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Community-based care vs. centralised hospitalisation for MDR-TB patients KwaZulu-Natal, South Africa

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Abstract

Setting—KwaZulu-Natal, South Africa a predominantly rural province with high burdens of TB, MDR-TB and HIV infection.

Objective—To determine the most effective model of care by comparing MDR-TB treatment outcomes at community-based sites with traditional care at a central, specialised hospital.

Design—A non-randomised observational prospective cohort study comparing community-based and centralised care. Patients at community-based sites were closer to home, had easier access to care and home-based care was available from treatment initiation.

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Ethics approval: The study protocol was approved by the University of KwaZulu-Natal Biomedical Research Ethics Committee (Ref: BF052/09), and by the KwaZulu-Natal Department of Health. Only secondary data, the data routinely collected by health workers for clinical care was used in this study. To protect patient confidentiality and anonymity the data bases were de-identified and access strictly limited. Informed consent was waived by the ethics committee, since all data used were previously collected during the course of routine medical care and did not pose any additional risks to the patients.

Conflicts of interest: There are no potential conflicts of interest relevant to this article. All authors reported no conflict of interest.

Results—Four community-based sites treated 736 patients, while 813 were treated at the centralised hospital (a total of 1549 patients). Overall, 75% were HIV co-infected (community: 76% vs. hospitalised: 73%, p=0.45) and 86% received antiretroviral therapy (community: 91% vs. hospitalised: 82%, p=0.22).

In multivariate analysis MDR-TB patients were more likely to have a successful treatment outcome if they were treated at a community-based site (adjusted OR=1.43, p=0.01). However, there was heterogeneity in outcomes at the four community-based sites, with Site 1 demonstrating that home-based care was associated with increased treatment success of 72% compared with success of between 52 - 60% at the other three sites.

Conclusion—Community-based care for patients with MDR-TB was more effective than care in a central, specialised hospital. Home-based care further increased treatment success.

Keywords

Models of care; HIV; outcomes

BACKGROUND

Multidrug-resistant tuberculosis (MDR-TB), defined as TB resistant to isoniazid and rifampicin, is a critical threat to global TB control and is associated with high mortality in settings with HIV co-infection.[1,2] MDR-TB treatment is more difficult for patients to tolerate than first-line TB therapy, due to the long duration of treatment (18–24 months), frequent medication toxicities, and daily administration of an injectable drug for at least six months. Consequently, most countries have adopted inpatient models of care at centralised, specialised hospitals.

South Africa has one of the largest drug-resistant TB epidemics in the world.[1] KwaZulu-Natal Province has emerged as a global hotspot of the TB, drug-resistant TB, and HIV syndemic, with 76% of MDR-TB patients co-infected with HIV, and MDR-TB mortality rates of 71%.[3-5] Local management of MDR-TB was based on hospitalisation in a centralised specialised hospital for the initial six months of treatment, to facilitate daily injections and allow close monitoring of adverse events and adherence. Following discharge, and for the remaining period of treatment (18 months or longer), patients were expected to return for monthly out-patient visits, which for some patients entailed travelling 500kms to reach the hospital. In this setting, the escalating burden of MDR-TB together with limited bed capacity resulted in long waiting lists, an average delay of 111 days for hospital admission and treatment initiation[3] and in 2007, only 32% of MDR-TB patients accessed treatment.[6] Furthermore, patients were discharged before the end of the injectable phase of treatment to facilities unfamiliar with MDR-TB treatment, resulting in poor treatment outcomes and high default rates. [3-5]

An alternate community-based model of care could increase MDR-TB treatment capacity (currently limited by hospital bed availability), and make treatment more accessible by being available closer to patient's homes, enhancing support to patients and their families. Lengthy arduous trips to receive health care could be limited, thus reducing patient default and improving treatment outcomes. Furthermore, shorter periods of hospitalisation would make

it possible to treat more patients and reduce the time to treatment initiation. Alternate models of care have been implemented in small study samples in other countries[7-11] and in other southern African settings.[12] However, to our knowledge, no study has compared treatment outcomes in a community with a centralised setting. And, little is known about the potential viability and ease of implementation of these alternate models of care on a large scale by a public health service, particularly in areas bruised by TB and HIV epidemics.

In 2008, the KwaZulu-Natal provincial Department of Health began piloting community-based care at four sites. This study was designed to evaluate the community-based model of MDR-TB care at these sites, based on relative treatment success for MDR-TB patients with and without HIV co-infection, in comparison with care in a centralised setting. Here we report final treatment outcomes and predictors for patients treated in community-based versus centralised care.

METHODS

Study design, patients and procedures

This prospective cohort study was conducted in the province of KwaZulu-Natal, South Africa. Between 1 July 2008 and 30 June 2010, 1549 patients aged ?18 years with a laboratory confirmed diagnosis of MDR-TB were enrolled (Figure 1). Patients were excluded if they were resistant to a single first-line TB drug (rifampicin, isoniazid, pyrazinamide or ethambutol), or were resistant to isoniazid and rifampicin with any second-line TB drugs. Patients who received care at both a community-based site and the centralised hospital, or who were participating in an MDR-TB clinical trial were also excluded. All patients who lived within the catchment area of each community-based site were enrolled at that site if they met the study criteria. At the centralised hospital all patients who met the study criteria were enrolled, unless they came from the catchment areas of the community-based sites.

Intervention

Patients diagnosed with MDR-TB were referred to either a community-based site or the centralised hospital for initiation of MDR-TB therapy, depending on where they lived. All patients received standardized MDR anti-tuberculosis therapy and ART in accordance with national guidelines.[13,14] During the initial intensive phase of treatment (usually 4-6 months), patients were started on a regimen of kanamycin (Km), pyrazinamide (Z), ethambutol (E), ethionamide (Eto), ofloxacin (Ofx), and cycloserine (Cs). This was followed by a continuation phase of at least 18 months of oral treatment (Z, E, Eto, Ofx and Cs).

The four community-based sites were attached to purposively selected rural hospitals in areas where large numbers of MDR-TB patients were being diagnosed. Non-specialist doctors provided care to MDR-TB patients at these sites, referring patients requiring specialist care to the centralised hospital. Once discharged, all patients attended monthly follow-up treatment monitoring visits at the community-based sites. Home-based care was available for patients discharged from the community-based sites during the intensive phase of treatment, with kanamycin injections administered daily either at a local clinic or by

mobile injection teams that visited patients in their homes. Mobile injection teams also followed up patients who had defaulted. The guiding principles and detailed implementation of this model have been reported previously.[15,16] The implementation of injection teams varied across the sites. At Site 1, 16 injection teams were mobilised in the first year of the programme (2008). Site 2 mobilised two teams in 2009; Site 3, two teams towards the end of 2011; and Site 4 none at all. Direct-observation of therapy (DOT) is included in the national TB and MDR-TB guidelines, but is seldom implemented; most patients self-administered oral treatment and adherence was seldom monitored.

At the community-based sites, home-based care from the time of treatment initiation was available, but for a number of reasons most patients (95%) were initially hospitalised: (1) many patients co-infected with MDR-TB and HIV were very ill at the time of MDR-TB diagnosis, requiring hospitalisation; (2) clinicians unfamiliar with the co-management of MDR-TB and HIV wanted to monitor patients closely; (3) the extent of implementation of home-based care varied across the community-based sites; (4) home circumstances assessed by a social worker were determined to be unsupportive of adherence. The median duration of hospitalisation was similar at the community-based sites and centralised hospital (143 versus 144 days), but varied across the four community-based sites from 96 days at Site 1, to 180 days at Site 3 (Table 3).

End points

The primary outcome variables were treatment outcome as defined by WHO in 2008 (Table 1),[17,18] and survival time over course of treatment (2008 definitions were used as most treatment outcomes had been assigned by the time the 2011 revised definitions were published). Treatment initiation delay, a secondary outcome, was defined as the interval between initial sputum collection and treatment start.

Statistical analysis

We reviewed medical records to collect patient-related demographic, clinical, pharmaceutical and laboratory data. Patients' response to treatment was monitored via continuous data collection from medical records and the laboratory database for the duration of treatment. Data collection was complete by October 2012. Baseline characteristics and treatment outcomes were described using simple frequencies. Medians among the individual community-based sites were compared using the Kruskal-Wallis non-parametric test. General linear models (GLM) using the binomial or normal distribution were used to compare proportions and/or means respectively between sites; also to compare medians using rank values. Logistic regression was utilized to assess the effect of risk factors on successful vs. unsuccessful outcomes. All models utilized the GEE (generalised estimating equation) procedure to adjust for clustering from the multiple hospitals comprising the community-based sites. The Cox proportional hazards model, incorporating a robust "sandwich" variance estimate to allow for clustering of patients from the same site, was used to assess the effect of certain risk factors on time to death. Patients who did not experience the event measured were considered censored at date of final outcome. All multivariate models used a univariate threshold of $p<0.25$ in order for variables to be considered for inclusion. Analyses were conducted using SAS V9.2 (SAS Institute, Cary, NC, USA).

Study oversight

The study protocol was approved by the Biomedical Research Ethics Committee at the University of KwaZulu-Natal (Ref: BF052/09).

RESULTS

Of the 1549 patients prospectively enrolled in the study, 736 were treated at the community-based sites and 813 at the centralised hospital (Figure 1). Ninety-four percent of all patients were tested for HIV, and co-infection rates were high at both the community-based sites and centralised hospital (76.3% vs. 73.1%), with 91.3% of patients at the community-based sites receiving ART compared with 82% at the centralised hospital (Table 2). Patients at the community-based sites were less likely to have a history of TB (55.8% vs. 95.7%, p<0.001), and had a lower median pre-treatment weight (50 vs. 53 kg, p <0.001). More patients at the community-based sites were smear-positive at diagnosis (75.7% vs. 60.4%, p<0.001).

At the community-based sites significantly more patients were cured (50.7% vs. 34.4%, p<0.001), and significantly fewer patients defaulted (14.5% vs. 28.3%, p=0.004) (Table 3). In addition, more patients achieved a successful treatment outcome (58%) than at the centralised hospital (54%). In multivariate analysis adjusting for HIV status, age, previous MDR-TB infection, and pre-treatment weight, patients were more likely to have a successful treatment outcome if they were treated at a community-based site (adjusted OR=1.43, p=0.01) (Table 4). There was no effect modification on MDR-TB outcomes of HIV status and ART. Regardless of site, HIV-positive patients were at greater risk of dying (16.3% vs. 11.4%, p=0.022) (Table 5).

Survival probability appeared slightly worse at the community-based sites (p=0.064), with higher mortality at Site 4 influencing overall mortality (Table 3). Multivariate analysis showed significantly increased mortality for patients who were older than 30 (HR=1.64, p=0.010); had low pre-treatment weight (HR=1.42, p=0.041); were HIV-positive and not on ART (HR=1.77, p=0.018, referent HIV-negative) (Table 4).

There was heterogeneity in treatment outcomes across the four community-based sites with treatment success varying from 72% (Site 1) to 51.7% (Site 4) (p<0.01). Seventy patients (10%) at the community-based sites received exclusive home-based care. There was no difference in successful treatment outcomes in these patients compared with those who were initially hospitalised at the community-based sites (59% vs. 61%, p=0.511).

Treatment initiation delay was shorter at the community-based sites than the centralised hospital (median=72 vs. 92 days respectively, p<0.001) (Table 3) - but delay was not associated with treatment outcomes or mortality.

DISCUSSION

Our study shows that community-based care is more effective than centralised care as evidenced by higher cure (50.7% vs. 34.3%, p<0.001), lower default (14.5% vs. 28.3%, p=0.004) and earlier treatment initiation (72 vs. 92 days, p<0.001). Confirmatory logistic regression models adjusted for HIV status and receipt of ART, showed that patients at

community-based sites were more likely to have a successful treatment outcome (adjusted OR=1.43, p=0.01) (Table 4).

WHO, together with others, is now promoting ambulatory models of care for MDR-TB patients.[19-21] Our study findings support these calls as the introduction of community-based care increased the capacity of the public health system to provide treatment to approximately 900 more MDR-TB patients.[22] Furthermore, higher successful treatment outcomes and lower default rates at community-based sites suggest that community-based care may address patients' needs more successfully as care closer to home is easier to access, convenient, allows family support and eliminates long and costly trips to a centralised hospital.

Other studies reporting outcomes for community-based MDR-TB care have documented similar success rates, but have involved small numbers of patients and been implemented with support of an external organisation.[7,8,12] In contrast, our study reports findings of a programme implemented and funded entirely by the Department of Health. This increases the generalizability of our findings to other resource-limited situations.

There was considerable heterogeneity in treatment outcomes across the four community-based sites as treatment success varied from a high of 72% at Site 1 to a low of 51.7% at Site 4 (p<0.002). Higher treatment success at Site 1 was as a consequence of it being in a well-functioning and supportive district, where district leadership took ownership of the MDR-TB problem, re-organised and re-aligned health service components and allocated sufficient financial resources. This translated into the provision of 16 injection teams, additional staff at the outpatients' clinic who established systems, implementation of a locally developed patient treatment literacy programme and home-assessment by a multi-disciplinary team prior to patient discharge. These programme components were partially implemented at other decentralised sites. However, even when removing Site 1 from the analysis, treatment at the community-based sites remained as effective as treatment in the centralised site. Although the heterogeneity in treatment success across the community-based sites was greater than expected, we believe this adequately reflects variation in health service provision across different sites when services are expanded or a new programme is introduced. The variation in the number of days of hospitalisation at the decentralised sites (Site 1= 96; Site 3= 180; p<0.002) illustrates the different interpretation and implementation of guidelines, highlighting the importance of regular monitoring and support during service expansion, to ensure health systems are functional and new programmes implemented in accordance with guidelines, thereby optimising the probability of treatment success.[23-25]

Survival rates at the community-based sites were somewhat lower than at the centralised site (Table 3). There are five possible explanations. Firstly, survival bias may play a role at the centralised hospital where the median treatment initiation delay was longer than at the community-based sites (92 vs. 72 days). Secondly, experienced clinicians at the centralised hospital with access to more sophisticated laboratory and other investigations were able to detect patients failing to respond to treatment more quickly. Thirdly, there were a number of patients from the centralised hospital whose treatment outcomes were not known as their clinical records were missing. Although we are confident that no patient with a successful

outcome was incorrectly classified, we may have misclassified patients as defaulters when in fact they had died, thus underestimating mortality at the centralised hospital. A number of studies evaluating ART programmes, particularly those with large proportions of TB co-infection, have documented high mortality in patients lost to follow up.[26,27] Fourthly, baseline characteristics of patients at the community-based sites differed from those at the centralised hospital, suggesting that this patient population was more physically impoverished. Fifthly, there was considerable heterogeneity in mortality across the decentralised sites. The mortality rate at Site 4 was twice that at Site 1, influencing overall mortality.

Survival improved for the duration of the study. Across all sites, MDR-TB patients starting treatment in 2008 and 2009 were – respectively – 1.77 and 1.53 times more likely to die than patients starting treatment in 2010 (Table 4). Possible reasons for this improvement include policy changes in 2009 which promoted earlier initiation of ART for patients with MDR-TB and HIV,[28] new drugs introduced into the MDR-TB regimen, and improvement of patient management at the community-based sites with time and experience.

This operational study evaluated an intervention implemented by the public sector and we therefore had limited control over the design, scope and quality of implementation. Data used for programme evaluation were routinely collected by health workers, and were occasionally incomplete. Furthermore, during the study, as clinical records for some patients at the centralised site could not be found, we took several steps to determine the treatment outcomes of these patients. These included searching the national laboratory database (which demonstrated on-going care) and consulting the national registration system to verify if the patient had died. At the end of the analysis all patients had been assigned an outcome.

CONCLUSION

We conclude that community-based care is more effective than care in a centralised setting, based on similar treatment success rate, lower defaulter rate and shorter time to treatment initiation at the four community-based sites. Even in the presence of HIV co-infection, community-based care increased treatment success. Still to be determined is whether exclusive home-based care can achieve the same treatment success.

As alternate models of care for patients are introduced or expanded, we recommend regular monitoring and support of district and facility managers and individual health workers to ensure that services are equitable, guidelines adhered to, quality of care is optimal and the chance of treatment success optimised.

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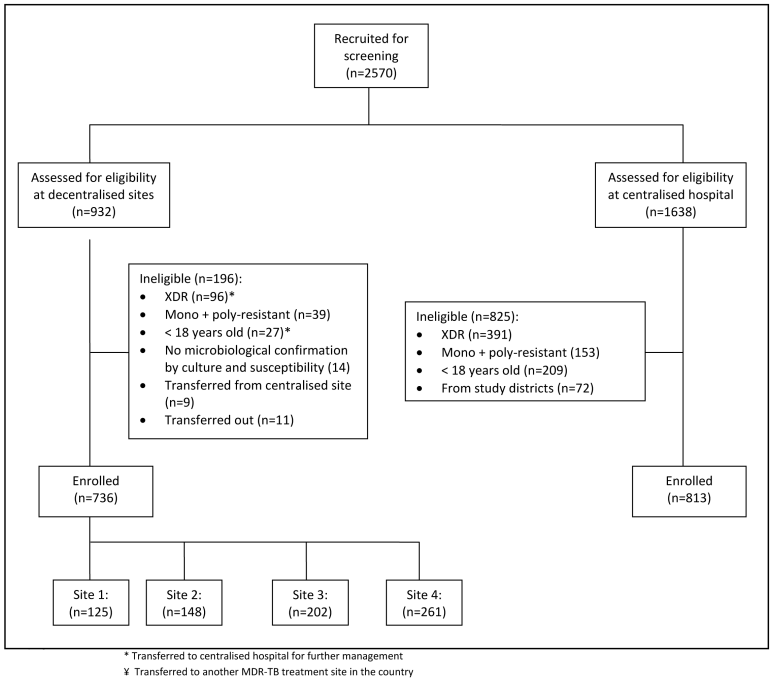

Figure 1.
Schema of enrolment

Table 1

Treatment outcome definitions*

Treatment outcome	Definitions
Cure	Cure was defined as completion of treatment and >5 consecutive negative culture results in the final 12 months of treatment. A patient was still considered cured If only one positive culture was reported during this time, was clinically well, and this positive culture was followed by at least 3 consecutive negative cultures taken at least 30 days apart.
Treatment completion	Treatment completion referred to completion of therapy but without bacteriologic documentation of cure.
Treatment success	Treatment success has been defined as the percentage of patients in whom the treatment outcome was either cured or completed. That is, "% successful = no. of patients cured + no. of patients completed treatment /Total no. initiated treatment × 100".
Treatment failure	Treatment failure was defined as having more than one positive culture in the final 12 months of therapy, or if any one of the final three cultures was positive, or if more than one drug in the treatment regimen was replaced, or if treatment was terminated due to adverse events or no clinical improvement.
Default	Default was defined as an interruption in treatment for ≥ 2 consecutive months for any reason.
Death	Death was defined as all-cause mortality during MDR-TB treatment.
Unsuccessful treatment	Unsuccessful treatment outcome has been defined as the percentage of patients in whom the treatment outcome was died, defaulted, or failed treatment.
Transferred out	A patient with MDR-TB who was transferred to another reporting and recording unit a year after study-enrolment whose treatment outcome is unknown.

*Treatment outcome definitions used are 2008 WHO definitions for the management of MDR-TB.[17,18]

Table 2

Baseline demographic and clinical characteristics of patients with MDR-TB in KwaZulu-Natal, South Africa

Characteristic	Centralised hospital	All community-based sites	Site 1	Site 2	Site 3	Site 4	p-value
	n=813	n=736	n=125	n=148	n=202	n=261	
Female	413 (50.8)	390 (52.9)	68 (54.4)	88 (59.5)	98 (48.5)	136 (52.1)	0.233 0.230
Median age (years, IQR)	34 (27-41)	36 (28-43)	36 (28-42)	37 (28-42)	34 (26-42)	36 (29-44)	<0.001 0.531
TB characteristics							
Previous TB	778 (95.7)	411 (55.8)	87 (69.6)	81 (54.7)	136 (67.3)	107 (41.0)	<0.001 <0.001
Previous MDR-TB	10 (1.23)	53 (7.2)	6 (4.8)	17 (11.5)	16 (7.9)	14 (5.4)	<0.001 0.098
Sputum-smear positive at diagnosis	491 (60.4)	557 (75.7)	75 (60.0)	121 (81.8)	152 (75.3)	209 (80.1)	<0.001 <0.001
Resistant to ≥3 drugs at diagnosis	467 (57.4)	410 (55.7)	74 (59.2)	91 (61.5)	101 (50.0)	144 (55.2)	0.364 0.149
Initial regimen ≥6 drugs	717 (88.2)	591 (80.3)	115 (92.0)	131 (88.5)	91 (45.1)	254 (97.3)	0.492 <0.001
HIV characteristics							
HIV-infected, n/total tested (%)	576/788 (73.1)	528/692 (76.3)	96/124 (77.4)	112/144 (77.8)	123/189 (65.1)	197/235 (83.8)	0.450 <0.001
HIV unknown	25 (3.1)	44 (6.0)	1 (0.8)	4 (2.7)	13 (6.4)	26 (10)	0.051 <0.001
Patients with available CD4 count	282	345	82	72	92	99	
Median baseline CD4 count (cells per μL), (IQR)	185, (106-300)	193, (88-329)	158, (71-286)	230, (136-366)	139, (64-322)	227, (96-365)	0.943 0.010
On ART, n/total HIV-infected (%)*	454/554 (82.0)	440/482 (91.3)	92/94 (97.9)	103/106 (97.2)	116/117 (99.2)	129/165 (78.2)	0.225 <0.001

Data are number (%), unless otherwise indicated

MDR-TB = multidrug-resistant tuberculosis

IQR = interquartile range

HIV = human immunodeficiency virus

ART = antiretroviral therapy

* On ART at start of MDR-TB therapy or within two weeks of MDR-TB treatment initiation. Denominator excludes HIV+ patients with missing ART information.

Table 3

Treatment outcomes and clinical course of patients with MDR-TB in KwaZulu-Natal, South Africa

	Centralised hospital	All community-based sites	Site 1	Site 2	Site 3	Site 4	p-value
	n=813	n=736	n=125	n=148	n=202	n=261	
Treatment outcomes[¶]							
Cured[*]	280 (34.4)	373 (50.7)	78 (62.4)	81 (54.7)	94 (46.5)	120 (46.0)	<0.001 0.009
Treatment completed[¥]	159 (19.6)	54 (7.3)	12 (9.6)	8 (5.4)	19 (9.4)	15 (5.8)	<0.001 0.265
Treatment success[**]	439 (54.0)	427 (58.0)	90 (72.0)	89 (60.1)	113 (55.9)	135 (51.7)	0.180 0.002
Died[‡]	113 (13.9)	133 (18.1)	17 (13.6)	22 (14.9)	25 (12.4)	69 (26.4)	0.211 <0.001
Failed[^]	29 (3.6)	49 (6.7)	7 (5.6)	11 (7.4)	12 (5.9)	19 (7.3)	<0.001 0.872
Default[‡‡]	230 (28.3)	107 (14.5)	9 (7.2)	20 (13.5)	50 (24.8)	28 (10.7)	0.004 <0.001
Transferred out[^^]	2 (0.25)	20 (2.7)	2 (1.6)	6 (4.1)	2 (1.0)	10 (3.8)	<0.001 0.130
Clinical course of treatment							
n Median no. of days from initial sputum collection to MDR-TB therapy initiation[¶¶], (IQR)	811 92, (69-120)	724 72, (54-97)	125 65, (42-91)	141 66, (50-86)	199 70, (52-99)	259 83, (63-107)	<0.001 <0.001
n Median duration of hospitalization (days), (IQR)	243 144, (83-185)	636 143, (90-179)	91 96, (57-132)	133 117, (83-146)	151 180, (120-197)	261 154, (115-175)	0.302 <0.001
Median duration of MDR-TB treatment (days), (IQR)	589, (285-700)	712, (270-740)	719, (588-735)	723, (273-753)	700, (341-733)	687, (176-742)	<0.001 0.062
Patients who culture converted, n/total culture-positive at treatment start (%)	511/638 (80)	536/672 (80)	95/111 (86)	118/139 (85)	140/174 (81)	183/248 (74)	0.983 0.017
n Median no of days to culture conversion[‡‡], (IQR)	511 83 (56, 111)	536 81 (56, 110)	95 63 (53, 84)	118 90 (58, 125)	140 87 (58, 120)	183 80 (54, 109)	0.651 0.003
n Median no of days follow up from diagnosis to treatment outcome, (IQR)	811 688 (386, 791)	724 771 (357, 822)	125 761 (696, 811)	141 787 (363, 824)	199 764 (423, 811)	259 771 (287, 831)	<0.001 0.877

Data are number (%), unless otherwise indicated

[¶]Treatment outcome definitions used are WHO definitions for the management of MDR-TB (Box 1). [17,18]

* **Cured:** Cure was defined as completion of treatment and >5 consecutive negative culture results in the final 12 months of treatment. A patient was still considered cured If only one positive culture was reported during this time, was clinically well, and this positive culture was followed by at least 3 consecutive negative cultures taken at least 30 days apart.

¥ **Treatment completed:** Treatment completion referred to completion of therapy but without bacteriologic documentation of cure.

** **Treatment success:** Treatment success has been defined as the percentage of patients in whom the treatment outcome was either cured or completed. That is, "% successful = no. of patients cured + no. of patients completed treatment /Total no. initiated treatment × 100".has been defined as the percentage of patients in whom the treatment outcome was either cured or completed. That is, "% successful = no. of patients cured + no. of patients completed Rx/Total no. initiated Rx × 100.

‡ **Died:** Death was defined as all-cause mortality during MDR-TB treatment.

^ **Failed:** Treatment failure was defined as having more than one positive culture in the final 12 months of therapy, or if any one of the final three cultures was positive, or if more than one drug in the treatment regimen was replaced, or if treatment was terminated due to adverse events or no clinical improvement.

‡‡ **Default:** Default was defined as an interruption in treatment for > 2 consecutive months for any reason.

^^ **Transferred out:** A patient with MDR-TB who was transferred to another reporting and recording unit a year after study-enrolment whose treatment outcome is unknown.

¶¶ This definition is an adaptation of the WHO definition, as date of DST results was not routinely recorded.[29]

‡‡ Culture conversion was defined as the interval between the treatment start date and the first of two consecutive negative sputum cultures taken at least one month apart.[17]

Table 4

Predictors of treatment success and death in patients with MDR-TB from the community-based sites and centralised hospital in KwaZulu-Natal, South Africa

Predictors of treatment success				
Variables	**Unadjusted Odds Ratio (95% CI)**	**p-value**	**Multivariate Odds Ratio (95% CI)**	**p-value**
Community-based site	1.19 (0.91 to 1.57)	0.207	1.43 (1.09 to 1.88)	0.010
Female gender	1.21 (1.09 to 1.36)	<0.001	1.19 (1.05 to 1.34)	0.007
Age≥30 years	1.28 (1.01 1.63)	0.042	1.40 (1.18 to 1.65)	<0.001
No previous MDR-TB	2.63 (2.05 to 3.39)	<0.001	2.51 (1.64 to 3.84)	<0.001
HIV and ART status				
HIV positive, on ART HIV negative HIV positive, not on ART	1.63 (1.40 to 1.89) 1.43 (1.08 to 1.90) Reference	<0.001 0.012	1.5 (1.38 to 1.62) 1.35 (1.05 to 1.75) Reference	<0.001 0.021
Weight, ≥50 kg female or ≥55 kg male	1.31 (1.06 to 1.63)	0.013	1.28 (1.06 to 1.56)	0.011
Length of hospitalization[^]	1.01 (0.99 to 1.01)	0.091	**	
Culture conversion <90 days from Rx start[¶]	1.71 (1.44 to 2.03)	<0.001	**	
Predictors of death				
Variables	**Unadjusted Hazards Ratio (95%) CI)**	**p-value**	**Multivariate Hazards Ratio (95% CI)**	**p-value**
Community-based Site	1.27 (0.82 to 1.96)	0.289	1.06 (0.87 to1.30)	0.567
Age, ≥30 years	1.70 (1.03 to 2.83)	0.039	1.61 (1.09 to 2.38)	0.018
Low pre-treatment weight, ≤50 kg female or≤55 kg male	1.35 (0.88 to 2.05)	0.161	1.40 (1.00 to 1.96)	0.048
Previous TB or MDR-TB	0.82 (0.58 to 1.19)	0.312	1.28 (0.78 to 2.09)	0.324
Year treatment started				
2008 2009 2010	1.78 (1.35 to 2.35) 1.27 (1.09 to 1.48) Reference	<.001 .002	1.77 (1.36 to 2.31) 1.53 (1.05 to 2.22) Reference	<0.001 0.027
HIV and ART status				
HIV positive, not on ART HIV positive, on ART HIV negative	2.12 (1.54 to 2.93) 1.23 (0.93 to 1.63) Reference	<0.001 0.154	1.59 (0.98 to 2.59) 1.01 (0.72 to 1.41) Reference	0.062 1.006
Median baseline CD4 count (cells per μL)			**	
<50 50-199 200+	1.90 (1.11 to 3.26) 1.02 (0.80 to 1.31) Reference	0.019 0.853		
Length of hospitalization[^]	0.92 (0.88 to 0.96)	<0.001	**	
Extensive chest disease[‡]	2.54 (1.00 to 6.44)	0.049	**	

HIV = human immunodeficiency virus

ART = antiretroviral therapy

[^] For every additional 14 day stay

[¶] culture conversion <90 days defined as two consecutive negative sputum cultures taken at least 1 month apart less than 90 days after treatment started.

[**] Not included in multivariate model because too few non-missing values.

[‡] Extensive chest disease defined if bilateral involvement or cavities present on chest X-ray.

Table 5

Treatment outcomes stratified by HIV status in patients with MDR-TB in KwaZulu-Natal, South Africa[¶]

	HIV positive			HIV negative		
	Centralised Hospital	All community-based sites	p-value	Centralised Hospital	All community-based sites	p-value
	n=576	n=528		n=212	n=164	
Cured[*]	200 (34.7)	286 (54.2)	<0.001	71 (33.5)	79 (48.2)	<0.001
Treatment completed[¥]	109 (18.9)	35 (6.6)	<0.001	46 (21.7)	16 (9.8)	<0.001
Treatment success[**]	309 (53.6)	321 (60.8)	0.013	117 (55.2)	95 (57.9)	0.372
Died[†]	82 (14.2)	98 (18.6)	0.114	24 (11.3)	19 (11.6)	0.970
Failed[^]	23 (4.0)	32 (6.1)	<0.001	5 (2.4)	14 (8.5)	0.008
Default[‡‡]	160 (27.8)	65 (12.3)	<0.001	66 (31.1)	32 (19.5)	0.025
Transferred out[^^]	2 (0.4)	12 (2.3)	**	0	4 (2.4)	**

Data are number (%), unless otherwise indicated

[¶]Treatment outcome definitions used are WHO definitions for the management of MDR-TB (Box 1). [17,18]

[*]**Cured:** Cure was defined as completion of treatment and >5 consecutive negative culture results in the final 12 months of treatment. A patient was still considered cured If only one positive culture was reported during this time, was clinically well, and this positive culture was followed by at least 3 consecutive negative cultures taken at least 30 days apart.

[¥]**Treatment completed:** Treatment completion referred to completion of therapy but without bacteriologic documentation of cure.

[**]**Treatment success:** Treatment success has been defined as the percentage of patients in whom the treatment outcome was either cured or completed. That is, "% successful = no. of patients cured + no. of patients completed treatment /Total no. initiated treatment × 100".has been defined as the percentage of patients in whom the treatment outcome was either cured or completed. That is, "% successful = no. of patients cured + no. of patients completed Rx/Total no. initiated Rx × 100.

[†]**Died:** Death was defined as all-cause mortality during MDR-TB treatment.

[^]**Failed:** Treatment failure was defined as having more than one positive culture in the final 12 months of therapy, or if any one of the final three cultures was positive, or if more than one drug in the treatment regimen was replaced, or if treatment was terminated due to adverse events or no clinical improvement.

[‡‡]**Default:** Default was defined as an interruption in treatment for > 2 consecutive months for any reason.

[^^]**Transferred out:** A patient with MDR-TB who was transferred to another reporting and recording unit a year after study-enrolment whose treatment outcome is unknown.