Research Paper

Outcomes of a nine-month regimen for rifampicin-resistant tuberculosis up to 24 months after treatment completion in nine African countries

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ABSTRACT

Background: Treatment outcomes of the shorter regimen for rifampicin-resistant tuberculosis are not completely established. We report on these outcomes two years after treatment completion among patients enrolled in an observational cohort study in nine African countries.

Methods: 1,006 patients treated with the nine-month regimen were followed every six months with sputum cultures up to 24 months after treatment completion. The risk of any unfavourable outcome, of failure and relapse, and of death during and after treatment was analysed according to patient's characteristics and initial drug susceptibility by Cox proportional hazard models.

Findings: Respectively 67.8% and 57.2% patients had >=1 culture result six months and 12 months after treatment completion. Fourteen relapses were diagnosed. The probability of relapse-free success was 79.3% (95% confidence interval [CI] 76.6−82.0%) overall, 80.9% (95% CI 78.0−84.0%) among HIV-negative and 72.5% (95% CI 66.5−78.9%) among HIV-infected patients. Initial fluoroquinolone (adjusted hazard ratio [aHR] 6.7 [95% CI 3.4−13.1]) and isoniazid resistance (aHR 9.4 [95% CI 1.3−68.0]) were significantly associated with increased risk of failure/relapse and of any unfavourable outcome.

Interpretation: The close to 80% relapse-free success indicates the good outcome of the regimen in low-and middle-income settings. Results confirm the lesser effectiveness of the regimen in patients with initial resistance to fluoroquinolones and support the use of high-dose isoniazid, but do not support exclusion of patients for resistance to drugs other than fluoroquinolones.

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Research in context

Evidence before this study

Treatment outcome of patients with multidrug-resistant tuberculosis (MDR-TB) is poor with low proportions of success worldwide, and few data are available on the frequency of relapses after treatment completion. Treatment recommendations released by the World Health Organization (WHO) are conditional and based on low quality of evidence due to the lack of clinical trial results. Until 2016, recommended regimens lasted 20 months or more with 8 months of injectable drugs. After the publication in 2010 and 2014 of results of an observational study in Bangladesh showing >80% success with a 9-month standardized regimen, similar success rates with this shorter regimen were reported in several observational studies conducted in low-income countries. The STREAM study, the first ever randomized clinical trial on MDR-TB regimens, demonstrated the non-inferiority of the shorter regimen compared with longer individualized regimens. The WHO guidelines for MDR-TB treatment recommend the shorter regimen since 2016. The recent 2018 revision based on results of an individual patient data meta-analysis maintained this recommendation with additional precautions and exclusion criteria.

Added value of this study

We report on the treatment outcome after treatment completion in an observational cohort study conducted among more than 1000 patients treated with the shorter regimen using normal-dose moxifloxacin in nine African countries. Results show that the regimen maintains a good effectiveness up to 24 months. The probability of relapse-free success is decreased and the risk of failure or relapse is increased in presence of initial resistance to fluoroquinolones or to isoniazid.

Implications of all available evidence

Results of this work support the continuing use of the shorter regimen in programmatic conditions after exclusion of patients with resistance to fluoroquinolones, and the inclusion of high-dose isoniazid in the regimen. They do not support exclusion criteria based on resistance to drugs other than fluoroquinolones.

1. Introduction

Rifampicin is the core drug in the standard six-month first-line treatment regimen for tuberculosis (TB). Resistance to rifampicin, whether or not associated with resistance to isoniazid, i.e. multidrug resistance (MDR), considerably complicates tuberculosis treatment, and the proportion of treatment success reported in 2017 was worldwide only 55% [1]. The guidelines published by the World Health Organization (WHO) in 2011 recommended regimens for rifampicin-resistant (RR) TB lasting 20 months or more, with an 8-month intensive phase [2].

In 2010, Van Deun et al. published results of an observational study with a nine-month standardised regimen for MDR-TB achieving an 88% relapse-free success [3]. High proportions of success were later observed in Cameroon and Niger with a similar 12-month regimen [4,5]. An observational study launched in 2013 in nine countries in Africa to determine the effectiveness of a 9-month treatment adapted from the Bangladesh regimen achieved 81.8% success among the 1006 patients [6]. Preliminary results of this and other observational studies in Swaziland and Uzbekistan, together with results published at the time [4,5,7], led the WHO to modify its international guidelines in 2016 by including the shorter "Bangladesh" regimen among the recommended regimens for MDR-TB treatment [8].

Treatment outcomes with the shorter regimen still need to be established more solidly. The STREAM trial, the first-ever conducted randomised clinical trial on MDR-TB treatment regimens, has demonstrated the non-inferiority of this regimen compared with the longer individualised regimen previously recommended by WHO [9]. A recent meta-analysis of individual data on patients treated in observational studies showed a higher proportion of success and a lower proportion of loss to follow-up, but suggested a higher risk of failure and relapse with the shorter regimen compared with a longer individualised regimen [10,11]. We supplement here our first published results during treatment [6] by reporting on the outcomes after up to 24 months of post-treatment follow-up among the initial cohort of 1006 patients.

2. Methods

2.1. Study population

The study was conducted in nine countries of West and Central Africa: Benin, Burkina Faso, Burundi, Cameroon, Central African Republic (CAR), Côte d'Ivoire, Democratic Republic of Congo (DRC), Niger and Rwanda. All patients with newly diagnosed bacteriologically confirmed pulmonary tuberculosis undergoing drug susceptibility testing for rifampicin during the 2013−2015 inclusion period were screened for eligibility, except in DRC and Côte d'Ivoire where inclusion was restricted to the capital city. Eligibility criteria were age ≥18 years, and resistance to rifampicin detected by genotypic (Xpert® MTB/RIF or line probe assay) or phenotypic methods, regardless of isoniazid susceptibility. Patients previously treated with second-line drugs, known to harbour bacilli resistant to fluoroquinolones or to any second-line injectable drug (SLID) before enrolment, pregnant women, patients with known intolerance to one drug in the regimen, or with a pre-treatment electrocardiogram (ECG) showing a QT interval >500 ms were not eligible. If fluoroquinolone or SLID resistance was identified after treatment initiation, the patient was not excluded nor was the regimen modified.

2.2. Treatment

The 4-month intensive phase consisted of seven drugs: kanamycin, clofazimine, normal-dose moxifloxacin, ethambutol, high-dose isoniazid, pyrazinamide and prothionamide. It was extended by monthly increments up to a maximum of 2 months if the sputum smear examination was still positive after 4 months. The continuation phase consisted of normal-dose moxifloxacin, ethambutol, pyrazinamide and clofazimine given daily for a fixed 5-month duration. Thus, the total treatment duration was nine to 11 months.

Treatment was daily and directly observed by a health worker throughout the entire duration. Patients were treated as in- or outpatients according to National Tuberculosis Programme guidelines. Details of patient's care scheme, patient support and monitoring and management of adverse events have been detailed elsewhere [6].

2.3. Bacteriological follow-up

Smears and cultures were performed on sputum specimens collected before treatment initiation, then monthly during treatment. After treatment completion, patients had appointments with the physician every six months up to 24 months. During these visits, patients were examined clinically and had a specimen collected for smear and culture. Patients not attending their scheduled appointment were reminded by phone. In December 2017, patients who had not attended their scheduled appointment 12 months after treatment

completion were actively searched for by phone and information on the main reason for not attending the appointment (death, refusal to attend, or not found) was recorded.

Drug susceptibility testing (DST) to first- and second-line drugs had to be performed on the initial positive culture and on any culture found positive after six months (both during or after treatment). DST was done in national reference laboratories and in two supranational reference laboratories (SRL): in Milan for Côte d'Ivoire and Burkina Faso, and in Antwerp for the seven other countries. Strains of only 585 patients (58%) could be tested in the SRL mainly because airlines refused to transport any biological specimen during the 2014−2015 Ebola epidemic.

DST was performed phenotypically and/or genotypically (line probe assay and targeted Sanger sequencing) for rifampicin, fluoroquinolones, SLID, isoniazid and ethionamide/prothionamide (*inhA* mutations), genotypically only for pyrazinamide (*pncA* mutations), and phenotypically only for ethambutol. Phenotypic test results followed the WHO definitions of critical concentrations. [12]. We defined high-level fluoroquinolone resistance if the minimum inhibitory concentration to ofloxacin was >=8 mg/L or there were certain gyrase mutations that are known to confer high-level resistance [12,13]. At country level, rifampicin susceptibility was mostly determined genotypically, and DST for other drugs mostly phenotypically. In case of discordance, the SRL result overrode that of the national laboratory, and a phenotypic result at the SRL overrode a molecular result, except for rifampicin for which a genotypic result defined inclusion.

Comparison of the initial strain with any strain isolated after six months was performed at the SRL whenever possible by spoligotyping or whole genome multilocus sequence typing [14,15].

2.4. Definitions

Treatment outcome was defined according to the 2013 WHO reporting framework definitions [16] except for failure and cure because of the short treatment duration. Failure was defined by any positive culture after six months during treatment, except when preceded by one negative and followed by at least two negative and no other subsequent positive culture, i.e. isolated positive culture [17]. Cure was defined as treatment completed without evidence of failure, and three or more consecutive negative cultures taken at least 30 days apart at any time during treatment, i.e. not necessarily after the intensive phase. Negative cultures obtained during post-treatment follow-up were also counted to contribute to the definition of cure.

Relapse was defined by a positive culture in a patient previously declared cured or treatment completed at the end of treatment, except for cases in which initial and post-treatment (recurrent) strains were found to have different profiles by spoligotyping or whole genome sequencing. Such cases were defined as reinfection disease rather than relapse.

Relapse-free success was defined as cure or treatment completion without evidence of relapse at the end of post-treatment follow-up.

2.5. Data management

Data were collected on standardised forms and registers specifically designed for the study, and entered in an EpiData Entry anonymous database (Version 3.1 EpiData Association, (http://www.epidata.dk). Data were double-entered on two occasions: in 2017 [6] and again after all patients had completed follow-up. Any identified discordance was resolved through verification in the original paper record.

2.6. Statistical analysis

We used EpiData Analysis (Version 2.2.2.187, http://www.epidata.dk) for dataset restructuring, univariate and bivariate analyses, and R (Version 3.6.0, http://www.r-project.org) for time-to-event data analysis.

Relevant endpoints were evaluated in three time-to-event analyses: (1) overall treatment success, (2) bacteriological treatment success, and (3) deaths during observation. All outcome probabilities were determined by the Kaplan−Meier estimator. The initial population at risk were all eligible patients who received at least one dose of the regimen. The observation time was censored at 33 months following treatment start. In the first analysis aiming to determine treatment success, loss to follow-up after treatment completion was treated as censored while loss to follow-up and death during treatment were treated as events following international definitions for tuberculosis treatment outcomes [16]. In the second and third analyses aiming to obtain a correct estimator for unfavourable bacteriological outcome (failure or relapse) and for death throughout observation, only these were treated as events while all other outcomes were treated as censored.

Outcomes were described and analysed according to patient's characteristics (age, sex, HIV status, body mass index and extent of lung lesions) and initial susceptibility to all drugs except clofazimine.

To ascertain factors potentially associated with the three respective events, Cox proportional hazard models were constructed by stepwise elimination of variables driven by z score probability. Because values were missing for a large proportion of cases for certain variables (notably drug susceptibility tests), missing data were retained as an analysed stratum to reduce the risk of selection bias but were not usually reported specifically.

2.7. Ethics

The study protocol was approved by The Union Ethics Advisory Group and by each country's ethics committee. Eligible patients accepting to participate were enrolled after informed consent.

Patients who were excluded from the study or declined to be enrolled were treated according to national or WHO guidelines, and patients who failed or relapsed were offered treatment following their DST pattern according to WHO recommendations [2].

3. Results

3.1. Follow-up

Of the 1006 enrolled patients, 565 (56.2%) had MDR-TB, 101 (10.0%) had RR/isoniazid-susceptible TB, and 340 (33.8%) had RR TB and no isoniazid DST result.

Among these 1006, 823 had treatment success assessed at completion of treatment. After treatment completion, 558 of them (67.8%) had one or more culture results available 6 months or later during post-treatment follow-up, 471 patients (57.2%) 12 months or later, 264 (32.1%) 18 months or later and 160 (19.4%) at 24 months. The median duration of follow-up was 15.9 months (range 0.2−36.6; mean 16.5) among the 558 patients with at least one follow-up culture result.

The proportion of patients with follow-up culture results did not significantly differ according to patient's age group, sex, underweight (defined as body mass index <18.5), extent of lung lesions and HIV status, but differed widely according to their country of enrolment, ranging from 48% in Côte d'Ivoire to 96.4% in Burundi (Table 1).

Among the 265 patients with no follow-up culture result, reasons retrieved by the telephone survey were: death for 51 patients (19.2%), and refusal to attend or to provide sputum specimen for 58 (21.9%), while the remaining 156 (58.9%) could not be found.

3.2. Relapse-free treatment success

Fifteen patients had a recurrent episode evidenced by a positive culture during post-treatment follow-up. Five pairs of initial and recurrent strains were available at the SRL. The genotypic comparison was interpretable for three of these pairs: profiles were identical for two, and different for one. After exclusion of the latter episode, 14

Table 1
Patients enrolled in the nine-country study with treatment success assessed at the end of treatment, and with at least one culture result available during post-treatment follow-up.

Patients characteristics		Total	Successfully treated	With >=1 follow-up culture		P-value
		N	N	n	%	
Country						$<10^{-3}$
	Burkina Faso	34	29	27	93.1	
	Burundi	61	56	54	96.4	
	Benin	29	25	24	96.0	
	DRC	301	242	129	53.3	
	CAR	45	36	29	80.6	
	Côte d'Ivoire	260	207	100	48.3	
	Cameroon	176	149	130	87.2	
	Niger	62	48	44	91.7	
	Rwanda	38	31	21	67.7	
Sex						0.300
	Female	338	275	193	70.2	
	Male	668	548	365	66.6	
Age group						0.196
	18−24 years	186	153	107	69.9	
	25−34 years	351	285	183	64.2	
	35−44 years	269	228	157	68.9	
	45−54 years	141	117	78	66.7	
	55−64 years	37	26	23	88.5	
	>=65 years	22	14	10	71.4	
HIV status						0.190
	Positive	200	145	105	72.4	
	Negative	806	678	453	66.8	
BMI						0.208
	<16.0	211	157	107	68.2	
	16.0−16.9	132	102	67	65.7	
	17.0−18.4	220	180	114	63.3	
	18.5−24.4	420	366	258	70.5	
	>=25.0	17	14	11	78.6	
	Missing	6	4	1	25.0	
Extent of lung lesions						0.144
	<50%	331	278	182	65.5	
	>=50%	617	500	350	70.0	
	Missing	58	500	26	57.8	
Category						0.240
	New case	134	109	67	61.5	
	Retreatment[a]	850	693	475	68.5	
	Other	22	21	16	76.2	
Total		1006	823	558	67.8	

BMI: body mass index in kg/m^2.

[a] Including 236 relapses after first-line treatment and 589 failures of first-line treatment.

patients met the definition of relapse. The median interval between treatment completion and relapse was 8·3 months, ranging from 3.6 to 21.1 months; 12 (85.7%) occurred within 13 months (Fig. 1).

The relapse-free treatment success among the cohort of 1006 patients was 79.3% (95% confidence interval [CI] 76.6−82.0%) (Fig. 2). After stratification, the success was 80·9% (95% CI 78.0−84.0%) among
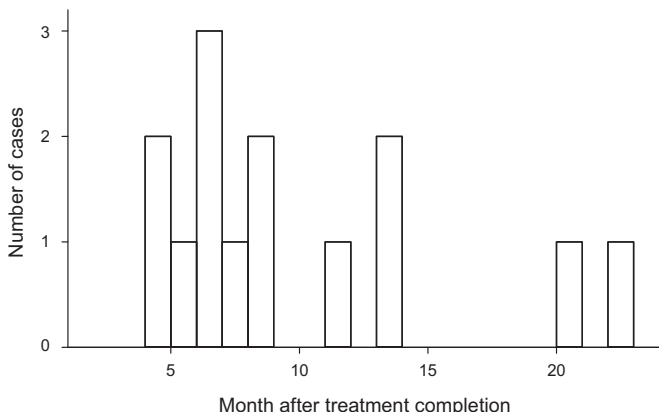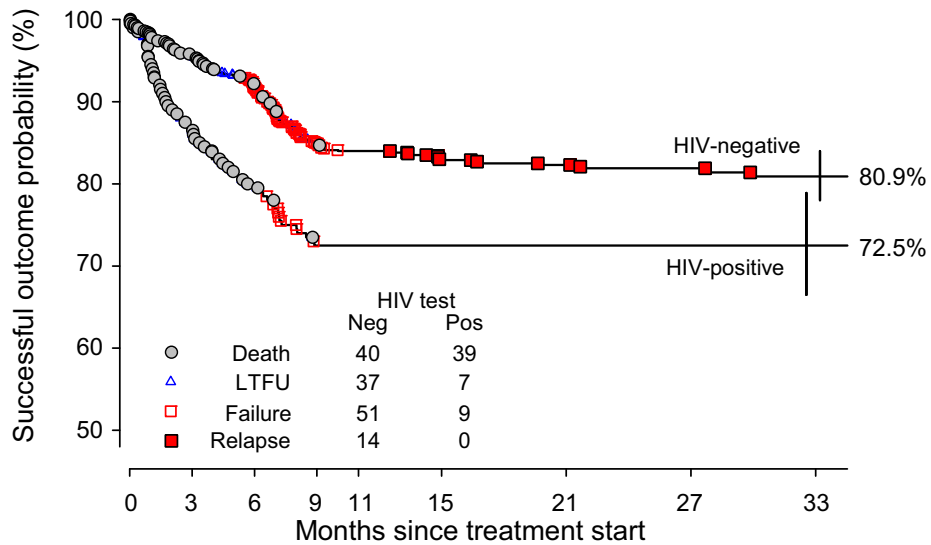

Fig. 1. Time to diagnosis of relapse after treatment completion.

HIV-negative and 72.5% (95% CI 66.5−78.9%) among HIV-positive patients (logrank test for difference in survival curves 0.0005).

Factors significantly associated with the probability of relapse-free success in the Cox model after stepwise elimination were HIV status, underweight, initial fluroquinolone, and initial isoniazid resistance. Because HIV status was shown to violate the proportionality assumption, the model was stratified by HIV. In this final model, underweight and initial fluoroquinolone resistance were significantly associated with an unfavourable outcome among HIV-negative, while underweight remained the only significant risk factor for HIV-positive patients (Table 2).

3.3. Unfavourable bacteriological outcome

All relapses occurred among HIV-negative patients. Patients who relapsed did not differ significantly from patients who failed according to any of their baseline characteristics or initial drug susceptibility; none had initial resistance to SLID and one had high-level fluoroquinolone resistance (Table 3). The 60 failures and the 14 relapses were thus combined into a single category of unfavourable bacteriological outcome. The Kaplan−Meier estimator of unfavourable bacteriological outcome frequency was 9.6% (95% CI 7.3%−11.8%) overall. It was non-significantly higher among HIV-negative than

Fig. 2. Kaplan−Meier successful treatment outcome probability from treatment start to end of post-treatment follow-up period.
LTFU: lost to follow-up.

Table 2
Adjusted hazard ratios for unfavourable outcome, failure/relapse, and death throughout observation, stratified by HIV status where proportionality assumption is unmet. All 1006 patients, strata for missing values not displayed.

Characteristic	HIV negative		HIV positive		Total	
	Ahr[d]	95% ci	ahr[d]	95% ci	ahr[d]	95% ci
Unfavourable outcome[a]						
BMI < 18.5	**1.6**	**(1.1−2.3)**	**2.9**	**(1.6−5.5)**	**1.8[e]**	**(1.4−2.5)**
FLQ resistance	**2.6**	**(1.4−5.1)**	1.8	(0.44−7.8)	**2.3[e]**	**(1.3−4.2)**
INH resistance	1.7	(0.82−3.5)	2.4	(0.84−6.6)	**1.9[e]**	**(1.02−3.4)**
Failure/relapse[b]						
BMI < 18.5					**2.0**	**(1.2−3.2)**
FLQ resistance					**6.8**	**(3.5−13.2)**
INH resistance					**9.4**	**(1.3−68.0)**
SLID resistance					0.27	(0.04−2.0)
Death[c]						
BMI < 18.5	**1.6**	**(1.03−2.6)**	**2.2**	**(1.3−3.8)**	**1.7[e]**	**(1.2−2.5)**
Lung lesions ≥50%	**2.5**	**(1.4−4.5)**	1.07	(0.60−1.9)	**1.6[e]**	**(1.06−2.3)**
SLID resistance	**6.1**	**(2.4−15.8)**	1.7	(0.23−12.6)	**3.6[e]**	**(1.6−8.3)**

BMI: body mass index (in kg/m²); FLQ: fluoroquinolone; INH: isoniazid; SLID: second-line injectable drug; CI: confidence interval.

[a] Unfavourable outcome (death during treatment, lost to follow-up during treatment, failure during treatment, or relapse) vs relapse-free success among all 1006 patients. Not shown are the strata with missing information for the respective variable.

[b] Failure during treatment or relapse during follow-up. Death throughout observation, and lost to follow-up throughout observation are censored. Not shown are the strata with missing information for the respective variable.

[c] Death throughout observation. Failure during treatment, relapse, and lost to follow-up throughout observation are censored Not shown are the strata with missing information for the respective variable.

[d] aHR: adjusted hazard ratio calculated from a Cox proportional hazard model using variables after stepwise elimination. Adjusted refers to the listed other variables for each characteristic.

[e] The calculation of hazard ratios on the total is calculated by excluding HIV from the model as it violates the assumption of proportionality.

among HIV-positive patients (Fig. 3): 10.4% (95% CI 7.7%−13.0%) vs 5·8% (95% CI 2.0%−9.4%).

DST could be performed for the four relapsing patients with available pairs of strains: two patients acquired fluoroquinolone resistance and one acquired pyrazinamide resistance. Among all patients with initial drug susceptibility, nine patients with failure or relapse among 571 (1.6%) acquired high-level resistance to fluoroquinolones, 6/581 (1.0%) to SLID, 1/101 (1.0%) to isoniazid and 2/184 (1.1%) to pyrazinamide. Three additional patients with initial low-level resistance to fluoroquinolones acquired high-level resistance during treatment.

Four factors (body mass index, initial resistance to fluoroquinolone, isoniazid and second-line injectable drugs) were retained in the final Cox model for the probability of unfavourable bacteriological outcome, among which three significantly increased the risk of failure/relapse: underweight, and initial resistance to fluoroquinolone and to isoniazid (Table 2).

3.4. Death throughout observation

A total of 79 deaths of any cause were reported during treatment. In addition, 73 deaths occurring after successful treatment completion were reported either spontaneously by the patient's family or through the 2017 phone survey. The Kaplan-Meier estimate of death frequency during treatment was 8.6% [95 CI 7.4%−11.2]) and the cumulative probability of death throughout observation was 31.8% (95% CI 21.9−40.4%).

The probability of death differed widely according to HIV status. By the end of treatment, the probability of death was 5·0% (95% CI 3.5−6.6%) among HIV-negative and 19·8% (95% CI 14.1−25.1%) among the HIV-positive patients (Fig. 4). As previously reported [6], this excess of deaths largely explained the lower treatment success among HIV-positive patients as compared to HIV-negative ones (Fig. 2). Deaths during follow-up occurred continuously throughout

Table 3
Characteristics of patients with failure and relapse.

Characteristic		Failure		Relapse		P-value
		N	%	N	%	
Total		60	100.0	14	100.0	
Sex	Male	39	65.0	11	78.6	0.33
	Female	21	35.0	3	21.4	
Age (years)[a]	>=35	38	63.3	10	71.4	0.57
	<35	22	36.7	4	28.6	
HIV status	Negative	51	85.0	14	100.0	0.12
	Positive	9	15.0	0	0.0	
Category	New	55	91.7	13	92.9	0.88
	Retreatment	5	8.3	1	7.1	
BMI	≥18.5	20	33.3	3	21.4	0.39
	<18.5	40	66.7	11	78.6	
Lung lesions[b]	<50%	16	27.1	2	13.3	0.32
	≥50%	43	72.9	12	85.7	
FLQ	Susceptible	32	76.2	11	91.7	0.47
	Low-level resistant	2	4.8	0	0.0	
	High-level resistant	8	19.0	1	8.3	
SLID	Susceptible	43	97.7	12	100.0	1
	Resistant	1	2.3	0	0.0	
INH	Susceptible	1	2.2	0	0.0	1
	Resistant	44	97.8	11	100.0	
PZA	Susceptible	9	33.3	2	33.3	1
	Resistant	18	66.7	4	66.7	
PTH	Susceptible	2	12.5	0	0.0	1
	Resistant	14	87.5	5	100.0	
EMB	Susceptible	1	12.5	0	0.0	1
	Resistant	7	87.5	1	100.0	

BMI: body mass index in kg/m²; FLQ: fluoroquinolones; SLID: second-line injectable drugs; INH: isoniazid; PZA: pyrazinamide; PTH: prothionamide/ethionamide; EMB: ethambutol.
Numbers do not add up to column totals if there are missing data. The percentages refer to the displayed values excluding any missing. This is the case for Lung lesions among failures and for all drug susceptibility test results.
[a] Mean (median) age 33.9 (31.0) and 30.8 (28.0) for failure and relapse cases, respectively.
[b] Each lung has been divided into three zones (superior, middle, inferior) by dividing the space between apex and hemi-diaphragm into three. The extent of lung lesions is defined as the proportion of zones affected among the 6 zones.

the post-treatment phase. The cumulative Kaplan−Meier probability of death among HIV-negative and -positive patients was respectively 28.9% (95% CI 16.8−39.2%) and 39.3% (95% CI 27.8−48.9%) (Fig. 4).

Factors significantly associated with the probability of death throughout observation in the Cox model were HIV status, underweight, extent of lung lesions and initial resistance to second-line injectable drugs. After stratification by HIV status because of violation of the proportionality assumption, underweight, extent of lung lesions and initial resistance to second-line injectable drugs remained significantly associated with the risk of dying throughout observation among HIV-negative, while underweight remained the only significant risk factor for HIV-positive patients (Table 2).

4. Discussion

The treatment outcome with the shorter regimen remained good after up to 24 months of post-treatment follow-up with 79.3% (95% CI 76.6−82.0%) of relapse-free success overall in our cohort of more than 1000 patients. A few patients were found to relapse after completing treatment, giving a combined failure and relapse probability of 9.6% (95% CI 7.3−11.8%) overall. These results are very close to those in the STREAM trial [9]. Despite the efforts made to actively search for patients and bring them back into observation, not all completed the scheduled 24 months of post-treatment follow-up, and only 57.2% were followed for at least 12 months. This may have led to underestimate the number of relapses. Although relapse and acquisition of resistance was infrequent, results contrast with the absence of relapse and the absence or very low frequency of acquired resistance previously reported in Cameroon, Niger and Bangladesh [4,5,7,18] where gatifloxacin was used instead of the normal dose of moxifloxacin used in this and the STREAM study. Because the fluoroquinolone is the core drug of the shorter regimen, the choice of the fluoroquinolone may explain these differences [19]. The activity of gatifloxacin is higher than that of moxifloxacin [13] and gatifloxacin has been found to be associated with lower risk of failure/relapse compared to moxifloxacin [20,21].
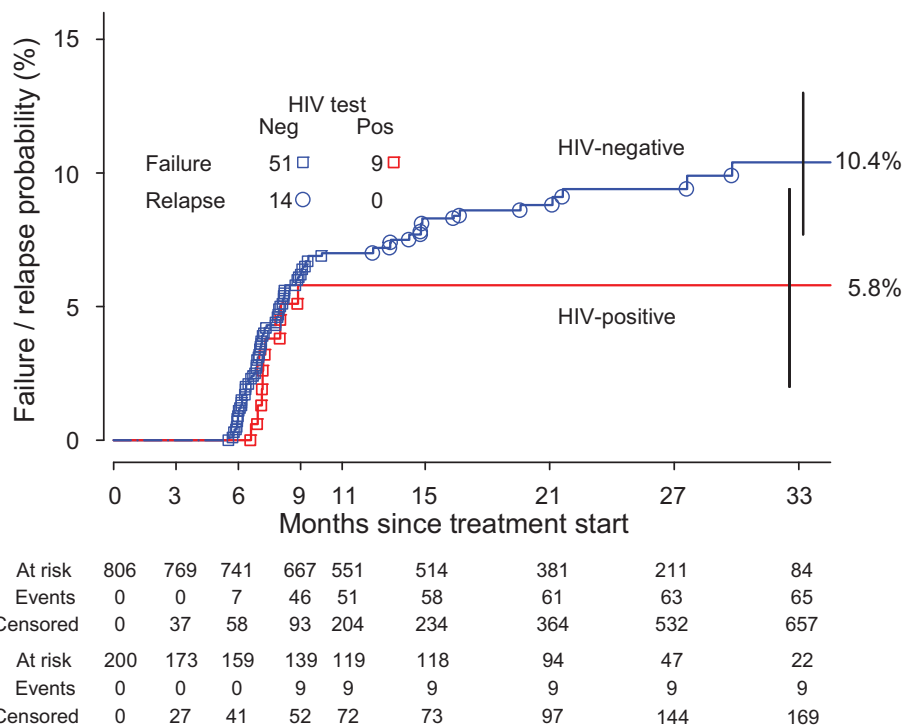

Fig. 3. Kaplan−Meier estimate of failure and relapse among patients on the 9-month MDR treatment, by HIV status, nine African countries.
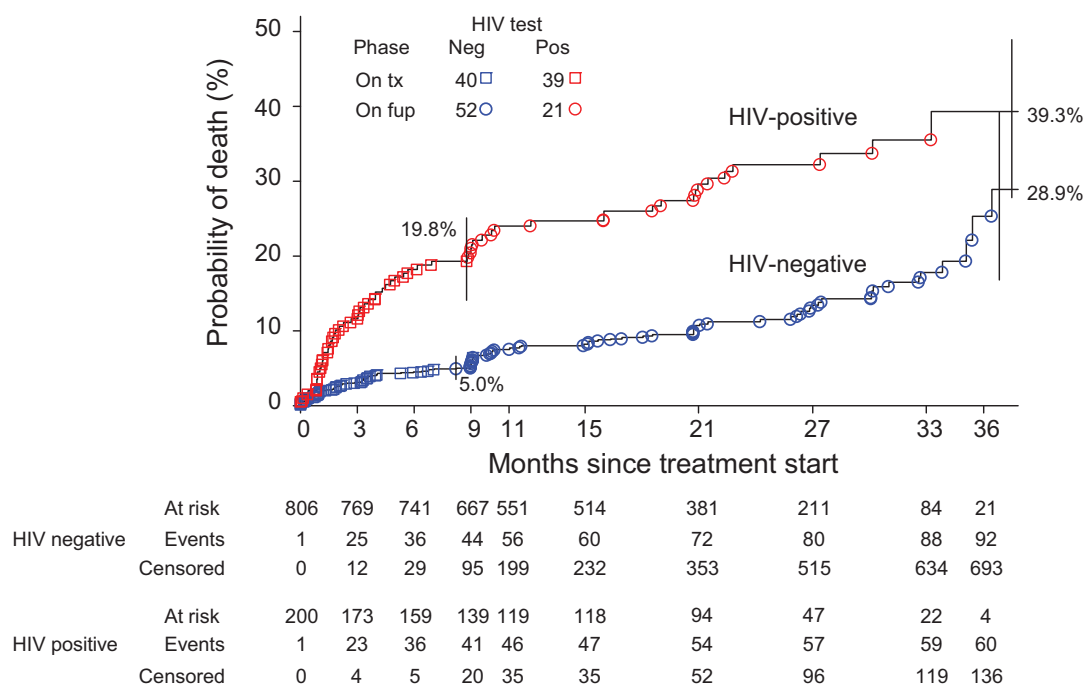
Fig. 4. Kaplan−Meier probability of death throughout observation among patients on the 9-month MDR treatment, nine African countries.
On tx = during treatment; on fup: during follow-up (after treatment completion).

The characteristics of patients who relapsed were very similar to those of patients with treatment failure, and both groups were diagnosed only a few months apart. The occurrence of relapses within the first year after treatment completion has been commonly observed in clinical trials, suggesting that early recurrences are actually "missed failures" [22]. This supports their combination into a single group of unfavourable bacteriological outcome.

Initial fluoroquinolone and isoniazid resistance were significant predictors of an unfavourable bacteriological outcome. These results are consistent with our previous findings and with data from Bangladesh and other settings showing a much higher risk of unfavourable bacteriological outcome in presence of − notably high-level − fluoroquinolone resistance [4−7,21]. Similarly, the risk of any unfavourable outcome was significantly increased for patients with fluoroquinolone or isoniazid resistance. Since isoniazid resistance was prevalent in 85% of the patients, their outcomes were very close to the cohort average, while the 15% patients harbouring isoniazid-susceptible strains had better than average outcomes. Results probably reflect the use of high-dose isoniazid in the regimen, which has been reported to improve outcomes in the treatment of MDR-TB [23].

Pyrazinamide, prothionamide and ethambutol resistance had no impact on the bacteriological outcome. The impact of resistance to these drugs on outcomes of the shorter regimen remains under debate. Reliability of DST results for these drugs is poor, particularly for prothionamide and ethambutol, and basing treatment decisions on these results is not currently recommended [12,24]. Pyrazinamide resistance has been reported to increase the risk of an unfavourable bacteriological outcome with the shorter regimen in one of the subgroup analysis of the STREAM study [9], and in a meta-analysis [21] but was found to have a negative effect only for patients with fluoroquinolone-resistant strains in Bangladesh [7]. A negative effect of prothionamide and ethambutol resistance has been reported in one recent analysis based on individual patient data [10,11], but not in prospective studies. The role of these drugs is probably limited to protect against the acquisition of resistance to the core drug of the regimen, i.e. the fluoroquinolone, and is thus likely to be essential only if all other companion drugs are ineffective [19].

Very few studies have reported on the risk of death after success of MDR-TB treatment in low-income settings. By definition none of the deaths was preceded by bacteriological evidence of failure or relapse. We cannot exclude that some of the deaths were due to relapses. However, neither fluoroquinolone nor isoniazid resistance, which were strong risk factors for unfavourable bacteriological outcome, were found to increase the risk of death. This, together with the timing of deaths with no clustering within the first year after treatment completion as opposed to relapses, makes it unlikely that these patients succumbed to undiagnosed tuberculosis. The higher mortality among the very few patients (15) harbouring SLID resistant strains remains unexplained. HIV infection, low body mass index, and initial radiographic extent were found to be independently associated with a higher risk of death. These factors have already been identified as risk factors for death during treatment in this cohort [6], similarly to other studies of MDR-TB patients [25−28]. Mortality after successful TB treatment is known to be higher than in the general population, and is most probably attributable to severe respiratory sequelae of TB or to causes not related to TB, particularly opportunistic infections among HIV-infected patients [29,30].

Our results have several limitations. Our inability to obtain a more complete post-treatment follow-up, with large inter-country variations, may have led to underestimating the number of relapses. Difficulties in performing cultures due to obstacles frequently encountered in resource-limited settings may also have led to underestimating the frequency of failures and relapses. These difficulties have been minimised by using a definition of failure based on a positive culture at or beyond six months of treatment. The definition is both reliable and applicable in low- and middle-income settings with a few adaptations [31]. Data on initial DST results were incomplete, particularly for pyrazinamide, prothionamide and ethambutol. However, this is not a likely source of bias since this incompleteness was due to an external cause (refusal of airlines to transport specimen) unrelated to any patient characteristic.

We conclude that the shorter regimen used under programmatic conditions retained its good effectiveness up to two years beyond treatment completion. The results reinforce the WHO recommendation to use this regimen in patients with rifampicin-resistant tuberculosis likely to be susceptible to the newest generation of fluoroquinolones. They do not

provide evidence to support other exclusion criteria such as resistance to other drugs. Further research to improve its tolerance, particularly by testing a short all-oral regimen without SLID, would be of major interest.

Declaration of Competing Interest

The authors have no conflict of interests to disclose.

Acknowledgments

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2020.100268.

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