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Comparing early treatment outcomes of MDR-TB in decentralised and centralised settings in KwaZulu-Natal, South Africa

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SUMMARY

SETTING: In KwaZulu-Natal, South Africa, a setting endemic for tuberculosis (TB) and the human immunodeficiency virus (HIV), prolonged hospitalisation for the treatment of the growing number of multidrug-resistant TB (MDR-TB) patients is neither possible nor effective.

OBJECTIVE: To compare early treatment outcomes in patients with MDR-TB with and without HIV co-infection at four decentralised rural sites with a central urban referral hospital.

DESIGN: This is an operational, prospective cohort study of patients between 1 July 2008 and 30 November 2009, where culture conversion, time to culture conversion, survival and predictors of these outcomes were analysed.

RESULTS: Of 860 patients with MDR-TB, 419 were at the decentralised sites and 441 at the central hospital. Overall, 71% were HIV co-infected. In the 17-month study period, there was a higher proportion of culture conversion at the decentralised sites compared with the centralised hospital (54% vs. 24%, $P < 0.001$, OR 3.76, 95%CI 2.81–5.03). The median time to treatment initiation was significantly shorter at the decentralised sites compared with the centralised hospital (72 vs. 93 days, $P < 0.001$). There was no significant difference in survival following treatment initiation.

CONCLUSION: In this study, early treatment outcomes suggest that decentralised care for MDR-TB patients is superior to that in a centralised setting.

KEY WORDS: operational research; high burden of TB and HIV

THE PROVINCE of KwaZulu-Natal has South Africa's highest recorded tuberculosis (TB) incidence, 1163 cases per 100 000 population, in a setting where 80% of all TB patients are human immunodeficiency virus (HIV) positive and, at 17%, HIV prevalence is among the highest in the world.[1,2] The high prevalence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) in this setting is due partly to a poorly functioning TB control programme and ongoing nosocomial transmission.[3–5] MDR-TB is defined as TB resistant to at least isoniazid (INH) and rifampicin (RMP), and XDR-TB as MDR-TB with additional resistance to any fluoroquinolone and at least one injectable second-line TB drug (amikacin, kanamycin [KM] or capreomycin).[6] In KwaZulu-Natal, drug susceptibility testing (DST) of positive cultures is performed routinely for INH, RMP, ethambutol (EMB), streptomycin, KM and ciprofloxacin.

Until 2008, the treatment of drug-resistant TB in KwaZulu-Natal mirrored the World Health Organization (WHO) guidelines—patients underwent prolonged hospitalisation in a centralised, specialist TB hospital, followed by monthly out-patient visits to the same institution.[6] However, the overwhelming and escalating burden of resistance resulted in inconsistent guideline implementation. With limited beds at the centralised hospital, treatment initiation was often delayed by 2–3 months. When admitted, MDR- and XDR-TB patients were in mixed congregate wards for 4–6 months due to space limitations. After discharge, the centralised hospital lacked the necessary personnel and infrastructure to address the adverse effects and socio-economic demands of patients travelling from across the province.[7] Consequently, of the 5165 MDR-TB patients treated between 1994 and 2004, 67% had unsuccessful treatment

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outcomes, of which 14% defaulted and 19% were not evaluated.[8]

The KwaZulu-Natal Department of Health, identifying the need for alternative MDR-TB treatment models, began piloting decentralised care in 2008 at four sites across the province, utilising regional district hospitals for initial hospitalisation and monthly out-patient follow-up.[9,10] Furthermore, unlike the centralised model, district health care workers and community resources were recruited to strengthen outpatient follow-up. Although similar models of decentralised MDR-TB treatment have been successfully implemented in other countries,[11,12] KwaZulu-Natal is uniquely challenged as the epicentre of both the TB and HIV epidemics in sub-Saharan Africa.[5]

To determine the impact of decentralised MDR-TB treatment, we compared early treatment outcomes in the decentralised care model with those in the centralised treatment programme.

METHODS

Setting

South Africa has a district health system in which community-based clinics provide primary level care and refer patients to district and regional hospitals for secondary level care. One aim of decentralised MDR-TB care was to create accessible treatment sites close to the patient's home. The four rural decentralised MDR-TB sites are geographically positioned throughout the province—with a strategic focus on areas with the highest incidence of MDR-TB (Figure 1).[13] The populations of these four sites are among the most socio-economically challenged in the country, with limited or no access to piped water.[14]

Situated in the biggest urban centre of the province, the centralised specialist TB hospital functions as the referral hospital for drug-resistant TB in KwaZulu-Natal. The in-patient population currently consists almost exclusively of patients with drug-resistant TB.

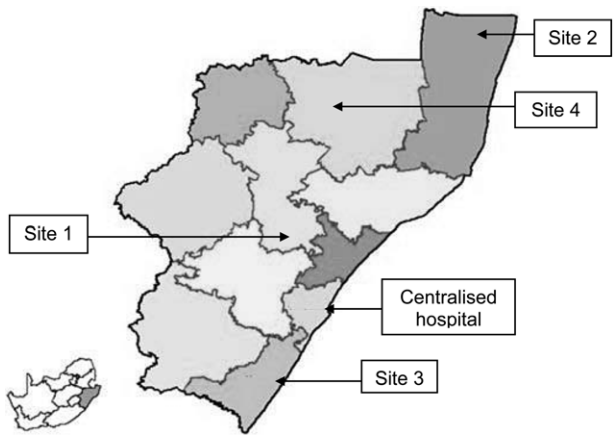

Figure 1 A map of KwaZulu-Natal showing the location of the centralised hospital and the four decentralised MDR-TB treatment sites. MDR-TB = multidrug-resistant tuberculosis.

By mid-2008, staff were deployed in the decentralised sites and area doctors were trained to initiate and manage MDR-TB treatment. More complicated patients, such as children and patients with XDR-TB, are referred to the centralised hospital for treatment initiation and continued care. Guidelines on decentralised care were developed by the health department and circulated to the four decentralised sites before treatment commenced.[9] In accordance with South African national treatment guidelines, all patients receive a standardised MDR-TB treatment regimen consisting of pyrazinamide, EMB, ethionamide, KM, ofloxacin and cycloserine.

Study design

An operational prospective cohort study was implemented in 2009. Patients were included in the study if they were aged ⩾18 years and had a laboratory-confirmed diagnosis of MDR-TB.[15] Patients with XDR-TB, mono- or polyresistant TB, and those receiving care at both a decentralised site and the centralised hospital were excluded. Inclusion criteria at the decentralised sites required that patients come from within the catchment area of the site. For the centralised hospital, patients were excluded if they were involved in a clinical trial (Figure 2). Patients who commenced treatment between 1 July 2008 and 30 November 2009 were included in the study. Patient follow-up ended when a treatment outcome was recorded or 30 November 2009, when data were extracted for the interim analysis, whichever occurred first.

The primary outcome was the proportion of MDR-TB patients whose culture converted in the decentralised sites compared to the centralised hospital. Conversion of sputum culture from positive to negative is considered a useful early indicator of programme effectiveness, as treatment outcomes are only available 18–24 months after the start of treatment.[16,17] Culture conversion is defined as two consecutive negative sputum cultures taken at least 1 month apart.[18] Secondary outcomes include time to conversion, treatment initiation delay and survival. Time to culture conversion is the interval between the treatment start date and the date of the first of two consecutive negative sputum cultures. Treatment initiation delay is the interval between the date of initial sputum collection for culture and treatment start date. This definition is an adaptation of the WHO definition, as diagnostic date was not routinely recorded in KwaZulu-Natal. Treatment outcomes are based on standard WHO definitions.[18,19] Patients were considered to have failed treatment if two or more drugs were replaced in the MDR-TB regimen, treatment was terminated due to adverse events or there was no clinical improvement,

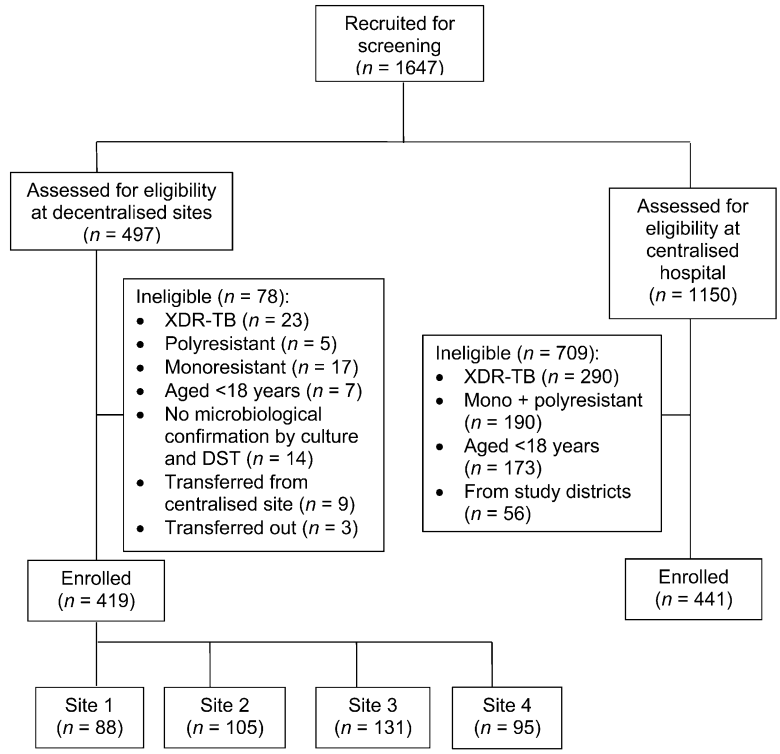

Figure 2 Enrolment flow chart. DST = drug susceptibility testing; XDR-TB = extensively drug-resistant TB.

with either no culture conversion or reversion after initial conversion.[20]

Data collection and analysis

Clinical and laboratory data were continually recorded at all sites by assigned data capturers, including demographic characteristics, previous exposure to TB treatment, HIV status and antiretroviral treatment (ART) regimen, DST results, MDR-TB treatment regimens, treatment outcomes and monthly sputum culture results.

Data were collected in MS Excel 2004 (Microsoft, Redwoods, WA, USA) and analyses were performed using STATA/SE version 11.0 (Stata Corp, College Station, TX, USA).

The comparison of the odds of culture conversion between sites was assessed through the computation of odds ratios (ORs). The effect of all variables listed in Tables 1 and 2 were analysed using logistic regression models. Categorical data were analysed using Fisher's exact or χ^2 test. Unpaired *t*-tests, the Wilcoxon two-sample test and Kruskal-Wallis non-parametric test were used for the analysis of continuous data. The Kaplan-Meier product limit method was used to calculate probabilities of culture conversion at different time points, and the log-rank test

Table 1 Baseline characteristics of study population

	Centralised hospital* *n* (%)	All decentralised sites† *n* (%)	*P* value	Decentralised sites† Site 1 *n* (%)	Site 2 *n* (%)	Site 3 *n* (%)	Site 4 *n* (%)	*P* value
Patients enrolled per site, *n*	441	419		88	105	131	95	
Sex, female	229 (52)	205 (49)	0.459	52 (59)	60 (57)	58 (44)	35 (37)	0.002
Age, years, mean [range] (95%CI)	35.2 [18–79] (34–36)	36.3 [18–80] (35–37)	0.140	35 [18–60] (33–38)	38 [18–80] (35–41)	34 [18–56] (32–35)	39 [18–70] (36–41)	0.002
HIV status								
HIV-positive	337 (79)	274 (75)	0.306	64 (73)	69 (66)	70 (54)	71 (75)	0.047
Unknown	16 (4)	52 (12)		6 (7)	12 (11)	24 (18)	10 (10)	
HIV-positive patients on ART	(*n* = 337) 171 (51)	(*n* = 274) 172 (63)	<0.001	(*n* = 64) 49 (77)	(*n* = 69) 54 (78)	(*n* = 70) 45 (64)	(*n* = 71) 24 (34)	<0.001

*Initial hospitalisation and ongoing care at a centralised specialist hospital.
†Initial hospitalisation and ongoing care at a district hospital and in the community.
CI = confidence interval; HIV = human immunodeficiency virus; ART = antiretroviral therapy.

Table 2 TB characteristics of study population

	Centralised hospital *n* (%)	All decentralised sites *n* (%)	*P* value	Decentralised sites				
				Site 1 *n* (%)	Site 2 *n* (%)	Site 3 *n* (%)	Site 4 *n* (%)	*P* value
Patients enrolled per site, *n*	441	419		88	105	131	95	
Sputum smear-positive	240 (54)	305 (73)	<0.001	56 (64)	72 (69)	101 (77)	76 (80)	0.039
Extra-pulmonary TB	1 (0.2)	4 (1)	0.164	0	3 (3)	1 (1)	0	0.170
Previous TB treatment	423 (96)	252 (60)	<0.001	65 (74)	51 (49)	95 (72)	41 (43)	0.395
Number of patients resistant to								
2 drugs	183 (42)	177 (42)	0.824	36 (41)	39 (37)	58 (44)	44 (46)	0.564
>2 drugs	258 (58)	242 (58)		52 (59)	66 (63)	73 (56)	51 (54)	
Number of patients in injectable phase on*								
<6 drugs	(*n* = 436)	(*n* = 413)		(*n* = 87)	(*n* = 100)	(*n* = 131)	(*n* = 95)	
	105 (24)	157 (38)	<0.001	9 (10)	28 (28)	111 (85)	9 (9)	<0.001
⩾6 drugs	(*n* = 436)	(*n* = 413)						
	331 (76)	256 (62)		78 (90)	72 (72)	20 (15)	86 (91)	
Median time to MDR-TB treatment initiation, days [IQR]	(*n* = 423) 93 [71–120]	(*n* = 406) 72 [56–99]	<0.001	(*n* = 87) 68 [50–93]	(*n* = 95) 70 [50–94]	(*n* = 129) 70 [54–97]	(*n* = 95) 83 [64–120]	<0.001

*Injectable phase: initial phase of MDR-TB treatment which includes an injectable.
TB = tuberculosis; MDR-TB = multidrug-resistant TB; IQR = interquartile range.

was used to compare these probabilities by site. The duration of follow-up was calculated as the number of days from treatment initiation to treatment outcome, or 30 November 2009, whichever occurred first. Cox proportional hazards regression models were fitted to determine risk factors associated with outcomes in time to event-based analyses. The proportionality assumption of the Cox models was tested with $-\ln(-\ln[\text{survival}])$ curves and regression of scaled Schoenfeld residuals on functions of time. Variables that did not satisfy the proportional hazards assumptions were included as strata in the stratified Cox proportional hazards model.

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

RESULTS

Between 1 July 2008 and 30 November 2009, 1647 patients started treatment for drug-resistant TB in KwaZulu-Natal. A total of 860 MDR-TB patients met the eligibility criteria: 419 at the decentralised sites and 441 at the centralised hospital (Figure 2). Table 1 presents the baseline characteristics of the participants. The decentralised and centralised cohorts were comparable in terms of sex, age and HIV status. Co-infection was high at both the decentralised sites and the centralised hospital (79% vs. 75%, $P = 0.306$). A significantly higher number of patients at the decentralised sites were on ART or commenced ART within 2 weeks of MDR-TB treatment initiation ($P < 0.001$). The decentralised site also had a higher proportion of smear-positive patients at the time of MDR-TB diagnosis ($P < 0.001$), a lower proportion had had previous TB treatment ($P < 0.001$) and a lower proportion were on a MDR-TB regimen of six or more drugs ($P < 0.001$; Table 2). The median duration of follow-up was 154 days (interquartile range [IQR] 48–296).

Culture conversion at the decentralised site occurred more often (54% vs. 24%, $P < 0.001$) and decentralised patients were more likely to culture convert than the centralised hospital patients (OR 3.76, 95% confidence interval [CI] 2.81–5.03). Not having a previous TB episode was the only significant predictor of culture conversion (OR 2.47, 95%CI 1.63–3.73). Fewer patients at the decentralised sites had a history of TB compared with patients at the centralised hospital (60% vs. 96%, $P < 0.001$).

Utilising Kaplan-Meier curves, there was no difference in the probability of culture converting over time between the decentralised sites and the centralised hospital ($P = 0.171$; Figure 3). The methodology governing the computation of Kaplan-Meier probability estimates differs from the method used to generate

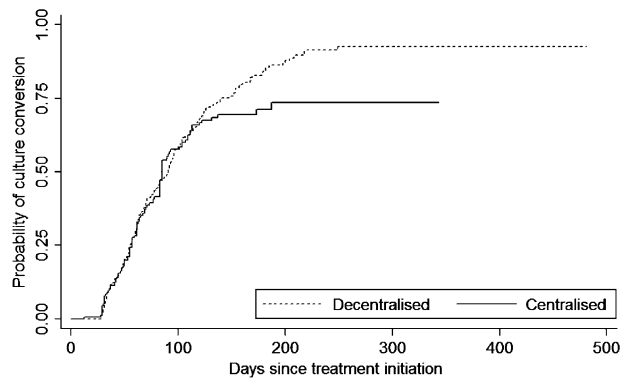

Figure 3 Comparison of the time to culture conversion in MDR-TB patients treated at a centralised hospital and decentralised sites, 1 June 2008–30 November 2009 ($P = 0.171$). MDR-TB = multidrug-resistant tuberculosis.

Table 3 Treatment outcomes

	Centralised hospital *n* (%)	Decentralised sites				
		All *n* (%)	Site 1 *n* (%)	Site 2 *n* (%)	Site 3 *n* (%)	Site 4 *n* (%)
Patients enrolled per site	441	419	88	105	131	95
Died	30 (7)	67 (16)	7 (8)	15 (14)	18 (14)	27 (28)
Failed	0	15 (4)	3 (3)	7 (7)	4 (3)	1 (1)
Defaulted	7 (2)	14 (3)	0	4 (4)	8 (6)	2 (2)
Total 'unsuccessful treatment outcomes'	37 (8)	96 (23)	10 (12)	26 (25)	30 (23)	30 (32)
Lost to follow-up	126 (29)	65 (15)	32 (36)	3 (3)	27 (21)	74 (56)
Still on treatment	278 (63)	258 (62)	46 (52)	76 (72)	3 (3)	62 (65)

culture conversion. Site, classified as either decentralised or centralised, did not satisfy the proportional hazards assumption, and hence a stratified Cox model was used to assess predictors of time to culture conversion while controlling for site. Although HIV status was not identified as a predictor of time to culture conversion, separate analyses were conducted for HIV-negative and HIV-positive patients, as HIV status significantly impacts MDR-TB treatment outcomes.[21] In univariate analyses of HIV-negative individuals, being female (females vs. males hazard ratio [HR] 1.62, 95%CI 1.01–2.60) and increased weight (HR 1.03, 95%CI 1.01–1.06) were associated with a shorter time to culture conversion.

The median treatment initiation delay was significantly shorter at the decentralised sites compared to the centralised hospital (72 vs. 93 days, $P < 0.001$; Table 2).

Overall, 16% (67/419) of patients in the decentralised sites died, significantly more than at the centralised hospital (7% [30/441], $P < 0.001$; Table 3). Decentralised patients initiated treatment significantly earlier (72 vs. 93 days, $P < 0.001$). The only significant predictor of death was age (HR 1.04, 95%CI 1.02–1.06).

The median time to death at the decentralised sites was 85 days (IQR 21–186) compared with 43 days (IQR 11–100) at the centralised hospital. In time to event analysis, there was no significant difference in the probability of survival between the decentralised sites and the centralised hospital (Figure 4, $P = 0.095$). In the univariate analysis, site was not significantly associated with time to death (HR 1.00, 95%CI 0.62–1.62).

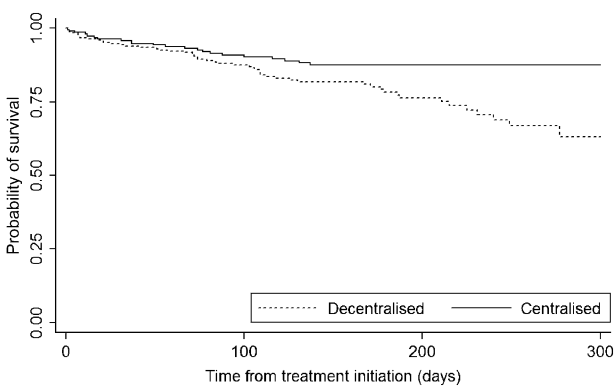

Figure 4 Comparison of the time to death in MDR-TB patients treated at a centralised hospital and decentralised sites, 1 June 2008–30 November 2009 ($P = 0.095$). MDR-TB = multidrug-resistant tuberculosis.

DISCUSSION

This study suggests that decentralised care for MDR-TB patients is more effective than care in a centralised hospital. Significantly more patients experienced culture conversion at the decentralised sites (54%) than at the centralised hospital (24%; $P < 0.001$; OR 3.76, 95%CI 2.81–5.03). However, the probability of survival did not differ between the two models of care ($P = 0.095$).

Successful treatment of MDR-TB patients in a decentralised setting was first documented in Peru.[12,22] More recently, three studies from southern Africa have confirmed that culture conversion is possible in HIV co-infected patients in a decentralised setting.[23–25] However, the cohorts in these studies were small and lacked a comparison group. In Lesotho, culture conversion was documented in 68% of 77 study patients.[23] In two rural South African settings, culture conversion was documented in 88% of 45 patients in Tugela Ferry[24] and in 83% of 53 patients in Hlabisa.[25] Our initial analysis of culture conversion suggests that decentralised care is more effective than centralised care in treating MDR-TB patients. Possible reasons as to why our culture conversion was lower than in the three other southern African studies cited above are that our study sample was far larger and was implemented within the routine health services with minimal use of external resources.

Concurrent ART and TB treatment has been shown to improve treatment outcomes in patients co-infected with drug-resistant TB and HIV.[26,27] Possible reasons for the lower culture conversion rate at the centralised hospital include longer treatment initiation delay, more patients with a history of TB and fewer patients on ART. In addition, the decentralised sites have initiated vigorous out-patient programmes utilising mobile injection teams and local clinics to administer drugs in the injectable phase of treatment, educating

patients and their families about MDR-TB and HIV and introducing follow-up procedures for patients who miss monthly appointments. At the centralised hospital, patients are often discharged before completion of the injectable phase and lack the intensive educational curriculum, as the large volume of patients and geographical dispersion prohibits an effective outpatient programme. The uncertain and irregular provision of the daily injectable may contribute to the lower culture conversion at the centralised hospital.

To curb the MDR-TB epidemic, early commencement of appropriate treatment is essential to limit the transmission of drug-resistant forms of *Mycobacterium tuberculosis*. DST results should be available between 42 and 56 days.[28] However, the median treatment initiation delay was 72 days at the decentralised sites and 93 days at the centralised hospital ($P < 0.001$). The shorter treatment initiation delays at the decentralised sites suggest that if treatment is available closer to patients' homes, treatment delays can be minimised (Table 2). This is an improvement to the mean treatment initiation delay of 111 days documented in a 2007 study,[13] but further reductions are needed, as mortality rates of 40% within 30 days of sputum collection in MDR-TB patients have been documented in the province.[29]

Only unsuccessful treatment outcomes were available for the interim analysis, as patients who were responding to treatment were still on treatment at the time data were extracted for analysis. More patients treated at decentralised sites died compared to the centralised hospital. We expected better survival at the decentralised sites given that delays in treatment initiation were shorter and the probability of culture conversion higher. One possible explanation is that twice the proportion of patients at the centralised hospital were lost to follow-up (Table 3), and the number of deaths at the centralised hospital is probably unrecorded. (Patients at the centralised hospital for whom there were no data in the 6 months prior to data extraction were classified as lost to follow-up and not as defaulters due to delays in data capture). In contrast, close follow-up and contact with patients and their family at the decentralised sites made it possible to record deaths and defaulting.

There was a lack of association between death and HIV status. This may be true, as many of the HIV-infected patients were on ART (36/67, 54%). However, it may not be true, as data were missing on HIV status for 13 (14%) of those who died. To achieve optimal MDR-TB outcomes, ongoing barriers such as long delays in diagnosis, limited integration with HIV services and poor adherence to medication need to be addressed.

The current study is pragmatic in that the intervention being implemented utilises pre-existing management and clinical staff resources, and subsequent evaluation was conducted with minimal use of external resources. This is the ideal context in which to evaluate effectiveness, as it reflects the reality of implementation in resource-constrained settings and can inform the roll-out of the programme in public health settings.[30,31] The rigorous monitoring process of this evaluation has ensured that challenges and successes have been brought to the attention of the provincial TB managers in a timely fashion and that the successes at one site are shared with the other sites.

However, an operational study presents both methodological and practical challenges, as the researcher had limited control over the design, scope and quality of the intervention. A further weakness of the study is that data routinely collected by health workers are at times incomplete and inaccurate. In some instances baseline (start of treatment) culture results were not available. In these instances, diagnostic culture results were used as the baseline results and time to conversion calculated from the date treatment was started. Some patients may have converted earlier. In addition, delays in data capturing at the centralised hospital may have resulted in fewer deaths being recorded. This paper is limited as it reports early outcomes, which may be misleading.

CONCLUSION

To our knowledge, this is the largest cohort reported worldwide of MDR-TB patients in an HIV-endemic area treated in a decentralised setting. Early results from this operational study suggest that decentralised care is feasible and, initially, superior to centralised care in treating MDR-TB patients in an area with a high HIV prevalence. However, the final treatment outcomes at the end of 2 years of treatment will be necessary to definitively demonstrate the effectiveness of decentralised care.

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RÉSUMÉ

CADRE : Au KwaZulu-Natal, Afrique du Sud, une région endémique pour la tuberculose (TB) et le virus de l'immunodéficience humaine (VIH), une hospitalisation de longue durée pour traiter le nombre croissant de malades atteints d'une tuberculose multirésistante (TB-MDR) n'est ni possible ni efficace.

OBJECTIF : Comparer les résultats précoces du traitement observés chez les patients atteints de TB-MDR avec ou sans co-infection par le VIH dans quatre sites décentralisés avec ceux obtenus dans un hôpital central urbain de référence.

SCHÉMA : Il s'agit de l'étude opérationnelle prospective d'une cohorte de patients entre le 1er juillet 2008 et le 30 novembre 2009 où l'on a analysé la négativation des cultures, la durée avant négativation, la survie ainsi que les facteurs prédictifs de ces résultats.

RÉSULTATS : Sur les 860 patients atteints de TB-MDR, 419 se situaient dans des sites décentralisés et 441 à l'hôpital central. Dans l'ensemble, 71% étaient co-infectés par le VIH. Pendant la période d'étude de 17 mois, la proportion de négativation des cultures est supérieure dans les sites décentralisés par rapport à l'hôpital central (54% vs. 24% ; $P < 0{,}001$; OR 3,76 ; IC95% 2,81–5,03). La durée médiane avant la mise en route du traitement est significativement plus courte dans les sites décentralisés qu'à l'hôpital central (72 vs. 93 jours ; $P < 0{,}001$). On n'a pas noté de différence significative de survie après la mise en route du traitement.

CONCLUSION : Dans cette étude les résultats précoces du traitement suggèrent que les soins décentralisés de patients TB-MDR sont meilleurs que ceux observés dans un contexte centralisé.

RESUMEN

MARCO DE REFERENCIA: Un entorno de KwaZulu-Natal en Sudáfrica, donde son endémicas la tuberculosis (TB) y la infección por el virus de la inmunodeficiencia humana (VIH) y la hospitalización prolongada para el tratamiento del número creciente de pacientes con TB multidrogorresistente (TB-MDR) no es posible o es ineficaz.

OBJETIVO: Comparar en el estudio los desenlaces terapéuticos tempranos en pacientes con TB-MDR, con y sin coinfección por el VIH, en cuatro centros rurales descentralizados y un hospital central urbano de referencia.

MÉTODO: Fue este un estudio de cohortes operativo, prospectivo, llevado a cabo entre el 1° de julio del 2008 y el 30 de noviembre del 2009. Se analizaron la conversión del cultivo, el lapso hasta la conversión, la supervivencia y los factores pronósticos de estos desenlaces.

RESULTADOS: De los 860 pacientes con TB-MDR, 419 acudieron a los centros descentralizados y 441 al hospital central. Globalmente, 71% de los pacientes presentaba coinfección por el VIH. En los 17 meses del estudio, se observó una mayor proporción de conversión del cultivo en los centros descentralizados que en el hospital central (54% contra 24%; $P < 0{,}001$; OR 3,76; IC95% 2,81–5,03). La mediana del lapso hasta el comienzo del tratamiento fue significativamente más corto en los centros rurales que en el hospital central (72 contra 93 días; $P < 0{,}001$). No se observó una diferencia significativa en la supervivencia después del comienzo del tratamiento.

CONCLUSIÓN: En este estudio, los desenlaces terapéuticos tempranos indican que el tratamiento descentralizado de los pacientes con TB-MDR es superior al que reciben los pacientes en el entorno centralizado.