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High treatment failure and default rates for patients with multidrug-resistant tuberculosis in KwaZulu-Natal, South Africa, 2000–2003

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SUMMARY

SETTING: Multidrug-resistant tuberculosis (MDR-TB) has emerged as a significant public health threat in South Africa.

OBJECTIVE: To describe treatment outcomes and determine risk factors associated with unfavorable outcomes among MDR-TB patients admitted to the provincial TB referral hospital in KwaZulu-Natal Province, South Africa.

DESIGN: Retrospective observational study of MDR-TB patients admitted from 2000 to 2003.

RESULTS: Of 1209 MDR-TB patients with documented treatment outcomes, 491 (41%) were cured, 35 (3%) completed treatment, 208 (17%) failed treatment, 223 (18%) died and 252 (21%) defaulted. Of the total number of patients with known human immunodeficiency virus (HIV) status, 52% were HIV-infected. Treatment failure, death and default each differed in their risk factors. Greater baseline resistance (aOR 2.3–3.0), prior TB (aOR 1.7), and diagnosis in 2001, 2002 or 2003 (aOR 1.9–2.3) were independent risk factors for treatment failure. HIV co-infection was a risk factor for death (aOR 5.6), and both HIV (aOR 2.0) and male sex (aOR 1.9) were risk factors for treatment default.

CONCLUSION: MDR-TB treatment outcomes in KwaZulu-Natal were substantially worse than those published from other MDR-TB cohorts. Interventions such as concurrent antiretroviral therapy and decentralized MDR-TB treatment should be considered to improve MDR-TB outcomes in this high HIV prevalence setting.

KEY WORDS: drug resistance; *Mycobacterium tuberculosis*; treatment outcomes; South Africa

MULTIDRUG-RESISTANT tuberculosis (MDR-TB), defined as *Mycobacterium tuberculosis* resistant to at least isoniazid (INH) and rifampicin (RMP), is a rapidly emerging disease characterized by difficulties in treatment and high rates of morbidity and mortality. There were an estimated 489 000 new cases of MDR-TB worldwide in 2006, of which only a small fraction were ever diagnosed and treated.[1] Although many countries have increased efforts to provide MDR-TB treatment, the recent global emergence of extensively drug-resistant tuberculosis (XDR-TB, defined as MDR-TB with resistance to a fluoroquinolone and either kanamycin [KM], amikacin [AMK] or capreomycin [CPM]) has highlighted the possibility that it may be worse to provide inadequate treatment for MDR-TB than to provide no treatment at all. To prevent mismanagement of MDR-TB, the Green Light Committee (GLC) was established in 2000 to provide access to affordable treatment and quality control for national MDR-TB programs. In 2006, however, fewer than 10% of patients treated for MDR-TB received their care in GLC-approved programs.[2] The quality of care in non-GLC programs is therefore of considerable concern.

The province of KwaZulu-Natal, South Africa, has one of the largest burdens of MDR-TB worldwide, with an estimated prevalence of 30 MDR-TB cases per 100 000 population.[3] Although the last systematic drug resistance survey in KwaZulu-Natal in 2002 revealed only a 1.7% prevalence among new tuberculosis (TB) patients,[4] the MDR-TB caseload rose nearly four-fold to over 3000 cases in 2007.[3] Furthermore, the discovery of XDR-TB in KwaZulu-Natal in 2005 has focused world attention on the drug-resistant TB epidemic in the province and prompted investigations into its cause.[5]

High default rates for drug-susceptible TB treatment likely resulted in the creation of large numbers of MDR-TB strains,[4] but the recent exponential rise in MDR-TB cases is difficult to explain by inadequate treatment alone. Primary transmission of MDR-TB has probably also played a critical role.[6] South Africa

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has the world's largest number of HIV-infected individuals, and such patients are significantly more likely to develop active TB disease following initial infection.[7] High rates of treatment failure or default from MDR-TB treatment may have created the ideal milieu for MDR-TB dissemination. Until 2007, King George V Hospital (KGH) in Durban had the only TB program in KwaZulu-Natal Province capable of treating MDR-TB patients. The program has long been under-resourced, and has been left to tackle the rapid rise in MDR-TB caseload.

With these factors in mind, we sought to describe the treatment outcomes for MDR-TB cases in this high HIV prevalence setting at KGH in KwaZulu-Natal, South Africa. Specifically, we wanted to examine outcomes prior to the rapid rise in MDR-TB caseload and the 'discovery' of XDR-TB in 2005. We also sought to identify risk factors for unfavorable outcomes of MDR-TB treatment to improve the future performance of the program.

METHODS

Study setting

KwaZulu-Natal is the most populous of South Africa's provinces, with approximately 10 million people, and the highest HIV prevalence in the country. KGH is a 160-bed specialist TB referral center located in Durban, KwaZulu-Natal. Until 2007, KGH was the only source of treatment for MDR-TB in the province. MDR-TB cases from all regions of KwaZulu-Natal were referred to KGH for admission and management.

Study population

All patients with culture-proven MDR-TB admitted to KGH between 1 January 2000 and 31 December 2003 were eligible for inclusion. Patients with no documented treatment outcome were excluded from analysis.

Management of MDR-TB

KGH used a modified standardized treatment regimen for MDR-TB: on admission, patients were started on a regimen of KM, ofloxacin (OFX), pyrazinamide (PZA), ethambutol (EMB), and ethionamide (ETH). Cycloserine (CYC) was substituted for EMB if the isolate had known resistance to EMB. During the study period, all patients were admitted until they completed the intensive phase of treatment, usually 4–6 months. They were then discharged home, with monthly follow-up at the out-patient clinic at KGH and another 18 months of oral treatment (PZA, EMB, OFX and ETH) scheduled. The continuation phase of therapy was not directly observed. Sputum culture and drug susceptibility testing (DST) were performed on a monthly basis throughout treatment.

Drug susceptibility testing

DST was performed on all positive sputum cultures at the KGH laboratory, using Löwenstein-Jensen media,[8] at the following drug concentrations: INH 0.2 and 1 mg/l, RMP 40 mg/l, EMB 2 mg/l, streptomycin (SM) 4 mg/l, ETH 20 mg/l, KM 20 mg/l, ciprofloxacin 5 mg/l, OFX 2.5 mg/l and thiacetazone 2 mg/l.

Data collection

Baseline information, including demographics, HIV status, prior history of TB and TB DST results, was entered into a database for all patients admitted to KGH. Information regarding treatment outcome was updated by the hospital data manager at hospital discharge and periodically thereafter.

Treatment outcome definitions

MDR-TB treatment outcome was classified according to standardized definitions.[9] Briefly, cure was defined as completion of treatment with consistently negative cultures in the final year of treatment. Completion of the treatment course without bacteriologic documentation of cure was considered treatment completion. Treatment failure was defined as having more than one positive culture in the last 12 months of treatment. Treatment was also considered to have failed if one of the last three cultures taken during treatment was positive, or if the patient was persistently culture-positive. Default was defined as treatment interruption for $\geqslant$2 consecutive months for any reason. Death was defined as death from any cause during MDR-TB treatment.

For the purposes of analysis, 'unfavorable outcome' was defined as treatment failure, default or death from any cause. Patients who were cured or who successfully completed treatment were considered to have had a 'favorable outcome'.

Statistical analysis

Baseline characteristics and treatment outcomes were described using simple frequencies, medians and interquartile ranges (IQR). Bivariate analysis was performed to examine associations between baseline characteristics and treatment outcomes using χ^2 tests. Baseline characteristics examined were age (categorized as $\leqslant$20, 21–30, 31–40, 41–50 and $\geqslant$51 years), sex, HIV status, admission year, previous history of treatment for TB and employment status. The TB drugs to which the initial isolate was resistant were examined in several ways: number of drugs (categorized as 2, 3, 4 or $\geqslant$5 drugs), resistance to specific drugs (e.g., EMB), and combinations of drug resistance (e.g., INH+RMP+EMB+SM). Variables with $P < 0.1$ on bivariate analysis were then incorporated into a multivariate logistic regression model for the composite 'unsuccessful outcome' as well as for individual unsuccessful outcomes 'treatment failure',

'death' and 'default'. Subjects with each of these unsuccessful outcomes were compared to those with a favorable outcome.

As HIV test results were not available for more than 40% of the subjects, we performed a sensitivity analysis imputing either positive or negative HIV results for the missing patients, to determine the influence of missing HIV data on the effect size of other variables in our model.

The study was approved by the Ethics Committees at the University of KwaZulu-Natal and Montefiore Medical Center, Bronx, New York.

RESULTS

From 2000 to 2003, a total of 1261 patients diagnosed with MDR-TB were admitted to KGH in Durban. Fifty-two (4.1%) patients had no recorded final outcome and were excluded from the final analysis. Baseline characteristics for the remaining 1209 patients are shown in Table 1. Of these, 472 (39%) were women and the median age was 33 years (IQR 26–41). Information on HIV status was available for 699 patients (58%), of whom 362 (52%) were HIV-positive. Information about prior TB was available for 1191 (99%) patients, of whom 959 (81%) had a history of previous TB. At baseline, 26% of the patients were resistant only to INH and RMP, while 32%, 18% and 23% of the patients were resistant to respectively 3, 4 and ⩾5 drugs.

Of the 1209 patients with known MDR-TB treatment outcomes, 491 (41%) were cured, 35 (3%) completed treatment, 208 (17%) failed treatment, 223 (18%) died while on treatment and 252 (21%) defaulted from treatment (Table 2). Overall, 526 (44%) had a favorable outcome (cure or completed), while 683 (56.5%) had an unfavorable outcome (failed, died or defaulted). There was no significant differences in the percentage of patients with a favorable treatment outcome from 2000 to 2003 ($P = 0.42$); however, there was a trend towards more patients with treatment failure and fewer with default in 2003 compared with 2000 (Figure).

HIV infection, resistance to three or five TB drugs, resistance to EMB, and age between 31 and 40 years were all risk factors for the composite 'unfavorable' outcome, but analysis of individual unfavorable outcomes revealed that each unfavorable outcome (i.e., failure, death or default) had unique, specific risk factors. No one risk factor was found for all three. We therefore present risk factor data from multivariable analysis for each outcome separately (Table 3).

For treatment failure, previous TB treatment (adjusted odds ratio [aOR] 1.7), diagnosis in 2001 (aOR 2.0), 2002 (aOR 1.9) and 2003 (aOR 2.3), and resistance to either three or five TB drugs (aOR 2.3 and 3.0, respectively) were all significant independent risk factors on multivariable analysis. In contrast, the only significant risk factor for death on multivariate analysis was HIV co-infection (aOR 5.6).

Table 1 Baseline characteristics

	n (%)
Total	1209
Female	472 (39.0)
Age, years, median [IQR]	33.0 [26–41]
Age, years	
⩽20	120 (9.6)
21–30	375 (32.2)
31–40	373 (30.9)
41–50	233 (18.4)
⩾51	100 (8.6)
HIV status available	699 (57.8)
HIV-positive	362 (51.8)
HIV-negative	337 (48.2)
Prior TB treatment status available	1191 (98.5)
Prior TB	959 (80.5)
No prior TB	232 (19.5)
Resistant to TB drugs, median [range]	3 [2–9]
Resistant to 2 drugs	315 (26.1)
Resistant to 3 drugs	391 (32.3)
Resistant to 4 drugs	223 (18.4)
Resistant to ⩾5 drugs	280 (23.2)
Employment status	
Employed	277 (22.9)
Unemployed	704 (58.2)
Unknown	228 (18.9)

IQR = interquartile range; HIV = human immunodeficiency virus; TB = tuberculosis.

Table 2 MDR-TB treatment outcomes, 2000–2003

	n (%)
Cure	491 (41)
Completed	35 (2.9)
Failed	208 (17)
Died	223 (18)
Defaulted	252 (21)
Total	1209 (100)

MDR-TB = multidrug-resistant tuberculosis.

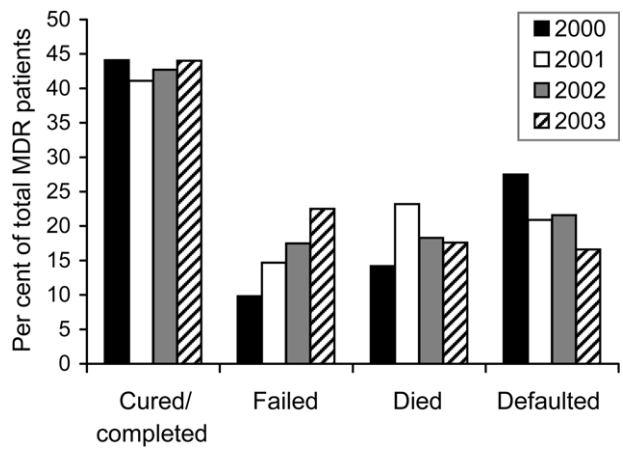

Figure Final MDR-TB treatment outcomes by year of diagnosis. MDR-TB = multidrug-resistant tuberculosis.

Table 3 Adjusted predictors of unfavorable outcomes

	Failed treatment		Died		Defaulted	
	n (%)	Adjusted OR (95%CI)	*n* (%)	Adjusted OR (95%CI)	*n* (%)	Adjusted OR (95%CI)
Prior TB	51 (25)	1.7 (1.0–2.8)*	160 (17)	0.6 (0.3–1.1)	—†	—†
2001	38 (15)	2.0 (1.1–3.7)*	60 (23)	1.2 (0.6–2.5)	54 (21)	0.7 (0.4–1.3)
2002	63 (18)	1.9 (1.1–3.4)*	66 (18)	1.5 (0.7–3.0)	78 (22)	0.9 (0.5–1.5)
2003	87 (23)	2.3 (1.3–4.1)‡	68 (18)	1.5 (0.7–3.0)	64 (17)	0.7 (0.4–1.3)
Number of TB drugs to which patient is resistant						
3	78 (20)	2.3 (1.3–4.1)‡	—†	—†	89 (23)	1.5 (0.9–2.5)
4	29 (13)	1.4 (0.7–2.8)	—†	—†	40 (18)	1.2 (0.6–2.7)
>5	71 (25)	3.0 (1.5–5.7)‡	—†	—†	47 (17)	0.7 (0.3–1.9)
Ethambutol	143 (20)	1.1 (0.7–1.8)	138 (20)	1.5 (0.9–2.4)	—†	—†
HIV	—†	—†	90 (25)	5.6 (3.3–9.4)‡	81 (22)	2.0 (1.3–3.1)‡
Male sex	—†	—†	—†	—†	175 (24)	1.9 (1.2–3.1)‡
Age, years						
21–30	—†	—†	—†	—†	74 (20)	1.3 (0.6–2.8)
31–40	—†	—†	—†	—†	91 (24)	1.5 (0.7–3.2)
41–50	—†	—†	—†	—†	44 (19)	0.8 (0.4–1.8)
⩾51	—†	—†	—†	—†	18 (18)	0.9 (0.3–2.7)

*$P < 0.05$.
†Non-significant on bivariate analysis.
‡$P < 0.01$.
OR = odds ratio; CI = confidence interval; TB = tuberculosis; HIV = human immunodeficiency virus.

For treatment default, HIV (aOR 2.0) and male sex (aOR 1.9) were the significant risk factors on multivariate analysis. Full details of aORs, 95% confidence intervals (95%CIs) and *P* values for these factors are given in Table 3.

Because HIV was a major risk factor for death and default, we performed a sensitivity analysis to determine the influence, if any, of the more than 40% of patients with unknown HIV status on other risk factors. Imputation of positive or negative HIV results did not significantly affect the direction or magnitude of effect of the other covariates in each of the models (data not shown). Even when negative results were imputed for all of the subjects with unknown HIV status, HIV infection remained a very strong predictor of death ($P < 0.0001$).

DISCUSSION

In this study, we describe treatment outcomes from the largest cohort to date of MDR-TB patients reported from a high HIV prevalence setting. Compared with published reports from low HIV prevalence settings, treatment outcomes in our cohort were poor, with fewer than 45% of patients achieving cure or treatment completion.[10–16] The unsuccessful outcomes were evenly divided among death, treatment failure and default, but the risk factors for each outcome varied. HIV co-infection was a major risk factor for death and default, but not for treatment failure. Conversely, a greater number of drugs to which patients were resistant, prior TB treatment and later year of diagnosis were risk factors for treatment failure, but not for death or default. Efforts to improve MDR-TB outcomes in this setting must therefore be multifaceted to address such differing risks.

MDR-TB is a marker of a TB control program's inability to adequately manage drug-susceptible TB. The South African TB program has been severely underresourced to handle the three-fold rise in TB caseload over the past 15 years. As a result, there is now a massive MDR-TB epidemic in KwaZulu-Natal, with a prevalence of more than 30 cases per 100 000 population.[3,17] Because culture and DST are performed only for retreatment cases and patients failing first-line therapy, these numbers are likely a substantial underestimate of the actual current MDR-TB burden.

Fewer than half of the subjects in our cohort achieved cure or treatment completion, making these treatment completion rates worse than most prior reports in the published literature. Among 34 published MDR-TB cohorts in 20 countries examined in a recent meta-analysis, the pooled treatment success rate was 62% (range 40–79%).[18] Other published cohorts, such as those from California, USA[19] and a DOTS-Plus program in Tomsk, Russia,[12] also demonstrate treatment success rates of >65%.

Although most of the published MDR-TB cohorts are from low HIV prevalence countries, the inferior outcomes in KwaZulu-Natal cannot be explained by HIV alone. HIV infection has been associated with unsuccessful MDR-TB treatment outcomes, but most of these data come from US outbreaks in the 1990s.[20–23] In those reports, the high rates of poor outcome were driven almost entirely by deaths, whereas in our study, the 'unfavorable outcomes' were evenly divided among treatment failures, deaths and defaults. Although these three categories are typically combined

and considered together, our data suggest that each differed in its risk factors.

The principal risk factor for failure was baseline resistance to a greater number of TB medications; nearly 25% of patients in this study were resistant to ⩾5 drugs. Current MDR-TB guidelines[24] emphasize using regimens that contain at least four TB drugs to which the patients are susceptible. The modified, standardized treatment regimen at KGH may therefore not have had a sufficient number of active TB drugs for patients with such severe drug resistance. Given the high rates of treatment failure in our study, consideration should be given either to individualizing treatment regimens based on DST results and treatment history, or to increasing the number of medications in the standardized regimen.

Our study took place before the availability of antiretroviral therapy (ART) in the public sector in South Africa, and it is thus no surprise that HIV was a risk factor for death. Efforts to reduce mortality among MDR-TB patients in high HIV prevalence settings should include the integration of ART with second-line anti-tuberculosis treatment.[25]

The risk factors for default, HIV infection and male sex suggest two ends of a spectrum for why individuals default. A large proportion die, but the treatment program lacks the resources to trace patients who miss clinic appointments.[26,27] Others improve sufficiently to once again seek employment, often in distant cities or provinces. MDR-TB treatment programs should have the resources to trace and prevent defaulters, as treatment interruption is a significant cause of amplification of resistance. As a centralized treatment program, KGH is unable to trace defaulters or even provide directly observed therapy in the continuation phase, as patients' homes and communities are often hundreds of kilometers away. To reduce the number of MDR-TB patients defaulting, decentralization of MDR-TB treatment should be considered, by creating community-based treatment programs or satellite in-patient centers.[11,28,29]

Although this cohort demonstrates the burden of MDR-TB in KwaZulu-Natal, our study is not without limitations. First, the study was performed retrospectively, relying on complete and accurate entry of treatment outcomes. Although more than 95% of patients did have a final outcome reported, we were unable to confirm the accuracy of the data. Second, the KGH database provides no information on the use of surgical pulmonary resection. An important adjunctive treatment for localized disease, this procedure is available to certain patients admitted to KGH and may have been an important predictor of treatment success.[30,31] Third, we were unable to demonstrate the development of XDR-TB while patients received MDR-TB treatment because end-of-treatment DST patterns were not available. Despite the high rates of drug resistance in our cohort, only 11 patients had XDR-TB on admission. Given the recent alarming rates of XDR-TB in KwaZulu-Natal[5] and the demonstration of nosocomial spread of XDR-TB,[6] it is likely that the source of the current XDR-TB epidemic was one of a few XDR-TB cases seen before 2005 and that it was therefore the result of a failing MDR-TB treatment program. Fourth, although we did not find that HIV was a risk factor for treatment failure, this could reflect a survival bias whereby HIV-infected patients who were failing therapy died or defaulted before meeting the outcome criteria for treatment failure. Finally, nearly 40% of the patients in our cohort were not tested for HIV. Public access to antiretrovirals was not available in South Africa until 2004, and many patients prior to this were reluctant to be tested for HIV. HIV, however, remained a significant predictor of death even when all of the unknown results were imputed to be negative.

The incidence of MDR-TB continues to increase in KwaZulu-Natal, and although some of this rise may be attributed to increased use of sputum culture and DST, the additional cases will further tax the TB control program. Only by strengthening the MDR program with increased staff and resources, providing integrated treatment for HIV, and addressing the many different risk factors for poor treatment outcomes, will South Africa be able to control this dire and growing epidemic.

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RÉSUMÉ

CONTEXTE : La tuberculose à germes multirésistants (TB-MDR) est devenue une menace significative pour la santé publique en Afrique du Sud.

OBJECTIF : Décrire les résultats du traitement et déterminer les facteurs de risque associés à des résultats défavorables chez les patients atteints de TB-MDR admis à l'hôpital provincial de référence TB de la province de Kwazulu-Natal, Afrique du Sud.

SCHÉMA : Etude observationnelle rétrospective des patients atteints de TB-MDR admis entre 2000 et 2003.

RÉSULTATS : Sur 1209 patients TB-MDR dont les résultats du traitement sont documentés, 491 (41%) sont guéris, 35 (3%) ont achevé leur traitement, 208 (17%) sont des échecs, 223 (18%) sont décédés et 252 (21%) sont des abandons. Parmi les patients dont le statut du virus de l'immunodéficience humaine (VIH) était connu, 52% sont séropositifs. Les facteurs de risque ont été différents pour le traitement avant l'échec, le décès ou l'abandon dans chacun des cas. Les facteurs indépendants de risque d'échec du traitement sont un taux de résistance plus élevé au départ (aOR 2,3–3,0), des antécédents de TB (aOR 1,7) et le diagnostic en 2001, 2002 ou 2003 (aOR 1,9–2,3). La co-infection VIH est un facteur de risque de décès (aOR 5,6), et tant le VIH (aOR 2,0) que le sexe masculin (aOR 1,9) sont des facteurs du risque d'abandon du traitement.

CONCLUSION : Les résultats du traitement de la TB-MDR au Kwazulu-Natal sont substantiellement plus mauvais que ceux publiés pour d'autres cohortes de TB-MDR. Des interventions comme le traitement antirétroviral simultané et un traitement décentralisé de la TB-MDR doivent être envisagées pour améliorer les résultats pour la TB-MDR dans ce contexte à haute prévalence du VIH.

RESUMEN

MARCO DE REFERENCIA: La tuberculosis multidrogoresistente (TB-MDR) se ha convertido en una amenaza considerable de salud pública en Sudáfrica.

OBJETIVO: Describir los desenlaces terapéuticos y determinar los factores de riesgo asociados con los desenlaces desfavorables en pacientes con TB-MDR hospitalizados en el hospital de referencia de TB de la provincia de KwaZulu-Natal, en Sudáfrica.

MÉTODO: Fue este un estudio de observación retrospectivo de los pacientes hospitalizados entre 2000 y 2003.

RESULTADOS: De los 1209 casos tratados por TB-MDR con información sobre el desenlace terapéutico, 491 (41%) alcanzaron la curación, 35 (3%) completaron el tratamiento, 208 (17%) tuvieron un fracaso terapéutico, 223 (18%) fallecieron y 252 (21%) abandonaron el tratamiento. Cincuenta y dos por ciento de los pacientes con examen serológico para el virus de la inmunodeficiencia humana (VIH) estaban infectados. Los factores de riesgo de fracaso terapéutico, fallecimiento y abandono fueron diferentes. Los factores asociados independientemente con el fracaso fueron una mayor farmacoresistencia inicial (aOR 2,3–3,0), el antecedente de TB (aOR 1,7) y el diagnóstico establecido en 2001, 2002 o 2003 (aOR 1,9–2,3). La coinfección por el VIH fue un factor de riesgo de fallecimiento (aOR 5,6), y la infección por el VIH (aOR 2,0) y el sexo masculino (aOR 1,9) fueron factores de riesgo de abandono del tratamiento.

CONCLUSION: Los desenlaces terapéuticos de la TB-MDR en KwaZulu-Natal fueron significativamente más desfavorables que los resultados publicados en otras cohortes de pacientes con este tipo de TB. Con el objeto de mejorar estos resultados sería importante considerar la posibilidad de introducir el tratamiento antirretrovírico simultáneo y descentralizar el tratamiento de la TB-MDR en este entorno de alta prevalencia de infección por el VIH.