

## Failure or relapse predictors for the STREAM Stage 1 short regimen for RR-TB

D. M. Kokebu,<sup>1</sup> S. Ahmed,<sup>2</sup> R. Moodliar,<sup>3</sup> C-Y. Chiang,<sup>4,5,6</sup> G. Torrea,<sup>7</sup> A. Van Deun,<sup>7</sup> R. L. Goodall,<sup>2</sup> I. D. Rusen,<sup>8</sup> S. K. Meredith,<sup>2</sup> A. J. Nunn;<sup>2</sup> on behalf of the STREAM Sub-study Collaborators

<sup>1</sup>St Peter's Tuberculosis Specialised Hospital/Global Health Committee, Addis Ababa, Ethiopia; <sup>2</sup>MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, University College London, London, UK; <sup>3</sup>Tuberculosis & HIV Investigative Network (THINK), Doris Goodwin Hospital, Pietermaritzburg, South Africa; <sup>4</sup>Division of Pulmonary Medicine, Department of Internal Medicine, Wanfang Hospital, Taipei Medical University, Taipei, <sup>5</sup>Division of Pulmonary Medicine, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; <sup>6</sup>International Union Against Tuberculosis and Lung Disease, Paris, France; <sup>7</sup>Institute of Tropical Medicine, Antwerp, Belgium; <sup>8</sup>Research Division, Vital Strategies, New York, USA

### SUMMARY

**BACKGROUND:** STREAM (Standardised Treatment Regimens of Anti-tuberculosis drugs for Multidrug-Resistant Tuberculosis) Stage 1 demonstrated non-inferior efficacy of a short regimen for rifampicin-resistant TB (RR-TB) compared to a long regimen as recommended by the WHO. The present paper analyses factors associated with a definite or probable failure or relapse (FoR) event in participants receiving the Short regimen.

**METHODS:** This analysis is restricted to 253 participants allocated to the Short regimen and is based on the protocol-defined modified intention to treat (mITT) population. Multivariable Cox regression models were built using backwards elimination with an exit probability of  $P=0.157$ , equivalent to the Akaike Information Criterion, to identify factors independently associated with a definite or probable FoR event.

**RESULTS:** Four baseline factors were identified as being significantly associated with the risk of definite or probable FoR (male sex, a heavily positive baseline smear grade, HIV co-infection and the presence of costophrenic obliteration). There was evidence of association of culture positivity at Week 8 and FoR in a second model and Week 16 smear positivity, presence of diabetes and of smoking in a third model.

**CONCLUSION:** The factors associated with FoR outcomes identified in this analysis should be considered when determining the optimal shortened treatment regimen.

**KEY WORDS:** rifampicin-resistant tuberculosis; short regimen; failure or relapse; factors predicting treatment outcome

Patients with multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB) have had poor outcomes for many years, as evidenced by the annual reports published by the WHO. Treatment success for MDR/RR-TB improved from 50% for the cohort starting treatment in 2012 to just 57% for the cohort starting treatment in 2017.<sup>1</sup> In view of the poor outcomes in patients receiving the long regimen of at least 20 months' duration recommended by the WHO,<sup>2</sup> Van Deun and colleagues conducted a series of observational cohort studies in Bangladesh to evaluate the possibility of developing shorter, less toxic and more effective regimens for the treatment of MDR-TB. Using a gatifloxacin (GFX) containing regimen of 9–11 months' duration, a relapse-free cure was achieved in 87.9% (95% confidence interval [CI] 82.7–91.6) of the patients enrolled.<sup>3</sup> Subsequently, a study in nine countries in West and Central Africa

demonstrated that the 9–11 month regimen was effective in a population that included HIV co-infected patients.<sup>4</sup>

In 2016, the WHO issued conditional recommendations, based on observational data, that patients with MDR/RR-TB who had not been previously treated with second-line drugs and in whom resistance to fluoroquinolones (FQs) and second-line injectable agents has been excluded, or is considered highly unlikely, could be treated with a MDR-TB regimen of 9–12 months instead of the conventional long regimen; the shortened regimen proposed was similar to that being tested in the STREAM (Standardised Treatment Regimens of Anti-tuberculosis drugs for Multidrug-Resistant Tuberculosis) Stage 1 study.<sup>5</sup>

In 2019, the results of STREAM Stage 1, a multi-country non-inferiority randomised trial assessing the

**Table 1** Baseline characteristics of patients receiving the Short regimen ( $n = 253$ )

Factor		Total $n$ (%)	Factor		Total $n$ (%)
Age, years	18–24	56 (22.1)	Culture result	1–9 colonies/ 1+	59 (23.3)
	25–34	88 (34.8)		2+	65 (25.7)
	35–44	58 (22.9)		3+	129 (51.0)
	≥45	51 (20.2)	Extent of opacities*	Minimal/moderate	154 (64.4)
Sex	Male	151 (59.7)		Far advanced	85 (35.6)
	Female	102 (40.3)	Cavitation*	No	55 (23.0)
Weight, kg	≤50	117 (46.2)		Yes	184 (77.0)
	>50	136 (53.8)	Costophrenic obliteration*	No	192 (80.3)
BMI, kg/m <sup>2</sup>	<16.0	31 (12.3)		Yes	47 (19.7)
	16.0–18.4	83 (32.8)		Pleural thickening*	No
	18.5–24.9	122 (48.2)	Yes		10 (4.2)
	≥25.0	17 (6.7)	Presence of diabetes <sup>†</sup>	No	231 (91.7)
HIV status	Negative	168 (66.4)		Yes	21 (8.3)
	Positive	85 (33.6)	Haemoglobin, g/dL <sup>‡</sup>	<11	53 (22.3)
ART at entry (if HIV-positive)	No	25 (29.4)		≥11.0	185 (77.7)
	Yes	60 (70.6)	Isoniazid susceptibility <sup>§</sup>	Susceptible	15 (6.1)
Previous treatment	No	18 (7.1)		Resistant	229 (93.9)
	Yes	235 (92.9)	Pyrazinamide susceptibility <sup>¶</sup>	Susceptible	76 (36.9)
Smoking status	Never	164 (64.8)		Resistant	130 (63.1)
	Ever smoked	89 (35.2)			
Smear result	Negative, rare or 1+	78 (30.8)			
	2+	62 (24.5)			
	3+	113 (44.7)			

\* 14 participants missing radiography results.

† 1 participant missing diabetes status.

‡ 15 participants missing haemoglobin test result.

§ 9 participants missing isoniazid drug susceptibility test result.

¶ 47 participants missing pyrazinamide drug susceptibility test result.

BMI = body mass index; ART = antiretroviral therapy.

Short regimen in comparison with the Long WHO regimen were published.<sup>6</sup> The Short 9 month regimen was shown to be non-inferior to the Long (approximately 20 month) regimen using a composite endpoint of an unfavourable outcome, which included changes of treatment for adverse events, as well as death from any cause, treatment failure or relapse (FoR); this finding was subsequently confirmed using a solely TB-related outcome.<sup>7</sup> In view of these findings, it is important to identify which factors are associated with failure or relapse on the Short regimen.

## METHODS

Data from the STREAM Stage 1 trial were used, as previously described.<sup>6</sup> The Union's Ethics Advisory Group and all national and local ethics committees approved the trial. All participants provided written informed consent; they were randomised in a ratio of 2:1 in favour of the Short regimen, which was identical to that used by Van Deun and colleagues in Bangladesh,<sup>3</sup> except that moxifloxacin was substituted for GFX because quality-assured GFX was not available. Randomisation was stratified by centre and HIV status. All participants were followed up to 132 weeks post-randomisation to determine the primary outcome. The pre-specified primary and secondary outcomes are published in the main report.<sup>6</sup>

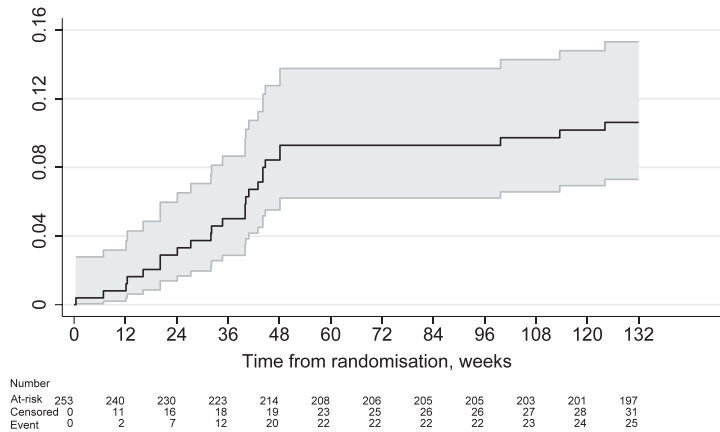
## Variables included in the analysis

The following characteristics were collected from participants at baseline: age, sex, weight, body mass index, presence of diabetes, HIV infection status, smoking status (current smoker, ex-smoker, non-smoker) and haemoglobin level. Baseline sputum samples were collected to determine smear and culture quantified positivity as described in Table 1. *Mycobacterium tuberculosis* complex isolated in the local laboratories were subjected to further tests at the reference laboratory, the Institute of Tropical Medicine (ITM) in Antwerp, Belgium. These tests included determination of phenotypic resistance to isoniazid and resistance to pyrazinamide using genotyping.<sup>6</sup>

A chest radiograph (CXR) obtained at baseline was read independently by two pulmonologists using methodology previously described.<sup>8</sup> CXRs with discordant readings between the two pulmonologists were assessed by a third, followed by discussion among the three readers aiming to achieve consensus. Assessments included extent of opacities, presence of cavitation and presence of costophrenic obliteration. To explore the predictive value of microbiological response to treatment in the intensive phase of the regimen the result of the Week 8 culture (positive or negative) and Week 16 smear result were also included in separate models.

## Endpoint

To examine the factors associated with a TB-related outcome, the STREAM primary endpoint of unfav-



**Figure** Kaplan-Meier graph: time from randomisation to failure or relapse.

ourable outcomes was re-classified on an individual basis according to the likelihood that they represented a FoR event on a 5-point Likert scale: definite, probable, possible, unlikely and highly unlikely. Further details on the methodology are available elsewhere.<sup>7</sup> In this analysis, the outcome of interest is whether or not the participant experienced a definite or probable FoR event in a time to event analysis. Participants not classified as experiencing a definite or probable FoR event were censored at the point they met the primary outcome criteria for unfavourable or unassessable, or at the end of follow-up (132 weeks post-randomisation) if they had a favourable outcome in the primary analysis.<sup>6</sup>

#### Statistical analysis

All analyses were based on the protocol-defined modified intention to treat (mITT) population. This was defined as all randomised participants with a positive culture at baseline, except for those who 1) were randomised in error, or 2) had isolates taken before randomisation or up to Week 4 subsequently found to be susceptible to rifampicin or resistant to both aminoglycosides and FQs on a phenotypic DST at the central reference laboratory.

Participants who were classified as unassessable in the STREAM primary analysis are included in these analyses. Thus, those who were lost to follow-up after 76 weeks but had culture converted when last seen and those whose treatment changed following proven reinfection with an exogenous strain of *M. tuberculosis* were included and were classified as unlikely to have had a FoR event. These participants were censored at the time last seen and at the time of change of regimen, respectively.

A multivariable Cox regression model was built using backwards elimination with an exit probability of  $P = 0.157$  equivalent to the Akaike Information Criterion.<sup>9</sup> HIV infection status, age and sex were considered a priori to be important confounding factors and were included in all models.

were stratified by country and were restricted to individuals with complete data. The most prevalent category was set as the reference in all models. Landmark analyses, with time at risk starting at Week 8 and Week 16, were used to assess the association between Week 8 culture and Week 16 smear results and FoR events, respectively. A Kaplan-Meier graph was structured using the KMunicate project format.<sup>10</sup> Analyses were performed using Stata v16.1 (Stata-Corp, College Station, TX, USA).

## RESULTS

A total of 253 participants were randomised to the Short regimen (Table 1). One third (85 participants) were co-infected with HIV, of whom 60 (70.6%) were on antiretroviral therapy (ART) at randomisation.

On the Short regimen, 25/253 (9.9%) participants had an FoR event, a Kaplan-Meier probability of an FoR event by Week 132 of 0.11 (95% CI 0.07–0.15; Figure). In the multivariable analysis of factors known at baseline, the factors remaining independently associated with an FoR event were male sex, a heavily positive baseline smear grade, HIV co-infection and the presence of costophrenic obliteration (Table 2). When the Week 8 culture result was included in the multivariable analysis, this was found to be associated with an FoR event, in addition to the four factors described above.

The third model included the smear result at Week 16 (the end of the intensive phase) and, in addition, the presence of diabetes at start of treatment or ever having smoked were significant but not the Week 8 culture.

## DISCUSSION

The primary objective of STREAM Stage 1 was to assess, in people with rifampicin-resistant pulmonary TB who have no evidence of resistance to FQs or aminoglycosides on line-probe assays, whether the

**Table 2** Results of three different multivariable models

		Baseline factors (n = 239)		Baseline factors and Week 8 culture (n = 223)		Baseline factors and Week 16 smear (n = 221)	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Age, years	18–24	3.35 (0.91–12.37)	0.082	3.39 (0.83–13.85)	0.061	14.94 (1.98–112.63)	0.025
	25–34	1		1		1	
	35–44	0.53 (0.14–2.08)		0.40 (0.10–1.65)		0.74 (0.14–3.80)	
	≥45	0.75 (0.23–2.47)		0.58 (0.17–1.99)		1.38 (0.35–5.54)	
Sex	Male	1	0.008	1	0.014	1	0.346
	Female	0.13 (0.03–0.58)		0.15 (0.03–0.67)		0.44 (0.08–2.40)	
HIV status	Negative	1	0.018	1	0.004	1	0.017
	Positive	6.03 (1.36–26.73)		11.10 (2.19–56.20)		10.15 (1.51–68.32)	
Smear result	Negative, rare or 1+	0.24 (0.08–0.76)	0.004	0.32 (0.10–1.03)	0.014	0.30 (0.08–1.07)	0.039
	2+	0.06 (0.01–0.49)		0.07 (0.01–0.56)		0.07 (0.01–0.80)	
	3+	1		1		1	
	Costophrenic obliteration	No		1		<0.001	
History of diabetes	Yes	7.30 (2.56–20.80)	*	7.29 (2.44–21.80)	*	3.93 (1.08–14.30)	0.109
	No	*		*		1	
Smoker	Never	*	*	*	*	4.72 (0.71–31.46)	0.010
	Ever	1		6.84 (1.57–29.80)			
Week 8 culture	Negative	Not applicable	0.011	1	0.011	*	*
	Positive	Not applicable		7.17 (1.56–3.29)			
Week 16 smear	Negative	Not applicable	0.095	Not applicable	0.095	1	0.095
	Positive	Not applicable		3.83 (0.79–18.46)			

\* Variables not found to be significant at the exit cut-off probability of 0.157. HR = hazard ratio; CI = confidence interval.

Short regimen developed in Bangladesh was non-inferior to the Long regimen recommended by the WHO in 2011.<sup>2</sup> The composite primary endpoint included not only unfavourable treatment outcomes, such as failure during treatment or relapse, but also death from any cause, loss to follow-up and treatment changes for adverse events. An alternative outcome based on an assessment as to whether the event that met the primary endpoint definition was likely to be an FoR event on a five-point Likert scale, ranging from definite to highly unlikely, has been published.<sup>7</sup>

The FoR rates reported here are similar to the failure/relapse rates reported in the West/Central Africa study report and the Bangladesh, Benin, Niger and Cameroon cohorts.<sup>11,12</sup> A comparison of observational studies of the effectiveness of the WHO-recommended shorter and longer regimens reported that the risk difference for relapse or failure was slightly higher with the shorter regimens.<sup>13</sup>

The current paper has assessed the association of baseline factors and two microbiological assessments during the intensive phase with a FoR event in the Short regimen. In the multivariable analysis, there were five factors associated independently with a FoR event. Four of these were not unexpected: male sex, HIV-positive status, a heavily positive baseline smear and failure to culture convert by 8 weeks. The finding that is difficult to explain was the association of costophrenic obliteration with a poor outcome. We consider that this association is likely to be an incidental finding, although it also occurred in a similar analysis of the Long regimen (not reported here).

HIV-positive status was predictive of a poor treatment outcome; this is consistent with findings in several studies,<sup>14–16</sup> although in the West/Central Africa study all relapses occurred in HIV-negative patients and in the review of shorter regimens, the frequency of relapse or failure did not differ significantly by HIV status.<sup>11,12</sup> The use of ART improves treatment outcomes and reduces the risk of relapse in HIV-positive patients.<sup>17–19</sup> Moreover, advanced HIV infection and low CD4 count have been associated with poor treatment success.<sup>18,20–22</sup> Antiretroviral therapy that is properly timed has been shown to improve treatment success and reduce mortality.<sup>23,24</sup> In the present study, 71% of the HIV-positive participants on the Short regimen were on ART at the time of initiation of MDR-TB treatment.

A systematic review and meta-analysis revealed treatment success was less likely among HIV-positive MDR-TB patients despite high ART uptake, which may be due to poor adherence and complications in management.<sup>25</sup> Initiation of an optimal ART regimen, and close monitoring for treatment adherence and ART failure can maximise the benefit of therapy. In a large retrospective South African cohort of patients with MDR-TB, opportunistic infections were reported as the main causes of death among HIV co-infected patients on ART.<sup>26</sup> There was, however, no evidence from the present study that those receiving ART on entry had better outcomes than HIV co-infected participants not on ART at that time. A study by Magis-Escurra et al. reported a low rate of relapse-

free cure among HIV-positive patients despite culture conversion rates, which were not significantly different from those in HIV-negative patients.<sup>27</sup> Our findings suggest that HIV-positive patients treated with shorter regimens should be closely monitored for signs of treatment failure or relapse. Modification of the regimen may need to be considered in individual cases to reduce the risk of treatment failure or relapse.

Higher smear grade at baseline and culture positivity after 8 weeks of treatment predicted a poor treatment outcome, which is consistent with several reports.<sup>14,28</sup> A KwaZulu-Natal study reported culture conversion to be poorly predictive of a successful treatment outcome but an important predictor of survival among patients with resistance to rifampicin, FQs and aminoglycosides.<sup>29</sup>

In the univariable analysis, cavitary disease and extent of opacities or advanced disease were radiologically predictive of FoR. This is consistent with several reports and may be reflective of a higher bacillary load.<sup>15,21,30</sup> Patients with extensive lung lesions may benefit from longer duration of treatment. A favourable radiological response may correlate with bacteriological and clinical response;<sup>31</sup> the role of CXR in treatment monitoring may need to be investigated further. In our study, CXRs were only taken at baseline and it was not possible to assess the radiological evolution of pulmonary lesions.

A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary TB reported patients with high smear grades and cavitation may require treatment durations of more than 6 months for a successful outcome.<sup>32</sup> Likewise, patients with RR-TB at risk for relapse receiving shorter regimens may benefit from tailored treatment durations. In the present study, clinicians were encouraged to consider extending the intensive phase of treatment for patients whose smears were slow to convert. This was not done consistently and consequently it was difficult to assess whether this approach was beneficial.

Smoking was associated with FoR in the third model; several studies have reported an association with poor treatment outcomes of TB and recurrent TB.<sup>33</sup> Unfortunately, we did not routinely collect information on alcohol use; it was therefore not possible to assess its association with FoR, although this may be associated with male sex and smoking. A meta-analysis and observational studies have reported alcohol use as a predictor of poor treatment outcomes in both drug-susceptible and MDR-TB.<sup>14,28,34</sup>

There was some evidence in our study to suggest that participants with a low baseline body mass index (BMI) had a higher risk of FoR than those with a normal BMI, in the range 18.5–24.9 kg/m<sup>2</sup>; an association between low BMI and poor outcomes has been shown elsewhere.<sup>16,30,35</sup> Failure to gain

weight has also been shown to be predictive of an unfavourable response to treatment in underweight MDR-TB patients.<sup>36</sup> Further analyses of BMI evolution in STREAM patients are planned.

It is important to consider the value of adherence in preventing treatment failure and improving the relapse-free cure rate. Even minimal non-adherence and missed doses can adversely impact treatment outcomes.<sup>32,37</sup> Adherence support strategies, which can be achieved more readily in the context of a clinical trial, should also be implemented alongside the delivery of all TB treatment. It is likely that participants experiencing a severe adverse drug reaction may adhere less well to treatment and consequently have a less favourable outcome following treatment modification.<sup>38</sup>

The use of bedaquiline, linezolid and later-generation FQs in regimens for MDR- and extensively drug-resistant TB has been associated with improved treatment success.<sup>19,39,40</sup> Some studies have reported that the use of moxifloxacin as compared with GFX in shorter regimens was associated with FoR, and that GFX is more effective in overcoming low-level FQ resistance and in preventing acquired resistance during treatment.<sup>11,41</sup> The WHO recently recommended an all-oral shorter regimen with levofloxacin and bedaquiline as the core drugs for selected patients with MDR/RR-TB.<sup>42</sup> The inclusion of the most effective drugs such as bedaquiline and linezolid, has the potential to improve treatment outcomes of shorter regimens. The results of STREAM Stage 2 will further guide evidence-based recommendations on all-oral shorter regimens.

There are a number of limitations of the present analysis. These include the size of the study population and the inability to include certain factors which have been shown to be predictors in other studies, in particular alcohol consumption, adherence (for which the data from the present study were not considered to be sufficiently reliable to include) and CD4 counts in HIV-positive participants.

In conclusion, the results presented here have identified factors associated with FoR when patients with RR-TB are treated with the STREAM 9-11 month regimen. The role of the risk factors should be considered when monitoring response to treatment. It is important to note that resistance to FQs, which would be expected to have a poor outcome with this regimen, was largely excluded from this patient population. Such patients are likely to require the addition of one of the new generation of drugs in the regimen to ensure a successful outcome.

#### *Acknowledgements*

The authors would like to thank all the participants and collaborators without whom the STREAM study would not have been possible.

This study was made possible by the United States Agency for

International Development (USAID) through the TREAT TB Cooperative Agreement No. GHN-A-00-08-00004, with additional funding from the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement. The MRC Clinical Trials Unit at University College London (London, UK) is supported by the MRC (programme number MC\_UU\_00004/04).

STREAM sub-study collaborators: M Teferi, H Teklu (Armauer Hansen Research Institute, Addis Ababa, Ethiopia); E Ndlovu, S Majola (King Dinuzulu Hospital Complex, Durban, South Africa); K Sanders, W Dodds (MRC Clinical Trials Unit at University College London, London, UK); B Rash, Z Khukhkhuuhen (National Center for Communicable Diseases, Mongolia); P T Dat, P T Khanh (Pham Ngoc Tach Hospital, Ho Chi Minh City, Vietnam); P Howell, F Conradie (Sizwe Tropical Disease Hospital, Johannesburg, South Africa); Y Tedla (St Peter's Tuberculosis Specialized Hospital, Addis Ababa, Ethiopia); L Dunn (Think Tuberculosis & HIV Investigative Network, Doris Goodwin Hospital, South Africa).

Conflicts of interest: none declared.

## References

- World Health Organisation. Global tuberculosis report, 2020. Geneva, Switzerland: WHO, 2020.
- World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update. Geneva, Switzerland: WHO, 2011.
- Van Deun A, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2010;182(5):684–692.
- Trébuq A, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. *Int J Tuberc Lung Dis* 2018;22(1):17–25.
- World Health Organisation. WHO treatment guidelines for tuberculosis - 2016 update. Geneva, Switzerland: WHO, 2016.
- Nunn AJ, et al. A trial of a shorter regimen for rifampin-resistant tuberculosis. *N Engl J Med* 2019;380(13):1201–1213.
- Phillips PPJ, et al. Investigation of the efficacy of the short regimen for rifampicin-resistant TB from the STREAM trial. *BMC Med* 2020;18(1):314.
- Chiang CY, et al. Glycemic control and radiographic manifestations of tuberculosis in diabetic patients. *PLoS One* 2014;9(4):e93397.
- Heinze G, Wallisch C, Dunkler D. Variable selection—a review and recommendations for the practicing statistician. *Biometric J* 2018;60(3):431–449.
- Morris TP, et al. Proposals on Kaplan–Meier plots in medical research and a survey of stakeholder views: KMunicate. *BMJ Open* 2019;9(9):e030215.
- Trébuq A, et al. Short-course regimen for multidrug-resistant tuberculosis: a decade of evidence. *J Clin Med* 2020;9(1):55.
- Schwöbel V, et al. Outcomes of a nine-month regimen for rifampicin-resistant tuberculosis up to 24 months after treatment completion in nine African countries. *EClinicalMedicine* 2020;20:100268.
- Abidi S, et al. Standardised shorter regimens versus individualised longer regimens for rifampin-or multidrug-resistant tuberculosis. *Eur Respir J* 2020;55(3):1901467.
- Kurbatova EV, et al. Predictors of poor outcomes among patients treated for multidrug-resistant tuberculosis at DOTS-plus projects. *Tuberculosis* 2012;92(5):397–403.
- Bhering M, Duarte R, Kritski A. Predictive factors for unfavourable treatment in MDR-TB and XDR-TB patients in Rio de Janeiro State, Brazil, 2000–2016. *PLoS One* 2019;14(11):e0218299.
- Meressa D, et al. Achieving high treatment success for multidrug-resistant TB in Africa: initiation and scale-up of MDR TB care in Ethiopia—an observational cohort study. *Thorax* 2015;70(12):1181–1188.
- Bastard M, et al. Outcomes of HIV-infected versus HIV-non-infected patients treated for drug-resistance tuberculosis: multicenter cohort study. *PLoS One* 2018;13(3):e0193491.
- Brust JC, et al. Improved survival and cure rates with concurrent treatment for multidrug-resistant tuberculosis–human immunodeficiency virus coinfection in South Africa. *Clin Infect Dis* 2018;66(8):1246–1253.
- Bisson GP, et al. Mortality in adults with multidrug-resistant tuberculosis and HIV by antiretroviral therapy and tuberculosis drug use: an individual patient data meta-analysis. *Lancet* 2020;396(10248):402–411.
- Pietersen E, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet* 2014;383(9924):1230–1239.
- Umanah TA, Ncayiyana JR, Nyasulu PS. Predictors of cure among HIV co-infected multidrug-resistant TB patients at Sizwe Tropical Disease Hospital Johannesburg, South Africa. *Trans R Soc Trop Med Hyg* 2015;109(5):340–348.
- Gandhi NR, et al. Risk factors for mortality among MDR-and XDR-TB patients in a high HIV prevalence setting. *Int J Tuberc Lung Dis* 2012;16(1):90–97.
- Havlr DV, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med* 2011;365(16):1482–1491.
- Blanc F-X, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* 2011;365(16):1471–1481.
- Van Hout MC, Hope V. Treatment outcomes and antiretroviral uptake in multidrug-resistant tuberculosis and HIV co-infected patients in Sub Saharan Africa: a systematic review and meta-analysis. *BMC Infect Dis* 2019;19(1):1–8.
- van der Walt M, Lancaster J, Shean K. Tuberculosis case fatality and other causes of death among multidrug-resistant tuberculosis patients in a high HIV prevalence setting, 2000–2008, South Africa. *PLoS One* 2016;11(3):e0144249.
- Magis-Escurra C, et al. Treatment outcomes of MDR-TB and HIV co-infection in Europe. *Eur Respir J* 2017;49(6):1602363.
- Chaves Torres NM, et al. Factors predictive of the success of tuberculosis treatment: A systematic review with meta-analysis. *PLoS One* 2019;14(12):e0226507.
- O'Donnell MR, et al. Treatment outcomes for extensively drug-resistant tuberculosis and HIV co-infection. *Emerg Infect Dis* 2013;19(3):416.
- Goswami A, et al. Correlates of treatment outcomes and drug resistance among pulmonary tuberculosis patients attending tertiary care hospitals of Kolkata, India. *PLoS One* 2014;9(10):e109563.
- Yadav AK, et al. Study of factors influencing response and outcome of Cat-IV regimen in MDRTB patients. *Indian J Tuberc* 2016;63(4):255–261.
- Imperial MZ, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. *Nature med* 2018;24(11):1708–1715.
- Chiang C-Y, Bam TS. Should tobacco control intervention be implemented into tuberculosis control program? *Expert Rev Respir Med* 2018;12(7):541–543.
- Ragan E, et al. The impact of alcohol use on tuberculosis treatment outcomes: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2020;24(1):73–82.
- Alemu A, Bitew ZW, Worku T. Poor treatment outcome and its predictors among drug-resistant tuberculosis patients in Ethiopia: a systematic review and meta-analysis. *International Journal of Infect Dis* 2020;
- Gler MT, et al. Weight gain and response to treatment for multidrug-resistant tuberculosis. *Am J Trop Med Hyg* 2013;89(5):943–949.
- Elliott E, Draper H, Baitsiwe P, Claassens M. Factors affecting treatment outcomes in drug-resistant tuberculosis cases in the

- Northern Cape, South Africa. *Public Health Action* 2014;4(3): 201–203.
- 38 Prasad R, Singh A, Gupta N. Adverse drug reactions in tuberculosis and management. *Indian J Tuberc* 2019;66(4):520–532.
- 39 Jeong B-H, et al. Outcomes of pulmonary MDR-TB: impacts of fluoroquinolone resistance and linezolid treatment. *J Antimicrob Chemother* 2015;70(11):3127–3133.
- 40 Collaborative Group for the Meta-Analysis of Individual Patient Data in MDR-TB treatment–2017; Ahmad N, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *Lancet* 2018;392(10150):821–834.
- 41 Khan FA, et al. Effectiveness and safety of standardised shorter regimens for multidrug-resistant tuberculosis: individual patient data and aggregate data meta-analyses. *Eur Respir J* 2017;50(1):1700061.
- 42 World Health Organization. WHO operational handbook on tuberculosis. Module 4: treatment–drug-resistant tuberculosis treatment. Geneva, Switzerland: WHO, 2020.

---

**R É S U M É**

**CONTEXTE :** L'essai clinique STREAM (Standardised Treatment Regimens of Anti-tuberculosis drugs for Multidrug-Resistant Tuberculosis) Étape 1 a démontré l'efficacité non inférieure d'un schéma court pour le traitement de la TB résistante à la rifampicine (RR-TB) par rapport au schéma long recommandé par l'OMS. Cet article analyse les facteurs associés à une récurrence ou à un échec (FoR) confirmé(e) ou probable chez les participants sous schéma court.

**MÉTHODES :** Cette analyse porte sur 253 participants sous schéma court et se fonde sur la population en intention de traiter modifiée (mITT) définie par le protocole. Les modèles multivariés de régression de Cox ont été construits en utilisant une approche d'élimination descendante avec une probabilité de sortie de  $P = 0,157$ , équivalente au critère d'information d'Akaike, afin d'identifier les facteurs

indépendamment associés aux FoR confirmés ou probables.

**RÉSULTATS :** Quatre facteurs présents à l'inclusion ont été identifiés comme étant significativement associés au risque de FoR confirmé(e) ou probable (genre masculin, frottis positif de grade très élevé à l'inclusion, co-infection par le VIH et présence d'oblitération de l'angle costophrénique). Une association entre une culture positive en Semaine 8 et la survenue d'un FoR a été observée dans un second modèle. Une association entre un frottis positif en Semaine 16, un diabète, un tabagisme et un FoR a été mise en évidence dans un troisième modèle.

**CONCLUSION :** Les facteurs associés à un FoR identifiés dans cette analyse doivent être pris en compte lors du choix optimal de schéma thérapeutique court.

---