated with the STR. Usually, such patients are treated with long Rr-TB treatment regimens. FQr/Rr-TB can also be treated with BPaL, a 6-8 month regimen that contains bedaquiline (BDQ), pretomanid and LZD (Conradie et al., 2020). This regimen has been approved by the World Health Organization (WHO) for the treatment of FQr/Rr-TB (World Health Organization, 2022). However, pretomanid is not yet widely available (Gomez et al., 2021).

There are only few experiences with STR for TB resistant to second-line drugs. It therefore remains relevant to study how to treat Rr-TB also resistant to second line TB drugs with drugs that are available. In Bangladesh, BDQ successfully replaced the FQ in the STR for a small cohort of patients with Rr-TB resistant to FQ and susceptible to SLI (Decroo et al., 2021). Another small cohort of patients with treatment failure after the 9–11-month STR was successfully treated with a BDQ-based modified TR in Niger (Piubello et al., 2020). In the same setting, LZD effectively replaced SLI in patients with a contra-indication for treatment with SLI (Souleymane et al., 2021).

No study assessed, among patients starting the 9–11-month STR or modified TR, the effect of second-line drug susceptibility testing (SL DST) at baseline. Moreover, for patients with treatment failure most studies do not correct the outcomes of Rr-TB treatment using the outcomes of the follow-up regimen. We therefore share experiences from a nationwide cohort from Cameroon. We used standard regimens based on SL DST for the management of Rr-TB. This cascade approach was used to safeguard BDQ for a minority of patients with baseline resistance to FQ, or for those with failure or relapse after a first 9–11-month STR, as described previously (Decroo et al., 2020a). All diagnosed Rr-TB patients were systematically initiated on the 9–11-month STR, while the sputum sample was sent for second-line probe assay (SL-LPA) and phenotypic drug susceptibility testing (pDST) (Table 1). Upon availability of the results, patients with FQr/Rr-TB, including those with resistance to both FQ and SLI, were switched to a novel 12–14-month standard BDQ/delamanid (DLM)-based (FQr-mTR). This regimen used the same structure as the STR, with BDQ, DLM and LZD replacing the FQ, the SLI, and also ethionamide (Ministry of public health of Cameroon, 2004). Patients with Rr-TB resistant to SLI (SLIr/Rr-TB), but susceptible to FQ, were switched to the same modified TR used in Niger, a 9–11-month standard SLIr-mTR, with LZD replacing the SLI (Piubello et al., 2020). SL DST was thus used to treat Rr-TB patient after starting treatment empirically. In previous publications, (Decroo et al., 2021; Piubello et al., 2020), SL DST results became available à posteriori. Data were used for research purposes, or in case of failure or relapse. But SL DST results did not guide clinical decisions during a first Rr-TB treatment, as this was the case in the Cameroonian context. While availability of SL DST results guides this process, access to SL DST is challenging in Cameroon and similar settings. The impact of SL DST availability on mortality after this cascade approach also has not yet been studied.

We conducted a retrospective cohort study of all Rr-TB patients initiated on either the STR or a modified TR between 2015-2019. We describe the frequency of acquired drug resistance during STR, and report definitive treatment outcomes, i.e. outcomes obtained after regimen switch for those who experienced treatment failure on the STR. We also estimate predictors, including availability of SL DST results, of early (first eight weeks) mortality and mortality overall.

Materials and methods

Design and study population

This retrospective cohort study included all patients diagnosed with Rr-TB on Xpert MTB/RIF® (Cepheid, Sunnyvale, CA, USA; Xpert MTB/RIF) between 2015-2019 in Cameroon. Patients who started treatment were followed up at least until the end of the treatment course (9 to 14 month).

Setting

In Cameroon, in 2019, the estimated TB and Rr-TB incidence was 179 and 3.6 per 100 000 population, respectively. The coun-

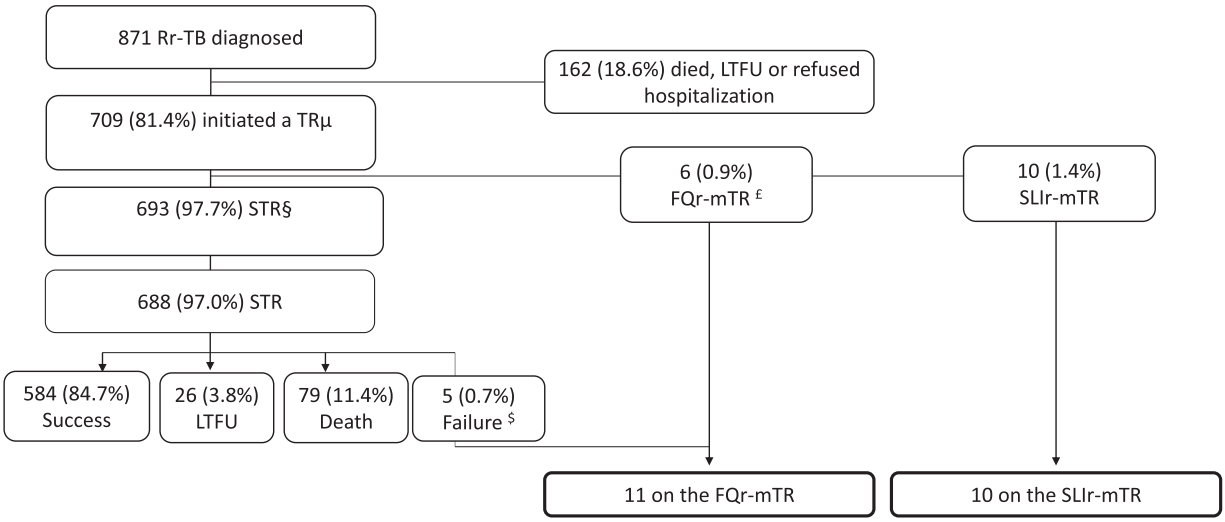

Fig 1. Cascade of regimens, considering second-line drug susceptibility testing results and outcomes with a first rifampicin-resistant TB treatment regimen.
FQr-mTR= fluoroquinolone-resistant modified treatment regimen; LTFU=lost to follow-up; Rr-TB=rifampicin-resistant tuberculosis with or without additional resistance to second-line injectable drugs, SLIr-mTR= second-line injectable resistant modified treatment regimen; SL DST= second-line drug susceptibility testing; STR=standard treatment regimen; TR=treatment regimen.
£ 6 started the FQr-mTR at baseline, among which two patients were relapse cases of Rr-TB with susceptible SL DST results.
$ All the 5 patients with treatment failure were switched to the FQr-mTR.
§ 210 (29.6) patients with missing SL DST results included.
μ while baseline sample was sent for SL DST for all patients.

try registered 7400 TB related deaths during the same period (World Health Organization (WHO), 2020). About 27% of young adults with TB were HIV co-infected (World Health Organization (WHO), 2020). The National TB Program provide Rr-TB care in ten treatment centres (including one in a prison) spread over the country.

Rr-TB diagnosis

Twenty-eight classic Xpert MTB/RIF machines served as point of care molecular diagnostic tools in the country. Patients at risk for paucibacillary TB (patients living with HIV, children <5 years old) or Rr-TB (treatment failure or relapse after a first-line regimen, Rr-TB contacts) as well as prisoners and foreigners from countries with a high prevalence of second-line TB drug resistance were eligible for Xpert MTB/RIF testing. For each patient diagnosed with Rr-TB on Xpert MTB/RIF, sputum samples were systematically sent for SL-LPA testing, culture, and pDST on solid culture media in one of the two accredited reference laboratories of the country (biosafety level 3) following clear distribution. Upon notification of Rr-TB, the patient was contacted by the site monitoring health care provider and linked to the nearest treatment centre where counselling and pre-therapeutic work-up were performed.

Rr-TB treatment

Cameroon uses a cascade approach for the management of Rr-TB (Decroo et al., 2020a). Each regimen uses no more than one core drug, and no patient was treated with long regimens. Patients with FQ-susceptible Rr-TB are treated with a STR. BDQ is safeguarded for the treatment of FQr/Rr-TB. All Rr-TB patients have their sputum sample sent for SL-LPA and pDST and are then started on the STR. For children, moxifloxacin was replaced by levofloxacin. Upon reception of SL-LPA or pDST results, the patient's regimen was adapted to fit the resistance profile. Patients with FQr/Rr-TB started the 12–14-month FQr-mTR regardless of the previous treatment episode duration (Ministry of public health of Cameroon, 2004). Patients with SLIr/Rr-TB started the 9–11-month SLIr-mTR. Patients without SL-LPA or pDST results continued the STR.

Each Rr-TB patient was hospitalized during the intensive phase (4–6 month) for directly observed treatment and disease education as per the standard of care in the country. During the continuation phase, monthly sputum collection appointments and drug refill were given to patients. Additional appointments were given at six and 12 months after treatment completion (month 15 & month 21, respectively) for clinical and bacteriological assessment of relapse.

Grading of the severity of adverse drug events (ADEs) was done using a standard approach in each treatment centre following the 2008 National AIDS and Hepatitis Research Agency scale described in the UNION guidelines (Piubello et al., 2018).

Variables and definitions

The World Health Organization (WHO) definitions were used for cure, treatment completion, death and loss to follow-up (World Health Organization, 2014b). Treatment failure was defined as lack of conversion on smear and/or on culture by the end of the intensive phase, or bacteriological reversion in the continuation phase. Early mortality on treatment was defined as death of a TB patient during the first eight weeks after treatment initiation (Bigna et al., 2015). However, when patients switched from one regimen to another due to resistance identified in the baseline sample or in the failure sample, we considered the outcome of the second episode with modified TR as definitive outcome. These patients thus had two treatment courses, each with a treatment outcome, but were considered once during analysis. We considered resistance as acquired when present in a failure sample but absent at baseline. We could not correct for re-infection as we could not distinguish the strain identity on the failure strain from the baseline one. The rate of acquired FQr was calculated among all with proof of FQ susceptibility at baseline. A high bacillary load was a baseline sputum smear result of 2+ or more, and a low bacillary load was either scanty or 1+. Susceptibility to FQ or SLI was considered unknown when there were no results reported for SL-LPA and/or pDST. In this case, baseline SL DST results were considered missing. Time to treatment initiation was calculated as the

Table 2
Baseline characteristics and definitive outcomes by initial treatment regimen for rifampicin-resistant TB patients starting first treatment episode between 2015-2019.

	Total		STR		SLIr-mTR		FQr-mTR	
	N	%	N	%	N	%	N	%
Total	**709**	**100**	**693**	**97.7**	**10**	**1.4**	**6**	**0.9**
Gender								
Female	254	35.8	247	35.6	4	40.0	3	50.0
Male	455	64.2	446	64.4	6	60.0	3	50.0
Median time to treatment initiation (days)	12 [7-23]		12 [7-23]		15 [11-61]		2 [1-8]	
Median age in years [IQR]	35 [27-44]		35 [27-44]		40 [26-42]		39 [28-51]	
Age								
0-20	68	9.6	68	9.8	0	0.0	0	0.0
21-40	404	57.0	395	57.0	6	60.0	3	50.0
41-90	237	33.4	230	33.2	4	40.0	3	50.0
Patient type								
New case	193	27.2	195	27.3	4	40.0	1	16.7
Failure + relapse	481	67.8	482	67.5	5	50.0	4	66.6
Unknown	35	5.0	37	5.2	1	10.0	1	16.7
BMI (kg/m²)								
0-18	255	36.0	259	36.2	1	10.0	2	33.3
>18	420	59.2	421	59.0	8	80.0	4	66.7
Missing	34	4.8	34	4.8	1	10.0	0	0.0
HIV status								
Negative	489	69.0	493	69.0	6	60.0	3	50.0
Positive	213	30.0	214	30.0	4	40.0	3	50.0
Unknown	7	1.0	7	1.0	0	0.0	0	0.0
Baseline bacillary load								
High[a]	436	61.5	440	61.6	6	60.0	6	100
Low[b]	125	17.6	126	17.7	2	20.0	0	0.0
Negative	148	20.9	148	20.7	2	20.0	0	0.0
Baseline 2nd line DST								
Available	499	70.4	483	69.7	10	100	6	100
Missing	210	29.6	210	30.3	0	0.0	0	0.0
ADEs								
Life threatening	0	0.0	0	0.0	0	0.0	0	0.0
Severe	15	2.1	15	2.2	0	0.0	0	0.0
Mild & moderate	515	72.6	502	72.4	9	90.0	4	66.7
None reported	179	25.3	176	25.4	1	10.0	2	33.3
Definitive outcome[c]								
Cured	459	64.7	445	64.2	9	90.0	5	83.3
Treatment completed	143	20.2	142	20.5	1	10.0	0	0.0
Treatment failure	2	0.3	1	0.1	0	0.0	1	16.7
Death	79	11.1	79	11.4	0	0.0	0	0.0
LTFU	26	3.7	26	3.8	0	0.0	0	0.0

a = sputum smear results 2+ or more, b = sputum smear results scanty or 1+, c = definitive outcome is the outcome of the last treatment regimen for all the patients. For five patients started on the standard treatment regimen and switched to the FQr-mTR after treatment failure, the later outcome is reported. ADEs = adverse drug events, BMI = body mass index, DST = drug susceptibility testing, FQr-mTR = fluoroquinolone-resistant modified treatment regimen, STR = standard treatment regimen, HIV = human immunodeficiency virus, IQR = interquartile range, LTFU = loss to follow-up, Rr-TB = rifampicin-resistant tuberculosis, SLIr-mTR = second-line injectable resistant modified treatment regimen.

difference in days between the day the Xpert MTB/RIF result was available and the date of treatment initiation. Time to definitive outcome was the total time between the date of treatment initiation of the first treatment episode and date of outcome of the last episode.

Data management and analysis

Patient data were written on a treatment card by the attending health care provider using a unique identification code per patient and per centre. On a quarterly basis, a trained data clerk entered these data in an electronic database. Data were verified by the National TB Program supervision team during their periodic visits. For this study all identifiers were removed. Treatment registers and electronic laboratories databases were reviewed to retrieve missing information and solve discrepancies.

Analysis was done using R Core Team (Core Development Team, 2020). Baseline demographics and clinical characteristics were presented using summary statistics (proportions, medians, interquartile ranges (IQR)). Logistic regression was used to estimate predictors of early mortality. For the multivariable models we first constructed a saturated model. Stepwise variables were removed until all remaining variables had a p-value $\leq$0.05. We used competing risk analysis regression to predict mortality, with lost-to-follow-up (LTFU) and treatment failure (versus death as competing risks). We present odds ratios (OR), and adjusted odds ratios (aOR), subgroup hazard ratio (SHR) and adjusted subgroup hazard ratio (aSHR) with their 95% confidence intervals (95% CI).

Table 3
Predictors of early mortality among rifampicin-resistant TB patients starting first treatment episode between 2015-2019.

	Total	Early mortality		OR	95%CI	aOR	95%CI
	N	N	%				
Total	**709**	**29**	**4.1**				
Gender							
Female	254	5	1.9	1		1	
Male	455	24	5.3	2.77*	[1.04,7.35]	4.06**	[1.41,11.64]
Age in years						NS	
0-20	68	1	1.4	0.44	[0.05,3.48]		
21-40	404	13	3.2	1			
41-90	237	15	6.3	2.03	[0.94,4.34]		
Patient type						NS	
New case	193	11	5.7	0.60	[0.27,1.31]		
Failure + relapse	481	17	3.5	1			
Unknown	35	1	2.8	0.48	[0.06,3.89]		
BMI (kg/m²)							
0-18	255	14	5.5	1		1	
>18	420	8	1.9	0.33*	[0.13,0.80]	0.34*	[0.13,0.87]
Missing	34	7	20.5	4.46**	[1.65,12.01]	6.98**	[2.32,20.98]
HIV status							
Negative	489	10	2.0	1		1	
Positive	213	18	8.4	4.42***	[2.00,9.74]	7.30***	[3.04,17.55]
Unknown	7	1	14.3	7.98	[0.87,72.60]	7.12	[0.71,71.24]
Baseline bacillary load (smear)						NS	
High[a]	436	17	3.8	1			
Low[b]	125	7	5.6	1.46	[0.59,3.60]		
Negative	148	5	3.4	0.86	[0.31,2.37]		
Baseline 2nd Line DST							
Available	499	14	2.8	1		1	
Missing	210	15	7.1	2.66*	[1.26,5.62]	2.20	[0.99,4.88]

* $p < 0.05$,
** $p < 0.01$,
*** $p < 0.001$.a sputum smear results 2+ or more; b sputum smear results scanty or 1+ aOR = adjusted odds ratio, BMI = body mass index, CI = confidence interval, DST = drug susceptibility testing, HIV = human immunodeficiency virus, NS = Not significant, OR = odds ratio.

Ethics

This study received approval from the Cameroon Ethic Committee: 2021/12/1783/L/CNERSH/SP and from the institutional review board of the Institute of Tropical Medicine: 1461/21.

Results

From 1st January 2015 to 31st December 2019, 871 patients were diagnosed with Rr-TB across the country, of whom 81.4% (709) started treatment. The remaining 18.6% (162) were not initiated on treatment, either because they died before getting to a treatment center, were LTFU after diagnosis or refused to be hospitalized for treatment initiation (Figure 1). The median age of patients was 35 [IQR:27-44] years and the median time to treatment initiation was 12 [IQR:7-23] days.

About a third (27.2%; 193) of Rr-TB treatment courses was provided to new TB patients (with a first TB episode), 36.0% (255) to patients with underweight and 30.0% (213) to patients co-infected with HIV. A high bacillary load was recorded for 61.5% (436).

709 patients started a baseline TR among which 693 (97.7%) the STR, ten (1.4%) the SLIr-mTR and six (0.9%) the FQr-mTR (Table 2). Five patients were recorded as treatment failure during the STR and were switched to the FQr-mTR. Among the 709 patients who started a TR, with or without baseline DST, 84.9% experienced treatment success (Table 2) and two (0.3%) with treatment failure as definitive treatment outcome. One patient with treatment failure had FQr-TB on the failure sample, was switched to the FQr-mTR and died later before we could initiate a salvage regimen. The second received FQr-mTR at baseline and was LTFU before we could build a salvage regimen (Rr-TB regimen without likely fully active core drug) (Van Deun et al., 2018). BDQ DST testing was not available during the study period. Of the 210 patients with unavailable baseline SL DST, 80.0% (169) were treated successfully, 16.0% (33) died, 4.0% (eight) were lost to follow-up.

Among patients treated with the STR (688, 97.0%), SLIr-mTR (10, 1.4%), and FQr-mTR (11, 1.6%) as final regimen, respectively 587 (84.7%), 10 (100%) and 8 (72.7%) were either cured or completed treatment. 78 (11.3%), 0 (0.0%) and 1 (9.1%) died during treatment; 26 (3.8%), 0 (0.0%) and 1 (9.1.%) were lost to follow-up; and 0 (0.0%), 0 (0.0%) and two (18.2%) experienced treatment failure. FQr was acquired in 0.6% (3/483) patients with initially FQ-susceptible/Rr-TB and treated with the STR.

Severe ADEs were diagnosed during 2.1% (15, all STR) of treatment courses. Eight patients were diagnosed with severe ototoxicity, six with severe nephrotoxicity and three with severe hepatotoxicity. No life-threatening ADE was reported (Table 2).

Early mortality was independently associated with male sex (aOR = 4.06, 95% CI:1.41-11.64), having a BMI of more than 18kg/m^2(aOR = 0.34, 95%CI: 0.13-0.87), and being HIV positive (aOR = 7.30, 95%CI: 3.04-17.55). Having missing SL DST was not associated with early mortality (aOR = 2.20, 95%CI:0.99-4.88) (Table 3). Using the competing risk regression analysis, overall mortality was associated with male sex (aSHR = 1.94, 95%CI:1.10-3.40), being HIV positive (aSHR = 4.27, 95%CI:2.56,7.10), and missing SL DST result (aSHR = 1.65, 95%CI:1.04-2.60) (Table 4). Among those cured or treatment completed, 16.1% (97/602) had documented data on post-treatment follow-up and were declared having relapse-free success.

Discussion

Our study included a large nationwide cohort of Rr-TB patients who initiated a treatment regimen in Cameroon over a five-year

Table 4
Competing risk regression for mortality among rifampicin-resistant TB patients starting first treatment episode between 2015-2019.

	Total	Overall mortality		SHR	95%CI	aSHR	95%CI
	N	N	%				
Total	709	79	11.1				
Gender							
Female	254	21	26.6	1		1	
Male	455	58	73.4	1.57	[0.95,2.59]	1.94*	[1.10,3.40]
Age in years							
0-20	68	1	1.2	0.15	[0.02,1.15]	0.20	[0.02,1.61]
21-40	404	36	45.6	1		1	
41-90	237	42	53.2	2.05**	[1.31,3.20]	1.62*	[1.01,2.60]
Patient type						NS	
New case	193	24	30.4	0.77	[0.47,1.26]		
Failure + relapse	481	48	60.8	1			
Unknown	35	7	8.9	1.58	[0.69,3.60]		
BMI (kg/m²)							
0-18	255	32	40.5	1		1	
>18	420	36	45.6	0.67	[0.42,1.09]	0.65	[0.40,1.04]
Missing	34	11	13.9	3.15**	[1.55,6.41]	3.32**	[1.56,7.08]
HIV status							
Negative	489	30	37.9	1		1	
Positive	213	47	59.5	3.90***	[2.47,6.16]	4.27***	[2.56,7.10]
Unknown	7	2	2.5	5.67*	[1.26,25.35]	6.27*	[1.49,26.41]
Baseline bacillary load (smear)						NS	
High[a]	436	43	54.4	1			
Low[b]	125	18	22.8	1.50	[0.86,2.61]		
Negative	148	18	22.8	1.24	[0.72,2.16]		
Baseline 2nd Line DST							
Available	499	46	58.2	1		1	
Missing	210	33	41.7	1.77*	[1.13,2.77]	1.65*	[1.04,2.60]

* $p < 0.05$,
** $p < 0.01$,
*** $p < 0.001$.Lost-to-follow up and treatment failure were considered competing risks a sputum smear results 2+ or more; b sputum smear results scanty or 1+, aSHR = adjusted subgroup hazard ratio, BMI = body mass index, CI = confidence interval, DST = drug susceptibility testing, HIV = human immunodeficiency virus, NS = Not significant, SHR = subgroup hazard ratio.

period. In addition, this study is among the first assessing the effect of the availability of SL DST on definitive outcomes of Rr-TB treatments.

Treatment success among patients treated with the STR was 84.7%. This result is consistent with findings from Niger (Piubello et al., 2020), Burundi (Ciza et al., 2020), Rwanda (Ngabonziza et al., 2020) and similar to results from a multi-country African study (Trebucq et al., 2018), including data from 176 patients from the January 2013-March 2015 Cameroon cohort. Five patients had treatment failure under the STR. FQ resistance was acquired in 0.6% of patients with initially FQ-susceptible Rr-TB and treated with the STR or SLIr-mTR. While 0.6% may seem low, it is still higher than the 0.1% reported for rifampicin, the first-line core drug (Loutet et al., 2018). Even at 0.1% it only took a few decades of widespread rifampicin use before Rr-TB increased to a level that impedes empiric use in patients for a first time diagnosed with TB (Wright et al., 2009). Our estimate of acquired resistance may be an overestimation as it was not corrected for re-infection. On the other hand, SL-LPA may miss some resistance, e.g. due to mutations not picked up by the LPA bands, especially when heteroresistance (presence of both wild type and resistant bacilli) is present (Rigouts et al., 2019).

During the past five years, for 70.4% (499) of all Rr-TB patients, baseline SL DST results were available. Among 210 patients with missing SL DST results at treatment initiation, treatment success was 80.0% (169). We found that missing SL DST result was associated with overall mortality (aSHR = 1.65, 95%CI:1.04-2.60) in competing risk analysis but not with early mortality (aOR = 2.20, 95%CI:0.99-4.88) in logistic regression. This suggests that undetected resistance contributed to overall death in this study population and shows the importance of SL DST availability during Rr-TB treatment in order to guide clinical decision and consequent regimen composition.

All 10 patients finally treated with the SLIr-mTR had a favourable treatment outcome. In Niger a similar TR was used with good outcomes (Piubello et al., 2020). Whether LZD can effectively provide the same early bactericidal and resistance preventing effect as SLI remains to be confirmed in larger cohorts.

Of 11 patients with the FQr-mTR as final regimen, eight had a favourable treatment outcome. Two patients had treatment failure and one was loss to follow-up. The FQr-mTR relies on BDQ as core drug and DLM and LZD for bactericidal activity. In a small Bangladesh FQr/Rr-TB cohort BDQ replaced the FQ and was combined with a SLI to show good results, suggesting that BDQ can be used as core drug in case it is well protected (Decroo et al., 2021). However, recent reports show relatively high levels of acquired BDQ resistance (between 2.3-5.7%) after the use of all-oral regimens (Ismail et al., 2021; Nimmo et al., 2020), especially in patients with FQr/Rr-TB, and when SLI were not adding resistance prevention (Tahseen et al., 2021). In Ismael et al, baseline resistance to BDQ was also reported in about 3.8% and was associated with previous exposure, while in Nimmo et al., 5% of patients had variants of the Rv0678 gene at baseline (Ismail et al., 2021; Nimmo et al., 2020). To make matters worse, at present, access to BDQ DST is poor or non-existent in most high TB burden countries. Data from the NIX study indicate that patients with base-

line resistance to FQs may be treated successfully with BDQ, pretomanid and LZD containing regimen if not previously exposed to these drugs (Conradie et al., 2020). Still, it remains uncertain how to manage patients who acquired resistance to FQs and/or BDQ under the all-oral regimens (Ismail al., 2021b). Our FQr-mTR results are better than those reported globally for the treatment of FQr/Rr-TB. In 2019, only 47% of patients with FQr/Rr-TB were treated successfully (World Health Organization, 2020). The higher frequency of success found in our FQr-mTR cohort can probably be explained using "new" drugs, such as BDQ, DLM, and LZD not used in the baseline regimen.

Cameroon will implement and evaluate a novel all-oral TR, with BDQ replacing the SLI, thus combining both FQ and BDQ in the same regimen. Its evaluation will prioritize the assessment of treatment failure, relapse after cure or treatment completion, and the rate of acquired resistance to both core drugs. How to treat those with treatment failure or relapse after such all-oral regimen is yet unclear. At present, there are no guidelines on how to treat TB resistant to rifampicin and resistant or exposed to both second-line core drugs, FQ and BDQ (WHO, 2020).

Severe ADEs were detected in 2.1% (15) of the Cameroon 2015-2019 Rr-TB cohort. Of 15 patients with severe ADE, eight had ototoxicity. Similar results were found in Niger (3.2%) (Piubello et al., 2020).

In our cohort 30% were HIV co-infected. People living with HIV were at a higher risk of early mortality and mortality overall which is coherent with findings from other Rr-TB cohorts (Bigna et al., 2015; Edessa et al., 2021; Kuaban et al., 2008). Patients were treated with antiretroviral therapy. Baseline CD4 count and viral load data were not available, which hampered interpretation of HIV-related mortality. Advanced HIV disease (AHD) is common in sub-Saharan Africa; between 32% and 71% of patients present to care with AHD (Calmy et al., 2018; Ndlovu et al., 2020). The WHO recommended package of care for detection of advanced HIV and opportunistic infections, including TB screening with urine TB-LAM, could be implemented to reduce mortality (World Health Organization, 2017).

The main strength of this study is the use of a large national cohort of patients under programmatic conditions. All patients diagnosed with Rr-TB between 2015-2019 were included. Our findings therefore represent the reality of Rr-TB care in Cameroon. Despite the retrospective nature of the study, we had only few variables with missing data except baseline SL DST. Missing values were updated after consultation of the patient files and the databases of the two national reference laboratories. This work also has some limitations. First, about one in five patients diagnosed with Rr-TB by the TB program were not put on treatment. Second, post-treatment follow-up was incomplete, which impeded the assessment of relapse after cure. Third, the fact that all patients were hospitalized during the intensive phase and treatment was directly observed has likely contributed to the good outcomes. Finally, the cohorts treated with either the FQr-mTR or the SLIr-mTR were small. More studies reporting the proportion of acquired drug resistance to core drugs and treatment options after failure or relapse of the baseline regimen are needed. Nevertheless, our findings show that in settings with a low prevalence of resistance to second-line TB drugs the bulk of Rr-TB patients can be treated with the highly effective STR, while good outcomes can be obtained by using modified TR guided by results of SL DST for those with additional resistance to key second-line TB drugs and not eligible for the STR.

Conclusion

In Cameroon, a country with a low prevalence of resistance to second-line TB drugs, the bulk of Rr-TB patients were successfully treated with the STR. Patients with baseline resistance to either FQ or SLI and those with treatment failure after the STR were successfully switched to a modified TR, and most of them were treated successfully. We show the importance of SL DST results to prevent overall mortality. Challenges to be addressed include pre-treatment attrition, assuring timely SL DST including BDQ for all patients starting all-oral Rr-TB treatment, and adequate management of advanced HIV disease.

Funding Source

This work was supported by the Belgian Development Cooperation [grant number: 0 410 057 701, 2021].

Ethical Approval statement

This study received approval from the Cameroon Ethic Committee (2021/12/1783/L/CNERSH/SP) and from the institutional review board of the Institute of Tropical Medicine (1461/21).

Author contributions

CGJ: (corresponding author) Conception and design of the study, acquisition of data, analysis, and interpretation of data, drafting the article, final approval of the version to be submitted.

TD, TG: Design of the study, analysis, and interpretation of data, revising it critically for important intellectual content, final approval of the version to be submitted.

VM, AE, AK, AN, AT, DM, EB: Acquisition of data, final approval of the version to be submitted.

AP, EA, JN, LL, PM: Design of the study, revising critically for important intellectual content, final approval of the version to be submitted.

All authors read and approved the final version to be submitted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are grateful to Mrs Kembou Mireille, Siewe Octavie, Enoka Marie-Francoise, Neh Angela and Mr Tchualack Ghislain in assisting to retrieve key information from patient and laboratory registers. We thank the Ministry of Public Health of Cameroon, all the NTP coordination teams, and the reference laboratories for the continuous support. Thank you to reviewers for their comments which greatly improve our manuscript. A special thanks to all the patients who participated in this program evaluation study.

References

Bigna JJR, Noubiap JJN, Agbor AA, Plottel CS, Billong SC, Ayong APR, et al. Early mortality during initial treatment of tuberculosis in patients co-infected with HIV at the Yaoundé Central Hospital, Cameroon: An 8-year retrospective cohort study (2006-2013). PLoS ONE 2015;10:1–13. doi:10.1371/journal.pone.0132394.

Calmy A, Ford N, Meintjes G. The Persistent Challenge of Advanced HIV Disease and AIDS in the Era of Antiretroviral Therapy. Clinical Infectious Diseases 2018;66:S103–5. doi:10.1093/cid/cix1138.

Ciza F, Gils T, Sawadogo M, Decroo T, Roggi A, Piubello A, et al. Course of adverse events during short treatment regimen in patients with rifampicin-resistant tuberculosis in burundi. Journal of Clinical Medicine 2020;9:1–15. doi:10.3390/jcm9061873.

Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM, et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. New England Journal of Medicine 2020;382:893–902. doi:10.1056/nejmoa1901814.

Core Development Team R. A Language and Environment for Statistical Computing, 2. R Foundation for Statistical Computing; 2020 https://www.R-project.org.

Decroo T, Jai K, Aung M, Hossain MA, Gumusboga M, Ortuno-Gutierrez N, et al. Bedaquiline can act as core drug in a standardized treatment regimen for fluoroquinolone-resistant rifampicin-resistant tuberculosis. European Respiratory Journal 2021. doi:10.1183/13993003.02124-2021.

Decroo T, de Jong BC, Piubello A, Lynen L, Van Deun A. Tuberculosis treatment: one-shot approach or cascade of regimens? 2020a. 10.1016/S2213-2600(19)30473-4.

Decroo T, Kya Jai Maug A, Hossain MA, Uwizeye C, Gumusboga M, Demeulenaere T, et al. Injectables' key role in rifampicin-resistant tuberculosis shorter treatment regimen outcomes. PLoS ONE 2020b;15. doi:10.1371/journal.pone.0238016.

Van Deun A, Decroo T, Piubello A, De Jong BC, Lynen L, Rieder HL. Principles for constructing a tuberculosis treatment regimen: The role and definition of core and companion drugs. International Journal of Tuberculosis and Lung Disease 2018;22:239–45. doi:10.5588/ijtld.17.0660.

Van Deun A, Maug AKJ, Salim MAH, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. American Journal of Respiratory and Critical Care Medicine 2010;182:684–92. doi:10.1164/rccm.201001-0077OC.

Edessa D, Adem F, Hagos B, Sisay M. Incidence and predictors of mortality among persons receiving second-line tuberculosis treatment in sub-Saharan Africa: A meta-analysis of 43 cohort studies. Plos One 2021;16. doi:10.1371/journal.pone.0261149.

Gomez GB, Siapka M, Conradie F, Ndjeka N, Garfin AMC, Lomtadze N, et al. Cost-effectiveness of bedaquiline, pretomanid and linezolid for treatment of extensively drug-resistant tuberculosis in South Africa, Georgia and the Philippines. BMJ Open 2021;11:51521. doi:10.1136/bmjopen-2021-051521.

Ismail NA, Omar SV, Moultrie H, Bhyat Z, Conradie F, Enwerem M, et al. Assessment of epidemiological and genetic characteristics and clinical outcomes of resistance to bedaquiline in patients treated for rifampicin-resistant tuberculosis: a cross-sectional and longitudinal study. The Lancet Infectious Diseases 2021. doi:10.1016/s1473-3099(21)00470-9.

Kuaban C, Pefura E, Bava DOI. Early Mortality in New Patients on Treatment for Smear Positive Pulmonary Tuberculosis in Yaounde-Cameroon. Health Science Diseases 2008;12:1–26.

Loutet MG, Davidson JA, Brown T, Dedicoat M, Thomas HL, Lalor MK. Acquired resistance to antituberculosis drugs in England, wales, and Northern Ireland, 2000–2015. Emerging Infectious Diseases 2018;24:524–33. doi:10.3201/eid2403.171362.

Ministry of public health Republic of Cameroon. Programme national de lutte contre la tuberculose: Guide de prise en charge de la tuberculose chez l'enfant. 2020th ed. 2004.

Ndlovu Z, Burton R, Stewart R, Bygrave H, Roberts T, Fajardo E, et al. Framework for the implementation of advanced HIV disease diagnostics in sub-Saharan Africa: programmatic perspectives. The Lancet HIV 2020;7:e514–20. doi:10.1016/S2352-3018(20)30101-6.

Ngabonziza JCS, Habimana YM, Decroo T, Migambi P, Dushime A, Mazarati JB, et al. Reduction of diagnostic and treatment delays reduces rifampicin-resistant tuberculosis mortality in Rwanda. International Journal of Tuberculosis and Lung Disease 2020;24:329–39. doi:10.5588/ijtld.19.0298.

Nimmo C, Millard J, Brien K, Moodley S, Van Dorp L, Lutchminarain K, et al. Bedaquiline resistance in drug-resistant tuberculosis HIV co-infected patients. European Respiratory Journal 2020;55. doi:10.1183/13993003.02383-2019.

Nunn AJ, Phillips PPJ, Meredith SK, Chiang C-Y, Conradie F, Dalai D, et al. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. New England Journal of Medicine 2019:1201–13. doi:10.1056/nejmoa1811867.

Piubello A, Aït-khaled N, Caminero J, Chiang C-Y, Dlodlo R, Fujiwara PI, et al. Field guide for the management of drug-resistant tuberculosis, September. Paris, France: THE UNION; 2018.

Piubello A, Bassirou Souleymane M, Hassane-Harouna S, Yacouba A, Lempens P, Mohamed Assao-Neino M, et al. Management of multidrug-resistant tuberculosis with shorter treatment regimen in Niger: Nationwide programmatic achievements. Respiratory Medicine 2020;161. doi:10.1016/j.rmed.2019.105844.

Rigouts L, Miotto P, Schats M, Lempens P, Cabibbe AM, Galbiati S, et al. Fluoroquinolone heteroresistance in Mycobacterium tuberculosis: detection by genotypic and phenotypic assays in experimentally mixed populations. Scientific Reports 2019;9. doi:10.1038/s41598-019-48289-9.

Souleymane MB, Piubello A, Lawan IM, Hassane-Harouna S, Assao-Neino MM, Soumana A, et al. High rifampicin-resistant TB cure rates and prevention of severe ototoxicity after replacing the injectable by linezolid in early stage of hearing loss. European Respiratory Journal 2021;57. doi:10.1183/13993003.02250-2020.

Tahseen S, Van Deun A, De Jong BC, Decroo T. Second-line injectable drugs for rifampicin-resistant tuberculosis: Better the devil we know? Journal of Antimicrobial Chemotherapy 2021;76:831–5. doi:10.1093/jac/dkaa489.

Trébucq A, Decroo T, Van Deun A, Piubello A, Chiang CY, Koura KG, et al. Short-course regimen for multidrug-resistant tuberculosis: A decade of evidence. Journal of Clinical Medicine 2020;9:55. doi:10.3390/jcm9010055.

Trebucq A, Schwoebel V, Kashongwe Z, Bakayoko A, Kuaban C, Noeske J, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. International Journal of Tuberculosis and Lung Disease 2018;22:17–25. doi:10.5588/ijtld.17.0498.

World Health Organization (WHO). Consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Geneva: Online annexes; 2020.

. Rapid Communication: Key changes to the treatment of drug-resistant tuberculosis. World Health Organization; 2022. p. 6.

. Global Tuberculosis Report 2020, 4. 2020th ed. Geneva: WHO; 2020.

World Health Organization (WHO). Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. 2017.

World Health Organization (WHO). Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. 20 Avenue Appia, 1211 Geneva 27, Switzerland: 2014a.

World Health Organization (WHO). Definitions and reporting framework for tuberculosis –2013 revision. WHO/HTM/TB. 20 Avenue Appia, 1211 Geneva 27, Switzerland: 2014b.

Wright A, Zignol M, Van Deun A, Falzon D, Gerdes SR, Feldman K, et al. Epidemiology of antituberculosis drug resistance 2002-07: an updated analysis of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. WwwThelancetCom 2009;373. doi:10.1016/S0140.