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Community-based treatment for multidrug-resistant tuberculosis in rural KwaZulu-Natal, South Africa

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SUMMARY

SETTING: Hlabisa health sub-district, KwaZulu-Natal, South Africa.

OBJECTIVE: To describe the establishment of a community-based multidrug-resistant tuberculosis (MDR-TB) treatment programme embedded in the district TB control programme and to evaluate whether early outcomes are comparable to those in the traditional hospital-based model of care.

DESIGN: Cases who initiated community-based MDR-TB treatment (CM) between March and December 2008 were compared with patients who initiated MDR-TB treatment under the traditional hospital-based model of care (TM) between January 2001 and February 2008. Time to initiation of treatment and time to sputum smear and culture conversion were compared for the two groups in Kaplan-Meier survival curves using the Mantel-Cox log-rank test.

RESULTS: Overall, 50 CM cases and 57 TM cases were included; 39 of the 50 CM cases (78.0%) were human immunodeficiency virus positive. The median time to initiation of treatment was 84 days for CM and 106.5 days for TM ($P = 0.002$). Median time to sputum smear conversion was shorter for CM than TM (59 vs. 92 days, $P = 0.055$), as was time to sputum culture conversion (85 vs. 119 days, $P = 0.002$).

CONCLUSION: Community-based treatment for MDR-TB can be implemented within the existing TB control programme in rural South Africa and should be scaled up where resources allow.

KEY WORDS: tuberculosis; drug resistance; HIV

THE PAST FEW YEARS have seen the escalation of combined epidemics of tuberculosis (TB) and human immunodeficiency virus (HIV) infection in Southern Africa.[1,2] Compounding this has been the emergence of multidrug-resistant TB (MDR-TB, defined as resistance to both isoniazid [INH] and rifampicin [RMP]) and extensively drug-resistant TB (XDR-TB, defined as MDR-TB with additional resistance to any fluoroquinolone and to at least one injectable second-line drug).[3-5] KwaZulu-Natal (KZN), in South Africa, is at the epicentre of these intertwined epidemics, with high HIV prevalence and incidence[6-8] and a TB incidence of 1094 per 100 000 person-years.[9] Over 2000 laboratory-confirmed cases of MDR-TB were identified per year in KZN in 2006 and 2007.[10]

The management of MDR-TB in South Africa has historically involved centralised treatment, including admission to specialist provincial hospitals for at least the intensive phase of treatment.[11] The rationale for this has been to monitor complex drug regimens, optimise adherence and limit community transmission. However, there is no evidence that hospitalisation actually limits community transmission, and it is likely that most patients have been infectious for several months before hospitalisation, given the delays in diagnosis and treatment under routine programme conditions.[12] Moreover, the risk of nosocomial transmission, both to other patients and to health care workers, is high.[13–15] There are also economic and social costs involved in keeping patients isolated in hospitals, often far from home, and this can lead to default from treatment programmes.[16] The estimated cost of MDR-TB hospitals accounts for half of the National TB Programme (NTP) budget in South Africa;[17] the centralised model of care currently lacks the capacity to deal with the burden of MDR-TB, and there is an urgent need to scale up and evaluate community-based treatment models (CMs).[18,19]

Community-based treatment for drug-resistant TB is not a new concept, and successful outcomes have been

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reported elsewhere, most notably from Peru.[20,21] However, most cases in these studies were HIV-negative, and the high rate of HIV co-infection in Southern Africa presents additional programmatic challenges.[4,5] Public-private partnerships and non-governmental organisations have developed community-based treatment projects in Southern Africa, but the sustainability of such programmes is always a matter of concern.[22,23] We describe the experience in Hlabisa sub-district, in the province of KwaZulu-Natal, South Africa, with the establishment of a community-based MDR-TB treatment model within the existing Department of Health TB programme.

METHODS

Setting

In KwaZulu-Natal, the majority of MDR-TB and XDR-TB patients are treated at a single 160-bed site, the King George V Hospital (KGH), Durban. Patients are referred with culture-proven MDR-TB or XDR-TB, and individualised drug regimens are prescribed according to national guidelines.[11] The most common MDR-TB regimen consists of 6 months of kanamycin (KM), ofloxacin (OFX), ethionamide (ETH), cycloserine (CS), ethambutol (EMB) and pyrazinamide (PZA), followed by 12 or 18 months of OFX/ETH/CS/EMB/PZA. Treatment is provided on an in-patient basis at least until sputum culture conversion, and is thereafter continued on an out-patient basis, with monthly clinic follow-up.

Hlabisa Hospital is a 300-bed district hospital with a 40-bed TB ward refurbished in 2008 (including isolation rooms for drug-resistant cases) which, with 16 primary health care (PHC) clinics, serves a population of 228 000 in rural northern KZN. Hlabisa is approximately 250 km north of Durban, and the travel time to KGH is approximately 3 h. The TB notification rate in 2008 was approximately 1700 per 100 000 population (personal communication, TB control programme, Umkhanyakude Health District Office), and 76% of TB cases were co-infected with HIV.[24] The TB control programme adheres to national guidelines. Sputum is sent for culture and drug susceptibility testing (DST) for the following patients: those with previous unsuccessful treatment (interruption, failure, relapse), those who remain sputum smear-positive at the end of the intensive phase or at the end of treatment, and those who are sputum smear-negative but in whom there is a strong clinical suspicion of TB.[25]

Due to the constraints of the centralised hospital-based treatment model, particularly the waiting list for admissions to KGH, a CM was established in March 2008. It involved the following changes: the lead TB physician at Hlabisa Hospital visited KGH for focused training on the management of drug-resistant TB, data capturers were instructed to search for TB culture results in the provincial computerised laboratory information system 6 weeks after specimen collection, proven drug-resistant TB cases were then referred as out-patients to KGH for assessment and initiation of treatment, followed by in-patient treatment for 4 weeks in Hlabisa Hospital. If no complications were observed, directly observed treatment (DOT) was continued in the PHC clinic nearest to the patient's home. Patients were sent for monthly follow-up visits at KGH and could be admitted to Hlabisa Hospital at any time if complications arose.

Analysis

Cases were included if pulmonary MDR-TB treatment was commenced between March and December 2008 within the CM. All patients who received MDR-TB treatment under the traditional hospital-based model (TM) of care between 2001 and February 2008 were included as a control arm. Routine DST in our programme included susceptibility to RMP, INH, EMB, streptomycin (SM), ciprofloxacin (CFX) and KM. MDR-TB was defined for the purpose of this analysis as *Mycobacterium tuberculosis* resistant to RMP and INH, but susceptible to CFX and KM. Patients were excluded from the analysis if they had other patterns of drug resistance (XDR-TB, pre-XDR-TB or monoresistance), missing DST results or had transferred in from another facility. Demographic, clinical and laboratory data were extracted from the routine TB programme databases at Hlabisa Hospital and KGH. Further information for the CM cases regarding CD4 cell counts and antiretroviral treatment (ART) was obtained from the Hlabisa HIV Treatment and Care Programme database. The baseline characteristics of the two groups were compared using the χ^2 test.

The primary outcome measures were: time to initiation of treatment (number of days between collection of diagnostic sputum culture and commencement of MDR-TB treatment) and time to sputum smear and culture conversion (number of days between commencement of treatment and collection of the first of two consecutive negative sputum smears or cultures).[26] Patients without a date assigned to their diagnostic sputum culture were excluded from the time to initiation analysis ($n = 13$). Patients with a negative sputum smear before the initiation of treatment ($n = 23$) or no sputum smear data after initiation of treatment ($n = 4$) were excluded from the smear conversion analysis. Patients with a negative sputum culture before the initiation of treatment ($n = 11$) or no sputum culture data after initiation of treatment ($n = 4$) were excluded from the culture conversion analysis.

The time to initiation of treatment for the two groups was compared using the Mann-Whitney *U*-test. Time to sputum smear conversion and time to culture conversion were compared for the two groups in

Kaplan-Meier survival analysis and using the Mantel-Cox log-rank test. Cox regressions of time to sputum smear conversion and time to culture conversion were performed with group category (TM vs. CM), sex, HIV status and TB drug resistance pattern as independent variables. Three additional patients were excluded from these regressions because data on baseline weight were missing. To avoid overestimating the duration of time to smear or culture conversion in the TM group relative to the CM group, observation time in the TM group was censored at the longest observation period in the CM group (250 days) in both the Kaplan-Meier and the Cox regression analyses. All analyses were performed using SPSS 15.0 (SPSS Inc, Chicago, IL, USA) and STATA version 10 (StataCorp, College Station, TX, USA).

The study was approved by the Hlabisa Hospital Ethics Committee and the KwaZulu-Natal Department of Health.

RESULTS

A total of 134 patients were identified as receiving treatment for drug-resistant pulmonary TB between 2001 and 2008 in Hlabisa health sub-district (57 CM, 77 TM). Seven patients were excluded from the CM group (three transferred in from another facility, two treated as XDR-TB and two with RMP monoresistance), and 20 cases were excluded from the TM arm (16 missing resistance data, three treated as XDR-TB and one with RMP monoresistance). Thus, 50 CM cases and 57 TM cases were available for analysis.

The baseline characteristics of the patients are shown in Table 1. Both the proportion with known HIV status and the proportion HIV-positive were higher in the CM group than in the TM group. The median CD4 count was not significantly different in the two groups, but the proportion already on ART was higher in the CM group than in the TM group (Table 1). Of the 15 CM patients not established on ART at the time of starting MDR-TB treatment, 7 (46.7%) subsequently initiated ART, 2 (13.3%) died before initiating ART and 6 (40.0%) had not yet started ART at the time of analysis.

The median time to initiation of MDR-TB treatment was 84 days (95% confidence interval [CI] 78.7–93.3) for CM ($n = 48$) and 106.5 days (95%CI 88.6–151.1) for TM ($n = 46$, $P = 0.002$). The median time to smear conversion was 59 days (95%CI 34.9–83.1) for CM ($n = 32$) and 91 days (95%CI 72.2–119.8) for TM ($n = 48$, $P = 0.055$). The median time to culture conversion was 85 days (95%CI 68.0–102.0) for CM ($n = 39$) and 119 days (95%CI 106.1–131.9) for TM ($n = 53$, $P = 0.002$). Kaplan-Meier plots for time to sputum smear and culture conversion are shown in the Figure.

When controlling for sex, weight, HIV status and resistance pattern in multiple Cox regression, time to sputum smear conversion was longer for the TM group than for the CM group (adjusted hazard ratio [aHR] = 1.78, $P = 0.062$), as was the time to culture conversion (aHR = 1.82, $P = 0.026$).

The 6-month outcomes for the two groups are shown in Table 2. Of the four deaths in the CM group, one occurred during the first month in hospital and was attributed to disease severity; the other three occurred after hospital discharge and no further details were available regarding the circumstances of these deaths. The final outcomes for the TM group (excluding 16 patients still receiving treatment) were as follows: cured ($n = 23$, 56.1%), failed ($n = 2$, 4.9%), defaulted ($n = 8$, 19.5%) and died ($n = 8$, 19.5%).

Table 1 Baseline characteristics of the TM group and the CM group

Patient characteristics	TM group ($n = 57$)	CM group ($n = 50$)	*P* value*
Female, %	52.6	54.0	0.887
Weight, kg, median [IQR]†	52.0 [46.0–59.0]	51.0 [46.0–57.5]	0.686
HIV status, *n* (%)			
Positive	30 (52.6)	39 (78.0)	0.004
Negative	17 (29.8)	10 (20.0)	
Unknown	10 (17.5)	1 (2.0)	
CD4 cell count, cells/mm^3			
Median [IQR]	256 [94–350]	151 [80–235]	0.626
<350, *n/N* (%)	8/11 (72.7)	35/38 (92.1)	0.117
<200, *n/N* (%)	5/11 (45.5)	25/38 (65.8)	0.298
Antiretroviral treatment, *n/N* (%)‡	9/30 (30.0)	24/39 (61.5)	0.015
M. tuberculosis resistance pattern, *n* (%)			
RMP+INH	15 (26.3)	20 (40.0)	0.003
RMP+INH+EMB	6 (10.5)	1 (2.0)	
RMP+INH+SM	26 (45.6)	29 (58.0)	
RMP+INH+EMB+SM	10 (17.5)	—	

*χ^2 test.
†Data missing for two TM patients and one CM patient.
‡Established on ART at time of MDR-TB treatment initiation.
TM = traditional treatment model; CM = community-based treatment model; IQR = interquartile range; HIV = human immunodeficiency virus; RMP = rifampicin; INH = isoniazid; EMB = ethambutol; SM = streptomycin.

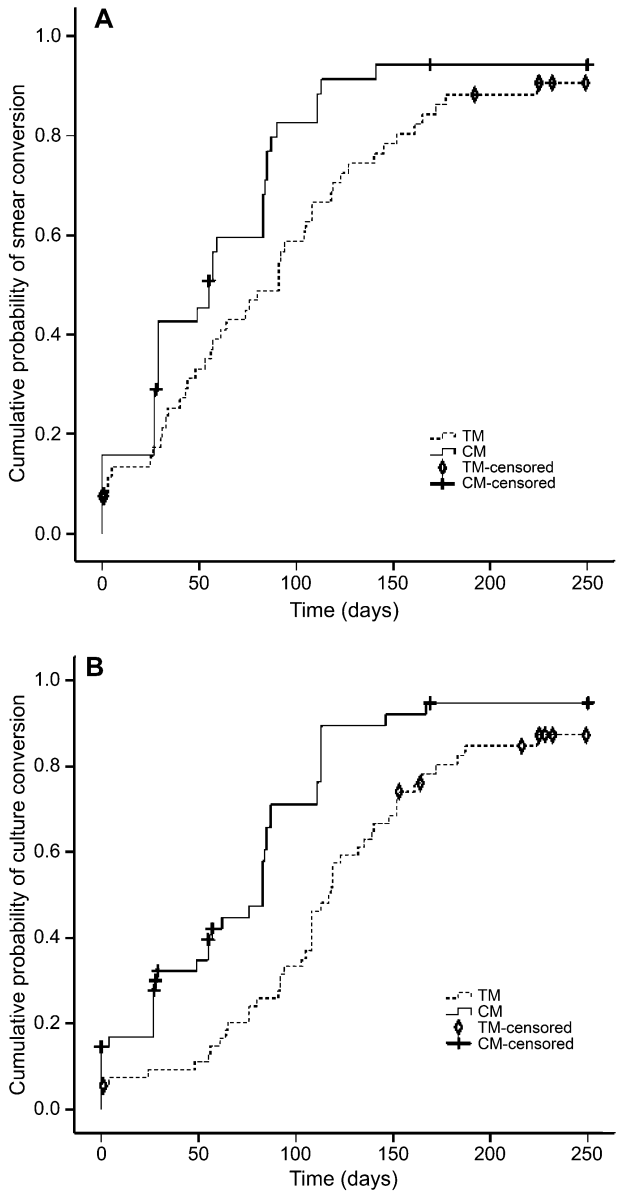

Figure Kaplan-Meier plots for **A**) time to sputum smear conversion and **B**) time to sputum culture conversion (TM group censored at 250 days, equivalent to the longest observation time in the CM group). TM = traditional treatment model; CM = community-based treatment model.

Three severe adverse drug reactions were observed among the CM cases: two patients suffered psychotic reactions (attributed to CS) and one patient developed Stevens-Johnson syndrome (attributed to ETH). All reactions occurred after the first month of in-patient treatment and necessitated re-admission to Hlabisa Hospital; all three patients recovered after cessation of the offending drug.

DISCUSSION

The growth of the drug-resistant TB epidemic in association with the HIV epidemic in South Africa has presented unique challenges for the NTP. The infrastructure of hospitals designed to deal with relatively small numbers of drug-resistant TB cases has been stretched, leading to the consideration of CMs. The emergence of MDR-TB in Hlabisa was reported many years ago, but recent years have seen the rapid growth of the TB-HIV co-epidemic in this area.[27] Our results suggest that it is feasible to develop a community-based treatment programme and that patients can be managed safely within the existing infrastructure of the TB programme with specialist expertise available on an out-patient basis.

Table 2 Six-month treatment outcomes for both groups

Outcome	TM group (n = 57) n (%)	CM group (n = 46)* n (%)	P value†
Active and on treatment	52 (91.2)	39 (84.8)	0.438
Died	4 (7.0)	4 (8.7)	
Defaulted	1 (1.8)	1 (2.2)	
Transferred out	—	2 (4.3)	

*Four persons were excluded from the CM group as they had not reached 6-month follow-up at the time of analysis.
†χ^2 test.
TM = traditional treatment model; CM = community-based treatment model.

The main arguments in favour of hospitalisation for drug-resistant TB relate to the need to administer and monitor complex, toxic drug regimens and to limit the community spread of drug-resistant TB. Expertise in the administration of drugs used for the treatment of drug-resistant TB can be achieved with focused training and adequate exposure to clinical cases. Most adverse drug reactions are well-characterised (e.g., psychosis with CS), and our study shows that these can be managed at a district hospital level.[28] Transmission of drug-resistant TB can occur both in the community and in health care facilities, and there needs to be increased focus on infection control strategies at all levels.[29] The majority of our patients remain sputum smear-positive at the end of the first month of treatment, and transmission could therefore occur after hospital discharge. We unfortunately do not have data on the identification and testing of contacts for the patients included in this analysis. Further work is required to determine the patterns of drug-resistant TB transmission in the community and to devise optimal strategies for TB screening and follow-up of close contacts.[30]

The need to expedite treatment is illustrated by reports of high early mortality with drug-resistant TB. In one study, also from rural KZN, the median survival time for MDR-TB cases (from the time of sputum collection) was 60 days.[31] Our programmatic data show that for March–December 2008, at the time the culture/DST result was obtained, 33% of MDR-TB cases were confirmed to have died and 16% could not be traced. The CM group included in this analysis therefore represents approximately 50% of all the laboratory-diagnosed MDR-TB cases, and they are

likely to have significant survival bias in this respect. This also emphasises that much work is still needed to facilitate more rapid identification, diagnosis and referral of drug-resistant TB cases.

The early results are encouraging in terms of the shorter time to smear and culture conversion, although only the time to culture conversion reached statistical significance. Culture conversion at 2 months has been shown to be a good predictor of eventual treatment outcome in MDR-TB; the median time to culture conversion in our study (85 days) is similar to that reported from a DOTS-Plus programme in Latvia (83 days).[32] This study was unable to look in depth at the factors associated with smear and culture conversion. We had no reliable data on extent of pulmonary disease and cavitation, which is likely to be a significant factor in conversion times.[32] All cases were by definition susceptible to KM and CFX, but we had no data on susceptibility to other second-line agents. While differences in CD4 count are unlikely to explain the variations, the concurrent use of ART was more common in the CM group and this may contribute to improved outcomes in co-infected patients. Further research is required to inform the optimal strategy for co-infected patients with MDR-TB, in particular whether the benefit of ART extends to those with CD4 counts above current treatment thresholds. We are working towards the integrated delivery of TB-HIV care through the primary health care system, and evidence from elsewhere suggests that this is feasible.[33]

There are clear limitations to our study inherent to retrospective comparisons. In particular, the TM cohort includes a period when staffing in local services was minimal and before the scale-up of HIV programmes brought about the development of local laboratory facilities. This means that the historical cohort suffers from incomplete data for important variables, such as CD4 counts, that could confound the results, and the direction in which such a theoretical bias might act cannot be known. We did consider alternative study designs for this work, for example the use of a contemporary cohort from another hospital within the region. However, this, too, would be subject to potential confounders, including different referral systems, different TB programme performance and different co-existing ART programmes. On balance, given the urgency and the need for data to inform policy, we opted for the methods outlined above.

In conclusion, we have shown that a community model can expedite treatment for MDR-TB without adversely affecting early treatment outcomes. The data presented here suggest that community-based treatment is both feasible and safe in rural South Africa and that, where resources allow, TB programmes should be both scaled up and integrated with HIV treatment and care programmes.

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RÉSUMÉ

CONTEXTE : Sous-district de santé de Hlabisa dans le Kwazulu-Natal, Afrique du Sud.

OBJECTIF : Décrire la mise en œuvre d'un programme de traitement de la tuberculose multirésistante (TB-MDR) basé sur la collectivité au sein du programme de district de lutte contre la tuberculose et évaluer dans quelle mesure les résultats précoces sont comparables à ceux obtenus par le modèle de soins traditionnel basé sur les hôpitaux.

SCHÉMA : On a comparé les cas qui ont commencé un traitement de la TB-MDR basé sur la collectivité (CM) entre mars et décembre 2008 avec ceux qui ont commencé le traitement de la TB-MDR selon le modèle de soins traditionnel basé sur les hôpitaux (TM) entre janvier 2001 et février 2008. On a comparé pour les deux groupes la durée avant le début du traitement et la durée avant la négativation du frottis de crachats et de la culture pour les deux groupes en utilisant les courbes de survie de Kaplan-Meier selon le test log rank de Mantel-Cox.

RÉSULTATS : On a inclus 50 cas CM et 57 cas TM. Trente-neuf des 50 cas CM (78,0%) étaient séropositifs pour le virus de l'immunodéficience humaine. La durée médiane avant la mise en route du traitement a été de 84 jours pour les CM et de 106,5 jours pour les TM (P = 0,002). La durée médiane avant la négativation du frottis de crachats a été plus courte pour CM que pour TM (59 vs. 92 jours, P = 0,055), tout comme la durée avant la négativation de la culture des crachats (85 vs. 119 jours, P = 0,002).

CONCLUSION : Le traitement de la TB-MDR basé sur la collectivité peut être réalisé au sein du programme de lutte antituberculeuse existant en Afrique du Sud rurale et devrait être étendu là où les ressources le permettent.

RESUMEN

MARCO DE REFERENCIA: La circunscripción sanitaria de Labias en KwaZulu-Natal, Sudáfrica.

OBJETIVO: Describir la introducción de un programa de tratamiento de la tuberculosis multidrogorresistente (TB-MDR) adscrito al programa distrital de control de la TB y comparar sus resultados iniciales con los obtenidos en el modelo convencional de atención hospitalaria.

MÉTODOS: Se compararon los casos que ingresaron al programa comunitario de tratamiento (CM) de la TB-MDR entre marzo y diciembre del 2008, con los casos

tratados en el programa de atención convencional (TM) hospitalaria entre enero del 2001 y febrero del 2008. La comparación del lapso hasta el comienzo del tratamiento y hasta la conversión de la baciloscopia y el cultivo de las muestras de esputo se estableció mediante las curvas de supervivencia de Kaplan-Meier, usando la prueba del orden logarítmico de Mantel-Cox.

RESULTADOS: Se incluyeron en el estudio 50 casos en CM y 57 casos en TM. Treinta y nueve de los 50 casos CM (78,0%) tuvieron prueba serológica positiva para el virus de la inmunodeficiencia humana. La mediana del lapso hasta el comienzo del tratamiento fue 84 días en los casos CM y 106,5 días en los casos con tratamiento TM (P = 0,002). La mediana del lapso hasta la conversión de la baciloscopia del esputo fue más corta en la estrategia CM que en la TM (59 contra 92 días; P = 0,055) y también el lapso hasta la conversión del cultivo (85 contra 119 días; P = 0,002).

CONCLUSION: Es posible introducir la estrategia CM de tratamiento de la TB-MDR en el programa existente de control de la TB en las zonas rurales de Sudáfrica y se debe ampliar donde los recursos lo permitan.