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Treating drug-resistant tuberculosis in an era of shorter regimens: Insights from rural South Africa

J-D K Lotz,[1,2] MB ChB, FCFP; **J D Porter,**[1,3,4] MB ChB, FCFP; **H H Conradie,**[5] MB ChB, FCFP; **T H Boyles,**[6,7,8] BM BCh, Cert ID; **C B Gaunt,**[9] MB ChB, MSc; **S Dimanda,**[2] BMCP; **D Cort,**[10] MA, PhD

[1] *Department of Family Medicine and Rural Health, Walter Sisulu University, Mthatha, South Africa*
[2] *Madwaleni District Hospital, Elliotdale, South Africa*
[3] *Division of Family Medicine, Department of Family, Community, and Emergency Care, University of Cape Town, South Africa*
[4] *False Bay District Hospital, Cape Town, South Africa*
[5] *Department of Family Medicine and Primary Care, Stellenbosch University, Cape Town, South Africa*
[6] *Right to Care, Centurion, South Africa*
[7] *Clinical HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa*
[8] *London School of Hygiene and Tropical Medicine, London, United Kingdom*
[9] *Zithulele District Hospital, Coffee Bay, South Africa*
[10] *Department of Sociology, University of Massachusetts, Amherst, USA*

Corresponding author: *J-D K Lotz (jdlotz@gmail.com)*

Background. Progressive interventions have recently improved programmatic outcomes in drug-resistant tuberculosis (DR-TB) care in South Africa (SA). Amidst these, a shorter regimen was introduced in 2017 with weak evidence, and has shown mixed results. Outcomes still fall short of national targets, and the coronavirus disease 2019 pandemic has undermined progress to date.
Objectives. To describe the outcomes of participants treated for DR-TB using a shorter, compared with a longer, regimen in a deeply rural SA setting, and to explore other factors affecting these outcomes.
Methods. This retrospective cohort study describes outcomes in short and long DR-TB treatment regimens, over 5 years, at two rural treatment sites in SA. Characteristics were analysed for outcome correlates using multivariable logistic regression models.
Results. Of 282 treatment episodes, 62% were successful, with higher success in shorter (69%) compared with longer regimens (58%). Mortality was approximately 21% in both groups. Characteristics included high proportions of HIV co-infection (61%). Injectables (adjusted odds ratio (aOR) 3.00, 95% confidence interval (CI) 1.48 - 6.09), bedaquiline (aOR 3.16, 95% CI 1.36 - 7.35), increasing age (aOR 0.97, 95% CI 0.95 - 0.99) and HIV viraemia defined as final HIV-RNA viral load >1 000 copies/mL (aOR 0.16, 95% CI 0.07 - 0.37) were all significantly and independently associated with treatment success. Injectables (aOR 0.22, 95% CI 0.08 - 0.57), bedaquiline (aOR 0.05, 95% CI 0.01 - 0.19), increasing age (aOR 1.09, 95% CI 1.05 - 1.13), extra-pulmonary TB (aOR 8.15, 95% CI 1.62 - 41.03) and HIV viraemia (aOR 9.20, 95% CI 3.22 - 26.24) were all significantly and independently associated with mortality.
Conclusion. In a rural context, treating DR-TB amid limited resources and a high burden of HIV co-infection, we found that after considering controls, a short regimen was no different to a longer regimen in terms of success or mortality. Therefore, by alleviating burdens on multiple stakeholders, a short regimen is likely to be favourable for rural patients, clinicians, and healthcare systems. Besides other previously described correlates of outcomes, HIV viraemia emerged as a novel marker for reliably predicting poor outcomes in DR-TB with HIV co-infection, and a pragmatic target for intervention.

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Despite being recently overshadowed by the urgency of the novel coronavirus disease 2019 (COVID-19) pandemic, tuberculosis (TB) remains a huge global burden. Approximately one-quarter of the world's population is infected by the bacillus *Mycobacterium tuberculosis*. Of these, 10.6 million cases progressed to active disease in 2021, and around 1.6 million people died.[1] In 2019, TB was still the leading global cause of death by a single infectious organism.[2] Drug-resistant TB (DR-TB) forms a significant proportion of this burden, comprising around 4% of incident cases.[1] In comparison to drug-susceptible strains (DS-TB), treatment up until recently has been prolonged (9 -24 months), is more expensive, and has less favourable outcomes.[1,3,4] As one of seven countries who shoulder two-thirds of the global burden, South Africa (SA) carries a disproportionately large share of global DR-TB.[1] The local DR-TB landscape included 13 005 patients diagnosed, and 8 743 (67%) initiated on treatment in 2019,[5] and a number of focused interventions have recently been introduced in response. However, set in the most unequal country in the world (based on Gini coefficients),[6] the contours of this landscape require careful mapping to understand the disaggregated effects of these interventions. A rural facet is, as far as the authors of this study are aware, yet to be well described.

Rurality is difficult to define, but according to the World Bank accounted for around one-third of South Africa's population in 2019.[7] Rural areas are marked by above-average levels of unemployment and poverty, poor infrastructure, lower proportions of healthcare workers employed, and unequal access to basic services, including healthcare.[8] Rural communities, and clinicians, therefore face unique barriers to care, but progressive iterations of national programmatic DR-TB care have provided potential ameliorants.[9] These include decentralisation of treatment sites,[10] improved diagnostics,[11] increasing access to novel and repurposed drugs,[12,13] and the introduction of a shortened (9 - 11-month) regimen[14] – subsequently modified

to replace injectable agents with bedaquiline.[15,16] Amidst these, however, a shorter (9 - 11-month) regimen was initially introduced with weak evidence, and has shown mixed results.[17] It was with a conditional recommendation based on very low quality of evidence that the World Health Organization (WHO) initially recommended its implementation in their 2016 update on DR-TB treatment guidelines,[14] and that it should be implemented programmatically in SA in 2017.[16] Despite performing well under study conditions,[18,19] a subsequent review under programmatic conditions by the WHO then found a pooled adjusted odds ratio (aOR) of 2.0 for treatment failure or relapse when compared with longer regimens (and an aOR of 1.2 for death).[20] Evolution of regimens continues, and an even shorter 6-month regimen for treating multidrug-resistant (MDR)/rifampicin-resistant (RR)-TB (comprising bedaquiline, pretomanid, linezolid and moxifloxacin) has recently been recommended by the WHO and awaits programmatic implementation.[4]

As new data emerge to inform an agile DR-TB programme in SA, high-level interventions remain blunt tools without careful guidance using nuanced data from different contexts, and with critical monitoring over time. In light of existing aggregate data, and on the brink of the next iteration of programmatic regimen changes, this study thus sought to critically analyse the effects that an initial (9 -11-month) shorter regimen had on DR-TB treatment outcomes, specifically in a deeply rural SA setting. Such an analysis, focusing on two district hospital treatment programmes, over 5 years of iterative interventions and programmatic changes, also presented the opportunity to retrospectively observe the impacts that various other factors may have had on the risks of a successful treatment outcome, or death.

Such contextual descriptions are vital for mapping out the varied contours of the local, and indeed global, DR-TB landscape. It is hoped that elucidating these nuances may help inform and sharpen current and future tools at our disposal in the fight against TB – especially in the ongoing work towards equitable and quality care that rural healthcare workers strive to achieve with the communities they serve. With a COVID-19 pandemic undermining the progress made in recent years, understanding how to improve TB care is now more urgent than ever.

Objectives

This study thus sought to describe the outcomes of participants treated for DR-TB using a shorter (9 - 11-month), compared with a longer (>18-month) regimen, at two facilities in a deeply rural SA setting. Other characteristics affecting these outcomes were then explored.

Methods

Study design and participants

We performed a retrospective cohort study by analysing all existing patient records for episodes of RR-TB or MDR-TB treatment initiated by either of the two sites, between 1 January 2015 and 30 June 2018 for those treated using a long treatment regimen, and between 1 January 2015 and 31 March 2019 for those treated using a short regimen. This ensured that all episodes received outcomes before data collection. Patient records included onsite patient folders, and online records such as the EDRweb (WAMtechnology, 2018) – an online register of DR-TB patients in SA – and National Health Laboratory Services records of patient results. These records were accessed between July 2019 and October 2020.

Episodes were selected for shorter or longer regimens by local clinicians at respective treatment sites as part of routine programmatic care, based on contemporary SA guidelines.[10,12,15,21,22] A summary of standardised regimens used by participants is available in the attached appendix (https://www.samedical.org/file/2128; Table A1). According to these guidelines, exclusion criteria for a short regimen included previous exposure to second-line anti-tuberculous drugs for more than 1 month, evidence of extended resistance (to fluoroquinolones, injectable agents, bedaquiline, clofazimine, or linezolid), and extensive extra-pulmonary TB (EPTB) disease (including meningitis, pericarditis, osteoarticular, or abdominal disease) or extensive, bilateral, cavitatory pulmonary disease. While regimen selection occurred at the point of treatment initiation, certain situations also required a switch from shorter to longer regimens. These included new evidence of resistance, persistently positive sputum culture results at month 4 of treatment, premature discontinuation of key drugs (including bedaquiline, linezolid, levofloxacin, or clofazimine) for reasons such as toxicity, or a clinical deterioration. In such cases, the episode would be classified programmatically according to the final regimen received.[15]

Study exclusion criteria included episodes with any migration between treatment sites, and those with extended resistance – including dual mutations to isoniazid (in both *inhA* and *katG* genes), or resistance to either fluoroquinolones or injectables. These resistance patterns required alternative regimens and precluded the use of a shorter regimen. There were no exclusion criteria based on age, so episodes of treatment in all age groups were included.

Study setting

Two rural district level hospitals were thus selected for participation in this study. Situated along the Wild Coast area of the Eastern Cape Province – an area comprising part of what was formerly known as the Transkei, a designated 'homeland' that suffered from systematic deprivation under Apartheid rule in South Africa – Madwaleni and Zithulele Hospitals have both been designated as decentralised sites for the initiation and ongoing management of DR-TB since 2014.

DR-TB programmes are serviced by generalist medical practitioners and clinical associates (CAs), and form only one component of a comprehensive package of 24-hour district-level generalist care being offered at each facility. The number of doctors and CAs varied between 8 and 14 for each of the facilities over the period of this study, servicing populations of around 150 000 and 130 000, respectively, via a referral network of nurse-led primary- and community-level healthcare facilities. Generalists had not received specialised training in the management of DR-TB, but had benefited from telephonic and electronic support from more specialised practitioners at other facilities. More recently, specialist family physicians were employed at both facilities to further support comprehensive clinical oversight.

Data analysis

Data were initially reviewed and cleaned by screening for missing data or erroneous (impossible) data entries (such as negative time durations). These were mitigated by correlation between various sources of patient records (such as patient files and online records) and removing erroneous entries if no reasonable correction could be found. Once reviewed, de-identified data were analysed using Stata version 15 (StataCorp., USA). For categorical data, frequencies and proportions were described as *n* (%) unless otherwise specified. To describe measured data that were not normally distributed, medians (with interquartile ranges (IQR)) were used.

The two treatment groups of short and long regimens were compared in terms of outcomes and characteristics (Table 1). In accordance with WHO norms on reporting,[20,23] two main outcomes were defined for this study: treatment success (defined as WHO

Table 1. Demographic and clinical characteristics

Characteristic	All (*N*=282); *n* (%)*	Regimen, *n* (%)*		*p*-value
		Short (*n*=105)	Long (*n*=177)	
Study outcome				
Success†	175 (62.06)	72 (68.57)	103 (58.19)	0.042
Death	60 (21.28)	23 (21.90)	37 (20.90)	0.422
Programmatic outcome‡				0.122
Cured	166 (58.87)	69 (65.71)	97 (54.80)	
Completed	9 (3.19)	3 (2.86)	6 (3.39)	
Lost to follow-up	45 (15.96)	9 (8.57)	36 (20.34)	
Treatment failure	2 (0.71)	1 (0.95)	1 (0.56)	
Death	60 (21.28)	23 (21.90)	37 (20.90)	
Demographic				
Female sex	103 (36.52)	43 (40.95)	60 (33.90)	0.118
Age, years (median (IQR))	40 (31 - 52)	41 (32 - 54)	40 (29 - 50)	0.068
TB characteristic				
Treatment history				
No previous TB	141 (50.00)	49 (46.67)	92 (51.98)	0.195
Previous DR-TB§	24/141 (17.02)	-	24/85 (28.24)	<0.001
Previous DR-TB unsuccessful¶	17/24 (70.83)	-	17/24 (70.83)	<0.001
Infection site				0.101
Pulmonary	271 (96.10)	103 (98.10)	168 (94.92)	
Lymphadenitis	4 (1.42)	2 (1.90)	2 (1.13)	
Pleural effusion	2 (0.71)	-	2 (1.13)	
Meningitis	5 (1.77)	1 (0.95)	4 (2.26)	
Disseminated or other EPTB	9 (3.19)	-	9 (5.08)	
Drug resistance profile				0.005
MDR	130 (46.10)	42 (40.00)	88 (49.72)	
RR‖	61 (21.63)	21 (20.00)	40 (22.60)	
RMR**	91 (32.27)	42 (40.00)	49 (27.68)	
Treatment cohort††				< 0.001
Old regimen era	142 (50.35)	-	142 (80.23)	
Short regimen era	100 (35.46)	71 (67.62)	29 (16.38)	
All-oral era	40 (14.18)	34 (32.38)	6 (3.39)	
Baseline sputum AFB				0.783
Negative	160 (56.74)	62 (59.05)	98 (55.37)	
Positive	109 (38.65)	39 (37.14)	70 (39.55)	
Not done	13 (4.61)	4 (3.81)	9 (5.08)	
Baseline sputum TB culture				0.380
Negative	90 (31.91)	32 (30.48)	58 (32.77)	
Positive	175 (62.06)	64 (60.95)	111 (62.71)	
Not done	17 (6.03)	9 (8.57)	8 (4.52)	
Treatment characteristics				
Short regimen‡‡	105 (37.23)	-	-	
Madwaleni programme§§	180 (63.83)	62 (59.05)	118 (66.67)	0.100
Days to initiation of treatment¶¶ (median (IQR))	10 (6 - 19)	8 (5 - 14)	10 (7 - 22)	0.359
Injectable agents used >1 month	116 (41.13)	25 (23.81)	91 (51.41)	< 0.001
Bedaquiline used	117 (41.49)	72 (68.57)	45 (25.42)	< 0.001
Baseline AFB positive	109 (38.65)	39 (37.14)	70 (39.55)	0.783
Baseline sputum culture positive	175 (62.06)	64 (60.95)	111 (62.71)	0.380
Days to AFB conversion (median (IQR))	35 (28 - 60)	30 (27 - 48)	43 (31 - 67)	0.089
Days to TB culture conversion (median (IQR))	49 (32 - 71)	45 (28 - 67)	50 (34 - 78)	0.098
Total inpatient days (median (IQR))	39 (22 - 66)	35 (20 - 57)	44 (25 - 77)	0.059
Number of admissions				0.014
0	12 (4.26)	-	12 (6.78)	
1	246 (87.23)	98 (93.33)	148 (83.62)	
>1	24 (8.51)	7 (6.67)	17 (9.60)	

(continued)

Table 1. (continued) Demographic and clinical characteristics

Characteristic	All (*N*=282); *n* (%)*	Regimen, *n* (%)*		*p*-value
		Short (*n*=105)	Long (*n*=177)	
HIV status				0.161
HIV negative	107 (37.94)	43 (40.95)	64 (36.16)	
Newly positive	28 (9.93)	5 (4.76)	23 (12.99)	
Known positive	145 (51.42)	56 (53.33)	89 (50.28)	
Not tested	2 (0.71)	1 (0.95)	1 (0.56)	
Baseline CD4 count (of available data), cells/mm^3 (median (IQR))	161 (53 - 291)	175 (32 - 317)	155 (62 - 283)	0.403
HIV viral load suppression (of available data; *n*/*N* (%))				
VL <1 000 at DR-TB start, copies/mL‖‖	77/173 (44.51)	30/61 (49.18)	47/112 (41.96)	0.459
VL <1 000 at DR-TB outcome, *n*/*N* (%))***	110/173 (63.58)	39/61 (63.93)	71/112 (63.39)	0.529

IQR = interquartile range; TB = tuberculosis; DR-TB = drug-resistant TB; EPTB = extra-pulmonary TB; MDR = multidrug-resistant; RR = rifampicin-resistant; RMR = rifampicin mono-resistant; AFB = acid-fast bacilli; VL = viral load.
*Unless otherwise specified.
†'Success' defined as episodes of treatment assigned with programmatic outcomes of 'cured' or 'completed'.
‡Programmatic outcomes as defined by South African National DR-TB Guidelines.
§Previously treated for DR-TB, of all previously treated for any TB: *n*/*N* (%)
¶Previous DR-TB interruption or treatment failure, of all previously treated for DR-TB: *n*/*N* (%)
‖Confirmed resistance to rifampicin, but unknown resistance to other drugs.
**Confirmed resistance to rifampicin, and confirmed sensitivity to isoniazid.
††'Old regimen era' describes patients initiated 1 January 2015 - 16 January 2017 and comprised only a long regimen requiring injectables (unless substituted with bedaquiline); the 'Short regimen era' describes those initiated 17 January 2017 - 30 June 2018 incorporating the introduction of a shorter regimen for eligible cases; and the 'all-oral era' describes those initiated 1 July 2018 onwards – during which injectables were removed from all regimens.
‡‡The (9 - 11-month) short regimen, referenced against the long (18 - 24-month) regimen.
§§Referenced against episodes from the Zithulele programme.
¶¶Data were missing for 42 observations of time to initiation, and median imputation was conducted to mitigate the effect of these missing data.
‖‖VL <1 000 copies/mL at initiation of DR-TB treatment; VL imputed as >1 000 for episodes categorised as newly diagnosed HIV.
***Final VL <1 000 copies/mL at the time of being assigned a DR-TB treatment outcome.

and SA National guideline definitions of 'cured' or 'completed'),[15,24] compared with any other outcome; and death compared with survival (i.e. death compared with all other programmatic outcomes). As this study used only programmatic definitions of DR-TB treatment outcomes and did not include further post-treatment follow-up, deaths that occurred after an outcome was assigned were not recorded. Characteristics were selected in accordance with data available in patient records, with additional categorisations including era of treatment initiation, and the clinical categorisation of HIV into 'negative', 'positive with successful viral load (VL) suppression' (defined as a final VL of <1 000 copies/mL before being assigned with a DR-TB treatment outcome) and 'positive with viraemia' (defined as a final VL of >1 000 copies/mL before being assigned with a DR-TB treatment outcome).

Outcomes and characteristics were initially compared, stratified according to shorter v. longer treatment regimens for a simple description. For hypothesis testing, Student's *t*-test was used to compare continuous, or binary, independent variables with a binary dependent variable. A χ^2 test was performed to compare categorical independent variables with binary dependent variables.

To elucidate the independent effect that regimen had on outcomes, as well as to explore factors that affected outcomes of treatment success or death, multivariable logistic regression models were built for each of the two study outcomes – a model for treatment success as a binary dependent variable of successful v. not successful, and a model for death as a binary dependent variable of death v. survival. A purposeful selection model-building strategy was performed.[25] Independent variables were selected for inclusion in the regressions based on known correlates demonstrated in other literature,[26,27] and variables deemed of clinical significance by the authors. Univariate followed by multivariable models are presented for each outcome in Tables 2 and 3. Summary plots of the multivariable models are presented in Fig. 1. All analyses were conducted according to existing data, with the exception of the 'time to initiation' variable, where median imputation was conducted for 42 cases of missing data in order to mitigate listwise deletion effects in the regression models. Further details can be obtained directly from the authors on request.

Ethical considerations

This analysis was approved by the Human Research Committee of Walter Sisulu University (ref. no. 116/2018), the Eastern Cape Health Research Committee (ref. no. EC-201904-024), and local management at research sites. The requirement for informed consent was waived as this retrospective record review had no influence on patient care. Adverse drug reactions were reported by clinicians prior to the study and are summarised in the appendix (https://www.samedical.org/file/2128; Table A.2).

Results

A total of 426 episodes of DR-TB treatment initiation were identified for inclusion, with 282 declared eligible according to study criteria (Fig. 2).[28] Baseline demographics and characteristics for all of these 282 eligible episodes are shown in Table 1. Of these, 105 (37%) were treated with the short treatment regimen, and 177 (63%) with the longer.

Overall, 175 episodes (62%) were successfully treated, and there were 60 deaths (21%). Rates of treatment success were significantly different between the short- and long-treatment groups; 72 episodes (69%) were successful after the shorter regimen treatment, compared with 103 episodes (58%) receiving the long regimen (p=0.042). There was no significant difference in deaths between the two treatment regimens (22% v. 21%, p=0.422). While a comparison of all categories of programmatic outcomes using a χ^2 test yielded no significant difference when tested together (p=0.122), there was a notable difference observed in proportions of those lost to follow-up (9% v. 20%).

HIV characteristics did not differ significantly between the two treatment groups. Overall, 173 patients (61%) were co-infected with HIV, with a median (IQR) baseline (at the time of initiating

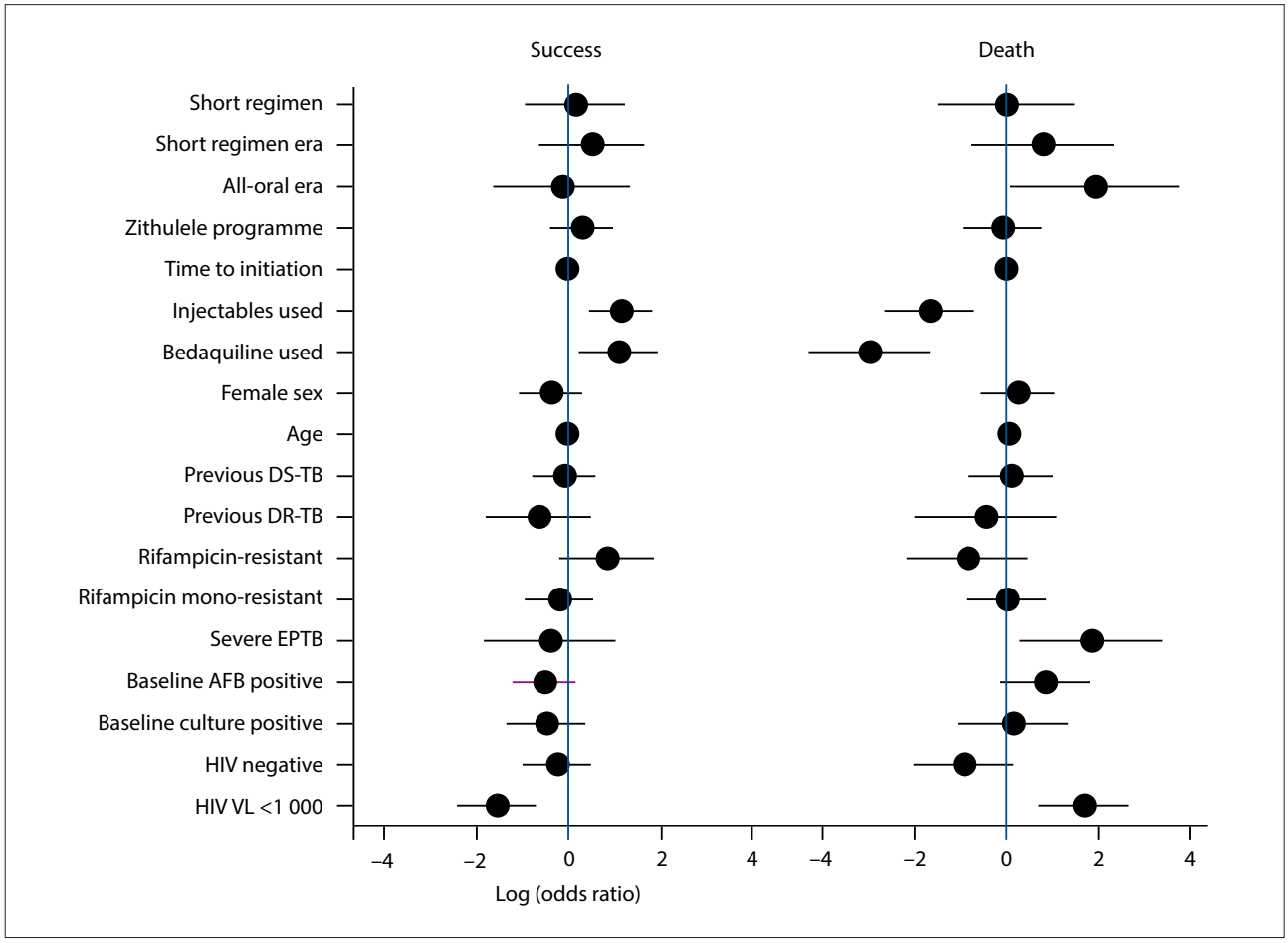

Fig. 1. Summary plot of the multivariable logistic regression models illustrating the adjusted effects of characteristics on outcomes of success and death. (DS-TB = drug-susceptible TB; DR-TB = drug-resistant TB; EPTB = extra-pulmonary tuberculosis; AFB = acid-fast bacilli; VL = viral load).
Raw coefficients are presented (as natural log of odds ratios, or log-odds) with their 95% confidence intervals on the X axis. Plots to the left of the vertical lines (which represent 0) indicate a decrease in odds of the outcome, to the right indicate an increase in odds, and those with lines crossing 0 indicate a lack of statistical significance. Increasing distance of a plotted point from the 0 line, in either direction, represents an increasingly strong effect by that variable on the respective outcome. Of note in the success model: the use of injectables and bedaquiline show statistically significant beneficial effects, while HIV viraemia (final HIV VL >1 000 copies/mL) shows a significant negative impact on success. In the death model, injectable use and bedaquiline again both show significant benefits by decreasing odds of death, while being treated in the all-oral era, having severe EPTB, and HIV viraemia all show significant negative effects on odds of death. While not clearly apparent in this figure, increasing age also had statistically significant effects on outcomes, decreasing odds of success and increasing odds of death.

DR-TB treatment) CD4 count of 161 cells/mm^3 (53 – 291). Of these, 77 patients (45% of those co-infected) arrived for DR-TB treatment initiation with HIV VL <1 000 copies/mL, while 110 episodes (64% of those co-infected) achieved suppression <1 000 copies/mL by the time they received an outcome for their DR-TB treatment episode.

When demographics and clinical characteristics were compared between the short and longer treatment groups, significant differences were noted. Programmatically, previous exposure to DR-TB treatment precluded the use of a shorter regimen, and therefore treatment history differed significantly, while treatment cohorts (patients were initiated over three distinct programmatic eras in time during the course of this study, and so divided into three cohorts) also differed significantly (p<0.001) with the more recent introduction of the short regimen.

Besides programmatic influences, other significant differences included drug resistance profiles with lower proportions of MDR, and higher proportions of rifampicin mono-resistance (RMR) in the shorter regimen group (p=0.005). Of note, lower proportions of injectable use were observed in the short regimen (24% v. 51%, p<0.001), with higher proportions of bedaquiline use (69% v. 25%, p<0.001). Numbers of admissions differed, with no patients avoiding admission when treated with the shorter regimen, but more of these episodes only requiring a single admission (p=0.014).

Adjusted comparison of short v. long treatment regimens

Table 2 presents the findings from a logistic regression model analysing the outcome of success, while Table 3 presents the analysis of death as an outcome. In contrast to an unadjusted analysis, controlling for other factors attenuated the treatment effect that a shorter treatment regimen had on a successful outcome. There was no impact on adjusted odds of treatment success (adjusted odds ratio (aOR) 1.19, 95% confidence interval (CI) 0.39 - 3.63), or mortality (aOR 1.02, 95% CI 0.23 - 4.51) when compared with a longer regimen (Fig. 1). In a further sensitivity analysis, the use of bedaquiline emerged as the leading variable responsible for the attenuation effect.

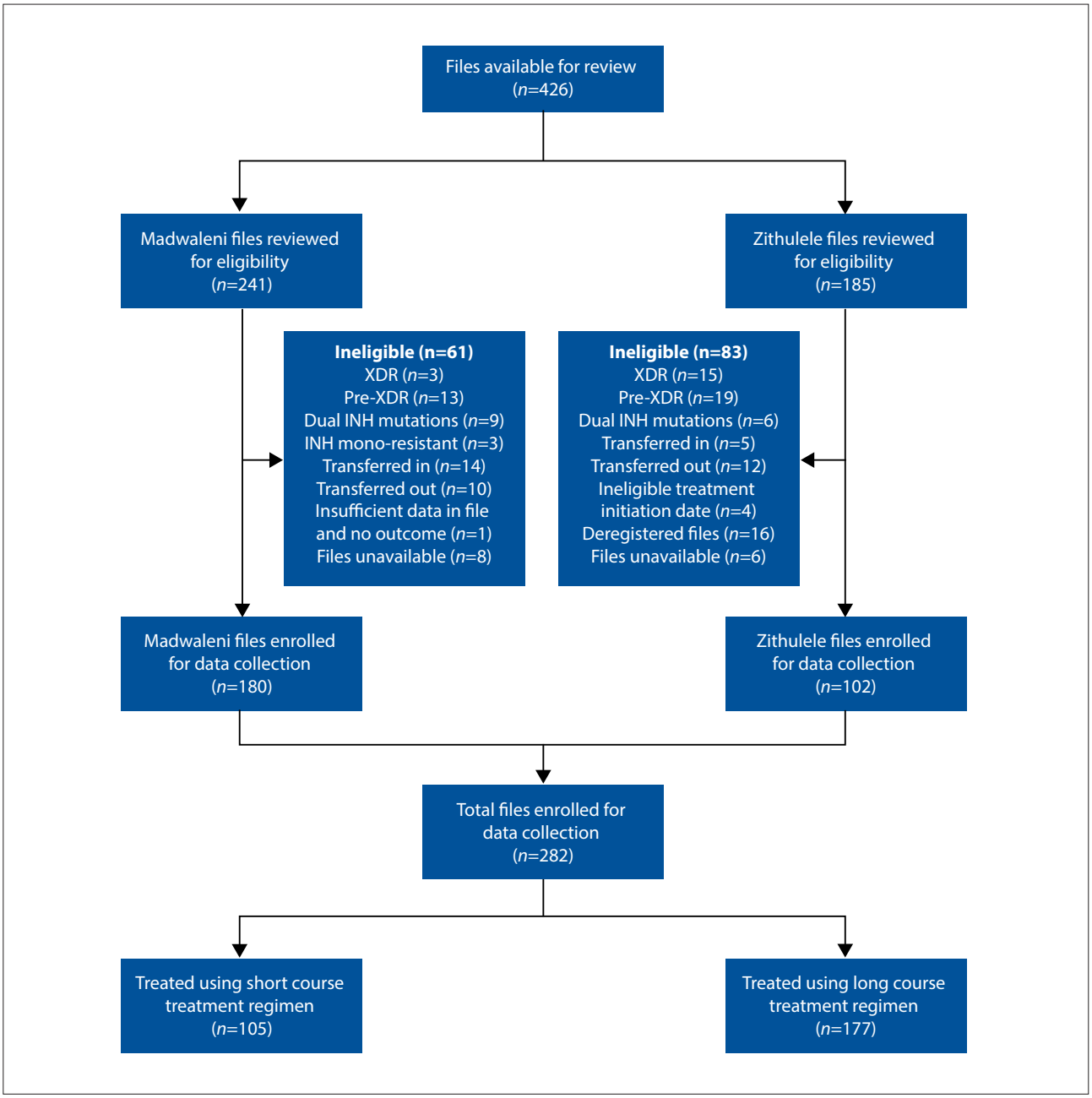

Fig. 2. CONSORT[28] diagram of process of inclusion and exclusion of files for data collection in groups of shorter and longer treatment regimens. (XDR = extensively drug-resistant TB; INH = isoniazid.)

Exploring characteristics affecting treatment success and mortality

In an exploratory approach, several other characteristics were identified that independently and significantly affected outcomes of success or death, including demographics, TB characteristics and HIV characteristics (Tables 2 and 3, and Fig. 1).

Each year of increasing age decreased odds of success by 2% (aOR 0.98, 95% CI 0.96 - 1.00), and increased odds of death by 8% (aOR 1.08, 95% CI 1.04 - 1.12). Among the three cohorts of treatment episode eras, and while using the 'old regimen era' as a reference, the only effect observed was an increase in odds of death among episodes in the 'all-oral' era (aOR 7.03, 95% CI 1.08 - 45.87).

Severe EPTB (including any extra-pulmonary site of infection besides pleural effusions and lymphadenitis) did not affect odds of success, but increased odds of death significantly by more than five-fold (aOR 6.50, 95% CI 1.37 - 30.90). Exposure to injectable agents for longer than 1 month increased the odds of success significantly by more than two-fold (aOR 3.23, 95% CI 1.60 - 6.50) compared with not being exposed for as long or having no injectable exposure. This exposure also decreased odds of death by 81% (aOR 0.19, 95% CI 0.07 - 0.50). Exposure to bedaquiline increased odds of treatment success by more than two-fold (aOR 3.04, 95% CI 1.32 - 7.02), and decreased odds of death by 95% (aOR 0.05, 95% CI 0.01 - 0.19).

HIV status was divided into three categories: those who were not infected; those infected with reasonable suppression of their VL during their DR-TB treatment course (with a final VL of <1 000 copies/mL before being assigned a DR-TB outcome); and those with HIV viraemia (final VL >1 000 copies/mL before being assigned a DR-TB outcome). When compared with a reference category of HIV-infected with VL suppression, not being infected

Table 2. Logistic regression analysis predicting odds of success

	Unadjusted model		Adjusted model	
Demographic and clinical characteristic	**OR**	**CI**	**aOR**	**CI**
Regimen				
Long	Ref.	-	-	-
Short	1.57*	0.94 - 2.61	1.19	0.39 - 3.63
Demographics				
Female sex	0.94	0.57 - 1.55	0.70	0.36 - 1.33
Age, years	0.99	0.97 - 1.00	0.98**	0.96 - 1.00
Programme				
Madwaleni	Ref.	-	-	-
Zithulele	1.05	0.63 - 1.73	1.37	0.70 - 2.66
Cohort era†				
Old regimen	Ref.	-	-	-
Short regimen	1.63*	0.95 - 2.79	1.71	0.54 - 5.41
All-oral	1.10	0.54 - 2.24	0.89	0.21 - 3.75
TB characteristics				
Severe EPTB infection‡	0.60	0.20 - 1.75	0.69	0.17 - 2.81
Time to treatment initiation§	1.00	0.99 - 1.01	1.00	0.99 - 1.01
Injectable agents used >1 month	2.32**	1.39 - 3.86	3.23**	1.60 - 6.50
Bedaquiline used	1.70**	1.03 - 2.80	3.04**	1.32 - 7.02
Baseline sputum AFB				
Negative	Ref.	-	-	-
Positive	0.46**	0.28 - 0.78	0.61	0.31 - 1.20
Not done¶	0.03**	0.00 - 0.26	0.04**	>0.00 - 0.73
Baseline sputum TB culture				
Negative	Ref.	-	-	-
Positive	0.45**	0.26 - 0.80	0.60	0.25 - 1.42
Not done	0.13**	0.04 - 0.43	0.98	0.12 - 8.22
Previous treatment history				
No previous TB	Ref.	-	-	-
Previous DS-TB	1.04	0.62 - 1.76	0.93	0.47 - 1.85
Previous DR-TB	0.48*	0.20 - 1.15	0.53	0.18 - 1.62
Previous TB, no details	0.45	0.12 - 1.76	0.37	0.07 - 1.93
Drug resistance profile‖				
MDR	Ref.	-	-	-
RR	1.49	0.78 - 2.87	2.37	0.84 - 6.70
RMR	0.83	0.48 - 1.44	0.84	0.42 - 1.67
HIV characteristics††				
HIV negative	0.67	0.38 - 1.17	0.80	0.39 - 1.63
HIV infected, final VL <1 000	Ref.	-	-	-
HIV infected, final VL >1 000	0.25**	0.13 - 0.49	0.22**	0.10 - 0.49
Intercept	-	-	4.70**	1.21 - 18.29
Sample size, *n*	282		282	

OR = odds ratio; CI = confidence interval; aOR = adjusted OR; ref. = reference; EPTB = extra-pulmonary tuberculosis; TB = tuberculosis; AFB = acid-fast bacilli; DS-TB = drug-susceptible TB; DR-TB = drug-resistant TB; MDR = multidrug-resistant; RR = rifampicin-resistant; RMR = rifampicin mono-resistant; VL = viral load; SA = South Africa.
*$p<0.10$; **$p<0.05$
†'Old regimen era' describes patients initiated 1 January 2015 - 16 January 2017 and comprised only a long regimen requiring injectables (unless substituted with bedaquiline); 'short regimen era' describes those initiated 17 January 2017 - 30 June 2018 incorporating the introduction of a shorter regimen for eligible cases; 'all-oral era' describes those initiated 01 July 2018 onwards – during which injectables were removed from all regimens.
‡Including any extra-pulmonary site of TB infection besides pleural effusion and lymphadenitis – a precluding criteria for using a short regimen in SA.
§To mitigate listwise deletion in this regression model, median imputation was performed for 42 cases of missing data for this variable.
¶AFB sputum samples could not be collected in 13 patients, of whom 8 died within the first 1 month of treatment, and 1 further died after 1 month. In this small category sample, this likely represents a confounder in patients who were too sick to produce sputum.
‖MDR = proven or suspected resistance to both rifampicin and isoniazid; RR = proven rifampicin resistance, with unknown sensitivity to other drugs; RMR = proven rifampicin resistance and isoniazid sensitivity.
††HIV negative, or HIV positive with a final HIV-RNA VL before DR-TB treatment outcome of <1 000 copies/mL (i.e. reasonable VL suppression), or final VL >1 000 copies/mL (failure to achieve suppression before DR-TB outcome).

with HIV did not have any effects on success or death, while HIV viraemia had significant effects on outcomes of both success and death – independently decreasing odds of success by 78% (aOR 0.22, 95% CI 0.10 - 0.49), and increasing odds of death by over four-fold (aOR 5.55, 95% CI 2.07 - 14.87).

While characteristics of previous TB treatment exposures were already controlled for, a further sensitivity analysis was conducted to analyse the effect of excluding the 24 episodes of treatment with prior exposure to DR-TB therapy. The only statistically significant differences noted were in the

Table 3. Logistic regression analysis predicting odds of death

	Unadjusted model		Adjusted model	
Demographic and TB/HIV characteristic	**OR**	**CI**	**aOR**	**CI**
Regimen				
Long	Ref.	-	-	-
Short	1.06	0.59 - 1.91	1.02	0.23 - 4.51
Demographics				
Female sex	1.10	0.61 - 1.99	1.33	0.58 - 3.04
Age, years	1.03**	1.01 - 1.05	1.08**	1.04 - 1.12
Programme				
Madwaleni	Ref.	-	-	-
Zithulele	1.47	0.82 - 2.63	0.94	0.41 - 2.16
Cohort era†				
Old regimen	Ref.	-	-	-
Short regimen	1.26	0.67 - 2.34	2.28	0.49 - 10.55
All-oral	1.91	0.86 - 4.25	7.03**	1.08 - 45.87
TB characteristics				
Severe EPTB infection‡	4.06**	1.36 - 12.06	6.50**	1.37 - 30.90
Time to treatment initiation§	1.00	0.99 - 1.01	1.00	0.99 - 1.02
Injectable agents used >1 month	0.25**	0.12 - 0.51	0.19**	0.07 - 0.50
Bedaquiline used	0.53**	0.29 - 0.98	0.05**	0.01 - 0.19
Baseline sputum AFB				
Negative	Ref.	-	-	-
Positive	2.06**	1.11 - 3.81	2.28*	0.89 - 5.87
Not done	13.40**	3.81 - 47.15	1.96	0.21 - 18.69
Baseline sputum TB culture				
Negative	Ref.	-	-	-
Positive	1.99*	0.96 - 4.12	1.29	0.39 - 4.29
Not done	13.17**	4.05 - 42.76	3.57	0.47 - 27.27
Previous treatment history				
No previous TB	Ref.	-	-	-
Previous DS-TB	1.40	0.76 - 2.59	1.14	0.46 - 2.78
Previous DR-TB	1.16	0.40 - 3.40	0.65	0.14 - 3.01
Previous TB, no details	2.21	0.52 - 9.43	1.60	0.22 - 11.64
Drug resistance profile¶				
MDR	Ref.	-	-	-
RR	1.26	0.59 - 2.70	0.44	0.12 - 1.61
RMR	1.67	0.87 - 3.19	1.02	0.43 - 2.40
HIV status‖				
HIV negative	1.14	0.56 - 2.30	0.41	0.14 - 1.21
HIV infected, final VL <1000	Ref.	-	-	-
HIV infected, final VL >1000	5.54**	1.71 - 7.33	5.55**	2.07 - 14.87
Intercept			0.01**	<0.01 - 0.07
Sample Size	*n* = 282		*n* = 282	

TB = tuberculosis; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; ref. = reference; EPTB = extra-pulmonary tuberculosis; AFB = acid-fast bacilli; DS-TB = drug-susceptible TB; DR-TB = drug-resistant TB; MDR = multidrug-resistant; RR = rifampicin-resistant; RMR = rifampicin mono-resistant; VL = viral load; SA = South Africa.
*p<0.10; **p<0.05
†'Old regimen era' describes patients initiated 1 January 2015 - 16 January 2017 and comprised only a long regimen requiring injectables (unless substituted with bedaquiline); 'short regimen era' describes those initiated 17 January 2017 - 30 June 2018 incorporating the introduction of a shorter regimen for eligible cases; 'all-oral era' describes those initiated 01 July 2018 onwards – during which injectables were removed from all regimens.
‡Including any extra-pulmonary site of TB infection besides pleural effusion and lymphadenitis – a precluding criteria for using a short regimen in SA.
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‖HIV negative, or HIV positive with a final HIV-RNA VL before DR-TB treatment outcome of <1 000 copies/mL (i.e. reasonable VL suppression), or final VL >1 000 copies/mL (failure to achieve suppression before DR-TB outcome).

regression model analysing death as an outcome; the effect observed in severe EPTB was marginally attenuated (aOR 5.75, 95% CI 0.97 - 34.00), while the effect of having a positive baseline acid-fast bacilli was slightly strengthened (aOR 2.77, 95% CI: 1.04 - 7.37).

Discussion

At the time of introducing a shorter (9 - 11-month) regimen to the SA DR-TB programme in 2017,[16] the WHO endorsed its use with very little evidence for its implementation.[14] It was in this landscape of scanty evidence that this study was designed and executed.

Since then, a large randomised non-inferiority trial has emerged showing it to be non-inferior to a longer regimen,[19] and a subsequent review by the WHO showed slightly poorer outcomes, but still supported its ongoing use in programmes.[20] While some of our individual patient data form part of those already analysed by the WHO, our methodology allowed for more detailed data to be collected directly from patient records, and we are able to present an analysis among a rural population facing very different barriers to care than those in urban settings.

In our rural SA context, over 5 years of treating RR/MDR-TB amid limited resources and a high burden of HIV co-infection, we observed a 69% rate of successful treatment using a shorter regimen, with a 22% mortality rate. For those treated using a longer regimen, the success rate was 58%, with 21% mortality.

Our outcomes were similar to those reported for the SA DR-TB programme. Nationally, those treated using a short regimen in 2017 had a collective success rate of 67%, with 18% mortality, while the longer regimen yielded 54% success and 20% mortality nationally in 2016.[17]

Despite these similarities, we found that a superficial report of outcomes belied a thorough understanding of the effects of a shorter regimen in our context. In a deeper analysis of these outcomes using multivariable logistic regression models, we found that after controlling for other characteristics, a shorter (9 - 11-month) regimen was no different to a longer (>18-month) regimen in terms of success (aOR 1.19, 95% CI 0.39 - 3.63) or mortality (aOR 1.02, 95% CI 0.23 - 4.51).

However, by alleviating burdens on multiple stakeholders, a short regimen is still likely to be highly favourable for rural patients, clinicians and healthcare systems. By reducing indirect costs such as travel expenses and time unable to work, a shorter regimen likely benefits the high proportion of our economically fragile population facing catastrophic household costs due to a diagnosis of DR-TB.[29-32] By reducing the time many patients need to be managed and monitored by almost a half, the workload on a stretched workforce of healthcare workers is dramatically relieved. Finally, costing studies have shown significant potential cost-saving for a healthcare system by choosing a shorter treatment regimen.[32,33]

Besides other previously described correlates of outcomes such as bedaquiline use, age and severe EPTB infection,[26,27] we found that HIV viraemia (in terms of poor virological suppression) emerged as a novel surrogate for reliably predicting poor outcomes in DR-TB with HIV co-infection.

The effect that HIV co-infection has on outcomes in DR-TB has been described in terms of whether patients are co-infected with HIV,[34,35] and whether they are receiving ART or not,[26,29] but according to our data signals it appears that distinguishing persistent HIV viraemia from suppression may be an important and as yet largely unexplored nuance that significantly affects DR-TB outcomes in co-infected patients. Due to the limitations of observational data, this study is only able to establish a relationship between HIV viraemia and the odds of successful DR-TB treatment or mortality, not causality. Therefore, the effects we observed may, for example, be due to immunological or other host factors at play, or it may be that HIV viraemia might reflect problems with patient adherence to ART and to DR-TB treatment. Whatever the underlying reason, the pragmatic conclusion for clinicians seems to remain: VL should be monitored carefully, a patient with HIV and DR-TB co-infection should be flagged as being at high risk for unfavourable DR-TB outcomes if VL remains >1 000 copies/mL, and measures should be taken to check adherence (to both ART and DR-TB treatment) and expedite the timely provision of adequate ART in order to achieve VL suppression. Reasons behind this relationship, and its utility for monitoring and guiding interventions during DR-TB treatment, should be further explored.

Study limitations

This study is limited in some respects: data are observational; relapse rates could not be determined from existing records; and some variables that may influence outcomes (such as body mass index, concomitant diabetes mellitus and the use of linezolid) were not included owing to limitations in data collection. However, results remain statistically significant and clinically relevant.

Conclusion

In reporting these findings, we look forward to a renewed emphasis on good HIV care in a setting burdened with co-infection of HIV and TB, as well as the evolution of shorter and all-oral DR-TB regimens incorporating bedaquiline – especially those recently recommended by the WHO[4] – and their ongoing careful analysis in real-world programmatic settings. This ongoing analysis would do well to consider the values and preferences of all stakeholders involved, not least of which are the people and communities affected by TB.

We therefore also acknowledge the vision by the WHO[36] and SA Department of Health,[37] that successful outcomes require more than a biomedical focus. While global and national therapeutic and programmatic interventions continue to drive ongoing improvements in outcomes, further progress in the fight against DR-TB likely requires more local nuances than simply relying on programmatic broad strokes and therapeutic silver bullets. As frontline workers in a rural setting, we too support the vision to strive toward a patient-centred approach to care, and seek to add weight to the multidisciplinary approach involving multiple stakeholders to address upstream determinants of TB in the communities we serve, to stop TB together.

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