Factors affecting treatment outcomes in drug-resistant tuberculosis cases in the Northern Cape, South Africa

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The Northern Cape Province has low cure rates (21%) for multidrug-resistant tuberculosis (TB). We audited the programme to identify factors affecting treatment outcomes. Cases admitted to two drug-resistant TB units from 2007 to 2009 had data extracted from clinical folders. Unfavourable treatment outcomes were found in 58% of the 272 cases. A multivariable regression analysis found that male sex was associated with unfavourable outcome ($P = 0.009$). Weight at diagnosis ($P < 0.001$) and oral drug adherence ($P < 0.001$) were also associated with an unfavourable outcome; however, injectable drug adherence was not ($P = 0.395$). Positive baseline smear and human immunodeficiency virus positive status were not associated with unfavourable outcome. Shorter, more patient-friendly regimens may go a long way to improving adherence and outcomes.

Despite advances in the detection of multidrug-resistant tuberculosis (MDR-TB, i.e., resistance to isoniazid and rifampicin) with the introduction of molecular testing and an increase in reported cases, treatment outcomes have not improved. In the 2010 global cohort, only 48% of MDR-TB cases completed treatment.¹ A review of MDR-TB treatment outcomes reported an average success rate of 54% with standardised regimens.² In the Northern Cape Province of South Africa, the cure rate in 2007 and 2008 was 21%.³

Inadequate MDR-TB treatment leads to unfavourable patient outcomes, and increases the risk of transmission and the development of extensively drug-resistant TB (XDR-TB, defined as MDR-TB plus resistance to a fluoroquinolone and an injectable aminoglycoside). We conducted an audit of drug-resistant (DR) TB cases to determine factors associated with unfavourable outcomes.

METHODS

This retrospective study was conducted in the Northern Cape, the largest province in South Africa, occupying 30.5% of the total surface of the country, but with only 2.2% of the total population.⁴

All cases aged >18 years with confirmed DR-TB who had been admitted to the two DR-TB treatment units in the province from 2007 to 2009 with clinical folders available for review were included. A study nurse captured age, sex, sputum smear and culture result on admission, final confirmed diagnosis, admission weight, human immunodeficiency virus (HIV) status, treatment site, treatment outcome and recorded adherence with oral and injectable treatment

on a case report form. The information was dual-entered into a database and discordant data corrected.

The final confirmed diagnosis was defined as MDR-TB, pre-XDR-TB (MDR-TB plus resistance to either a fluoroquinolone or an injectable aminoglycoside) or XDR-TB. A favourable treatment outcome was defined as cured or completed treatment for DR-TB, and an unfavourable outcome as died during treatment, lost to follow-up or failed treatment.

Baseline characteristics were analysed by treatment outcome. Adherence to injectable and oral drugs was calculated as percentages, using the predicted total number of doses that should have been received in the 6 and 24 months, respectively, as the denominator. Oral and injectable drug adherence were analysed dichotomously in the baseline analysis, with $\geq 80\%$ defined as good adherence.

Missing values were imputed using multiple imputation by chained equations: logistic regression was used for DR-TB outcome, sex and baseline smear; multinomial logistic regression for HIV status; and predictive mean matching for weight, age, oral and injectable drug adherence. Adherence was analysed continuously after square root transformation to normalise adherence distributions. Forty imputations were created, combined and analysed. Multivariable imputed logistic regression was used to determine factors associated with an unfavourable outcome. Results were generated using Stata 12/SE (Stata Corp, College Station, TX, USA).

Ethics approval was obtained from the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France, (No. 04/12) and the University of the Free States Ethics Committee, Bloemfontein, South Africa (No. 137/2011).

RESULTS

Of the 272 cases who met the criteria for inclusion, 245 had MDR-TB and 27 XDR or pre-XDR-TB. Baseline characteristics for the 155 DR-TB cases with an unfavourable and the 113 with a favourable outcome are presented in Table 1. Male sex ($P = 0.021$), smear positivity ($P = 0.028$) and confirmed pre- or XDR-TB ($P = 0.012$) were associated with unfavourable outcomes. Mean weight among those with unfavourable outcomes was lower (45 kg) among those with favourable outcomes (50 kg, $P < 0.001$). Poor adherence to oral drugs was observed in 91% and to injectables in 68% of cases; both were associated with unfavourable outcomes ($P = 0.009$ and $P = 0.024$, respectively).

Results from the adjusted multivariable logistic re-

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TABLE 1 Demographic and clinical characteristics of confirmed cases of MDR-TB on treatment in Northern Cape Province, South Africa, by outcome* (*n* = 268)

	Unfavourable MDR-TB outcome (<i>n</i> = 155) [†] <i>n</i> (%)	Favourable MDR-TB outcome [‡] (<i>n</i> = 113) <i>n</i> (%)	<i>P</i> value
Age at registration, years, mean (±SD)	38 (±11) (<i>n</i> = 135)	39 (±12) (<i>n</i> = 100)	0.57
Sex			
Male	87 (64)	48 (36)	0.02
Female	65 (50)	64 (50)	
Baseline smear			
Positive	84 (64)	47 (36)	0.03
Negative	54 (50)	54 (50)	
Baseline culture			
Negative	5 (83)	1 (17)	0.24
Positive	125 (56)	97 (44)	
Diagnosis			
Confirmed MDR-TB	133 (55)	108 (45)	0.01
Confirmed pre-XDR or XDR-TB	22 (81)	5 (19)	
Weight at diagnosis, kg, mean (±SD)	45 (±9) (<i>n</i> = 139)	50 (±12) (<i>n</i> = 109)	<0.01
HIV status			
Negative	82 (58)	60 (42)	0.93
Positive	53 (57)	40 (43)	
Unknown	14 (54)	12 (46)	
Treatment site			
Site A	78 (61)	49 (39)	0.26
Site B	77 (55)	64 (45)	
Oral adherence			
Poor	123 (60)	82 (40)	0.01
Good	6 (29)	15 (71)	
Injection adherence			
Poor	89 (64)	51 (36)	0.02
Good	31 (47)	35 (53)	

*Missing values were not displayed and were found in the following variables: anti-tuberculosis treatment outcome (*n* = 4, 1.5%), sex (*n* = 4, 1.5%), baseline smear (*n* = 29, 10.7%), oral adherence (*n* = 42, 15.4%), injectable adherence (*n* = 62, 22.8%), HIV status (*n* = 7, 2.6%), baseline culture (*n* = 40, 14.7%), weight (*n* = 20, 7.4%) and age (*n* = 33, 12.1%). Continuous variables were compared using *t*-tests and categorical variables were compared using χ^2 or Fisher's exact tests.

[†]Defined as died, lost to follow-up or failed.

[‡]Defined as cured or completed treatment.

MDR-TB = multidrug-resistant tuberculosis; SD = standard deviation; XDR-TB = extensively drug-resistant TB; HIV = human immunodeficiency virus.

gression analysis to determine factors associated with unfavourable outcomes among MDR-TB cases are presented in Table 2. Male sex (adjusted odds ratio [aOR] 2.32, *P* = 0.009) was associated with unfavourable outcomes. Weight (aOR 0.93, *P* < 0.001) and oral drug adherence (aOR 0.73, *P* < 0.001) were associated with an unfavourable outcome; however, injectable drug adherence (aOR 0.94, *P* = 0.395) was not. Positive baseline smear (aOR 1.57, *P* = 0.174), HIV-positive status (aOR 1.05, *P* = 0.879) and age (aOR 1.00, *P* = 0.810) were not associated with unfavourable outcomes.

DISCUSSION

A high proportion of MDR-TB cases in the Northern Cape (58%) had an unfavourable outcome; this is similar to the 52–56% reported in other South Africa studies.^{2,5,6} A higher proportion of pre- and XDR-TB cases (82%) had an unfavourable outcome, similar to the 80% reported elsewhere in South Africa.⁷

Unlike studies in Turkey⁸ and in Pakistan,⁹ where MDR-TB was more common among women, we had similar proportions of male and female DR-TB cases. However, in our study, being

TABLE 2 Estimated aOR from imputed multivariable logistic regression to determine factors associated with unfavourable treatment outcome in drug-resistant cases (*n* = 245)*

Predictor	aOR (95%CI)	<i>P</i> value
Weight at TB treatment initiation	0.9 (0.9–1.0)	<0.01
Male sex	2.3 (1.2–4.4)	0.01
Treatment Site A	0.5 (0.3–1.1)	0.07
Oral drug adherence (sqrt)	0.7 (0.6–0.9)	<0.01
Injection adherence (sqrt)	0.9 (0.8–1.1)	0.40
Positive baseline smear	1.6 (0.8–3.0)	0.17
HIV	Combined <i>P</i> = 0.394	
Negative	Reference	Reference
Positive	1.1 (0.5–2.1)	0.88
Unknown	0.5 (0.2–1.5)	0.22
Age at DR-TB registration	1.0 (1.0–1.0)	0.81

*As pre- and XDR-TB are clinically different and are managed differently from MDR-TB cases, they were not included in the multivariable logistic regression analysis.

aOR = adjusted odds ratio; CI = confidence interval; sqrt = square root transformation; HIV = human immunodeficiency virus; DR-TB = drug-resistant tuberculosis; XDR-TB = extensively drug-resistant TB; MDR-TB = multidrug-resistant tuberculosis.

male was associated with a higher risk of an unfavourable outcome.

A 45 kg baseline weight has been found to be a risk factor for death and treatment failure in South Africa.⁶ Our study found that the mean weight at admission for cases with unfavourable outcomes was 45 kg. In other studies, low body mass index (BMI) was associated with unfavourable treatment outcomes.¹⁰ BMI is a more objective measure of underweight; however, as height was not recorded in patient files, we could not assess this. We recommend that both height and weight be recorded in clinical notes so that BMI can be used to identify individuals who may need early nutritional support.

We were surprised to find that HIV-positive status was not associated with an unfavourable outcome ($P = 0.934$). This may reflect the provision of antiretroviral treatment to these cases, which we did not assess and which can improve outcomes.⁷

Treatment adherence of at least 80% with both oral and injectable drugs was poor. It is unclear why good adherence to injectable drugs did not have a significant effect on unfavourable outcomes; this requires further investigation. Shorter, more effective regimens with fewer side effects, particularly of oral treatment, may go a long way to improving outcomes. Efforts also need to be made to improve record keeping, as data in clinical folders were sometimes missing.

CONCLUSION

Interventions are required to improve adherence and reduce the high number of unfavourable DR-TB treatment outcomes. Inter-

ventions such as social and financial support and nutritional supplementation,¹⁰ as well as shorter, more effective treatment should be considered. As poor outcomes were more likely if cases were male, weighed <45 kg at diagnosis and had poor oral drug adherence, interventions should target these specific groups.

References

- 1 World Health Organization. Global tuberculosis report 2013. WHO/HTM/TB/2013.11. Geneva, Switzerland: WHO, 2013.
- 2 Orenstein E, Basu S, Shah N, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis* 2009; 9: 153–161.
- 3 Northern Cape Department of Health. Annual Report. Kimberley, South Africa: Northern Cape Department of Health, 2008.
- 4 Statistics South Africa. Mid-year population estimates. Pretoria, South Africa: Statistics South Africa, 2011.
- 5 Brust J, Gandhi N R, Carrara H, Osburn G, Padayatchi N. High treatment failure and default rates for patients with MDR-TB in KwaZulu-Natal, South Africa, 2000–2003. *Int J Tuberc Lung Dis* 2010; 14: 413–419.
- 6 Farley J E, Ram M, Pan W, et al. Outcomes of multidrug-resistant tuberculosis (MDR-TB) among a cohort of South African patients with high HIV prevalence. *PLOS ONE* 2011; 6: e20436.
- 7 Gandhi N R, Weissman D, Moodley P, et al. Nosocomial transmission of extensively drug-resistant tuberculosis in a rural hospital in South Africa. *J Infect Dis* 2013; 207: 9–17.
- 8 Unsal E, Güler M, Oflluglu R, Capan N, Cimen F. Factors associated with treatment outcome in 64 HIV negative patients with multidrug-resistant tuberculosis. *J Thorac Dis* 2013; 5: 435–439.
- 9 Ejaz M, Siddiqui A, Rafiq Y, et al. Prevalence of multidrug-resistant tuberculosis in Karachi, Pakistan: identification of at risk groups. *Trans R Soc Trop Med Hyg* 2010; 104: 511–517.
- 10 Johnston J C, Shahidi N C, Sadatsafavi M, Fitzgerald J M. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *PLOS ONE* 2009; 4: e6914.

La province du Nord du Cap a des taux de réussite thérapeutique faibles (21%) pour les tuberculoses (TB) multirésistantes. Nous avons effectué un audit du programme afin d'identifier les facteurs affectant les résultats du traitement. Les dossiers cliniques des cas admis dans deux unités de traitement de la TB pharmacorésistante de 2007 à 2009 ont permis d'extraire les données requises. Sur 272 patients, 58% ont eu un échec thérapeutique. Une analyse de régression multivariée a constaté que le sexe masculin était associé à un résultat

défavorable ($P = 0,009$). Le poids au moment du diagnostic ($P < 0,001$) et l'adhérence au traitement oral ($P < 0,001$) étaient également associés à un mauvais résultat, mais l'adhérence aux médicaments injectables ne l'était pas ($P = 0,395$). Un frottis positif au départ et un statut du virus de l'immunodéficience humaine positif n'étaient pas associés à un mauvais résultat. En bref, des protocoles mieux adaptés aux patients ont du chemin à faire pour améliorer l'adhérence et les résultats.

La Provincia Septentrional del Cabo presenta bajas tasas de curación (21%) de la tuberculosis (TB) multidrogorresistente. Se practicó una auditoría del programa con el fin de detectar los factores que influyen sobre los desenlaces terapéuticos. Se analizaron los casos hospitalizados entre el 2007 y el 2009 en dos unidades de atención de la TB resistente a partir de los datos de las historias clínicas. Se observaron desenlaces desfavorables en 58% de los 272 casos. Un análisis de regresión multifactorial puso en evidencia que el sexo masculino se asociaba con desenlaces desfavorables ($P = 0,009$). El

peso en el momento del diagnóstico ($P < 0,001$) y el cumplimiento con el tratamiento por vía oral ($P < 0,001$) se asociaron con un desenlace desfavorable, pero no así el cumplimiento con el tratamiento intravenoso ($P = 0,395$). Los resultados iniciales de la baciloscopia del esputo y de la serología frente al virus de la inmunodeficiencia humana no se asociaron con desenlaces desfavorables. La utilización de regímenes de tratamiento más cortos y más centrados en el paciente podría contribuir a mejorar considerablemente el cumplimiento y los desenlaces terapéuticos.