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

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SUMMARY

Setting Hlabisa health sub-district in KwaZulu-Natal, South Africa

Objective To describe the establishment of a community-based 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 between March and December 2008 (CM) were compared to patients who initiated MDR-TB treatment under the traditional hospital-based model of care between January 2001 and February 2008 (TM). 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 50 CM cases and 57 TM cases were included. 39/50 CM cases (78.0%) were HIV 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 days vs. 92 days; p = 0.055) as was time to sputum culture conversion (85 days 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.

Keywords: TB, drug resistance, HIV

INTRODUCTION

The past few years have seen the escalation of combined epidemics of tuberculosis (TB) and HIV infection in Southern Africa[1,2]. Compounding this has been the emergence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB)[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 TB incidence of 1,094 per 100,000 person years[9]. Over 2,000 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 to 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 to 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 in South Africa and there is an urgent need to scale-up and evaluate community-based treatment models[18,19].

Community-based treatment for drug-resistant TB is not a new concept and successful outcomes have been 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 (NGO) have developed community-based treatment projects in Southern Africa but the sustainability of such programmes is always a concern[22,23]. We describe 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 site: King George V Hospital (KGH), Durban (160 beds). 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 involves 6 months of kanamycin (Km), ofloxacin (Ofx), ethionamide (Eto), cycloserine (Cs), ethambutol (E) and pyrazinamide (Z) followed by 12 to 18 months of Ofx/Eto/Cs/E/Z. Treatment is provided on an inpatient basis at least until sputum

93 culture conversion and thereafter continued on an outpatient basis with monthly clinic follow-
94 up.
95
96 Hlabisa hospital is a 300-bed district hospital with a 40-bed TB ward refurbished in 2008
97 (including isolation rooms for drug-resistant cases) which, with 16 primary health care (PHC)
98 clinics, serves a population of 228,000 in rural northern KwaZulu-Natal. Hlabisa is approximately
99 250km north of Durban and the travel time to KGH is approximately three hours. The TB
100 notification rate in 2008 was approximately 1,700 per 100,000 (personal communication, TB
101 control programme, Umkhanyakude Health District Office), and 76% of TB cases are co-infected
102 with HIV[24]. The TB control programme adheres to national guidelines and sputum is sent for
103 culture and drug sensitivity testing (DST) in the following circumstances: patients with previous
104 unsuccessful treatment (interruption, failure, relapse); those who remain sputum smear
105 positive at the end of intensive phase or at the end of treatment; and those who are sputum
106 smear negative but in whom there is a strong clinical suspicion of TB[25].
107
108 Due to the constraints of the centralised hospital-based treatment model, particularly the
109 waiting list for admissions to KGH, a community-based treatment model was established in
110 March 2008. It involved the following changes: the lead TB physician at Hlabisa hospital visited
111 KGH for focused training on management of drug-resistant TB; data capturers were instructed
112 to search for TB culture results in the provincial computerised laboratory information system six
113 weeks after specimen collection; then proven drug-resistant TB cases were referred as
114 outpatients to KGH for assessment and initiation of treatment, followed by inpatient treatment

for 4 weeks in Hlabisa hospital. If no complications were observed then 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 community-based treatment model (CM). All patients who received MDR-TB treatment under the traditional hospital-based model of care between 2001 and February 2008 were included as a control arm (TM). Routine DST in our programme included susceptibility to rifampicin, isoniazid, ethambutol, streptomycin, ciprofloxacin, and kanamycin. MDR-TB was defined for the purpose of this analysis as *M. tuberculosis* resistant to rifampicin and isoniazid but sensitive to ciprofloxacin and kanamycin. Patients were excluded from the analysis if they had other patterns of drug resistance (XDR-TB, pre-XDR-TB, or mono-resistance), 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 therapy was obtained from the Hlabisa HIV Treatment and Care Programme database. The baseline characteristics of the two groups were compared using χ^2 test.

The primary outcomes measures were: time to initiation of treatment (number of days between collection of diagnostic sputum culture and commencement of MDR-TB therapy); and

time to sputum smear and culture conversion (number of days between commencement of treatment and collection of first of two consecutive negative sputum smears or culture[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 prior to 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 prior to 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 in these regressions because data on baseline weight were missing. In order 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) both in the Kaplan-Meier and the Cox regression analyses. All analyses were performed using SPSS 15.0 (SPSS inc., Chicago, Illinois) and STATA version 10 (StataCorp, College Station, Texas). The study was approved by the Hlabisa Hospital Ethics Committee and the KwaZulu-Natal Department of Health.

RESULTS

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 rifampicin mono-resistance). Twenty cases were excluded from the TM arm (16 missing resistance data; three treated as XDR-TB; and one with rifampicin mono-resistance). Thus 50 CM cases and 57 TM cases were available for analysis.

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 compared to 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 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%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 Figure 1.

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 compared to the patients in 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 23 (56.1%), failed 2 (4.9%), defaulted 8 (19.5%), died 8 (19.5%).

Three severe adverse drug reactions were observed amongst the CM cases: two patients suffered psychotic reactions (attributed to cycloserine) and one patient developed Stevens-Johnson syndrome (attributed to ethionamide). All reactions occurred after the first month of inpatient treatment and necessitated re-admission to Hlabisa hospital; all three patients recovered after cessation of the relevant drug.

DISCUSSION

The growth of the drug-resistant TB epidemic in association with the HIV epidemic in South Africa has presented unique challenges to the national TB control programme. The infrastructure of hospitals designed to deal with relatively small numbers of drug-resistant TB cases has been stretched and this has driven the consideration of community-based treatment models. The emergence of MDR-TB in Hlabisa was reported many years ago but recent years have seen the rapid growth of the HIV/TB 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 outpatient basis.

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 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. pyschosis with cycloserine) 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 therefore transmission could occur after hospital discharge. We unfortunately do not have data on the identification and testing of

224 contacts for the patients included in this analysis. Further work is required to determine the
225 patterns of drug-resistant TB transmission in the community and to devise optimal strategies
226 for TB screening and follow-up of close contacts[30].
227
228 The need for expediting treatment is illustrated by reports of high early mortality with drug-
229 resistant TB. In one study also from rural KwaZulu-Natal the median survival time for MDR-TB
230 cases (from time of sputum collection) was 60 days[31]. Our programmatic data show that for
231 March-December 2008, at the time the culture/DST result was obtained 33% of MDR-TB cases
232 were confirmed to have died and 16% were unable to be traced. The CM group included in this
233 analysis therefore represent approximately 50% of all the laboratory diagnosed MDR-TB and
234 are likely to have significant survival bias in this respect. This also emphasises that much work is
235 still needed to facilitate more rapid identification, diagnosis, and referral of drug-resistant TB
236 cases.
237
238 The early results are encouraging in terms of the shorter time to smear and culture conversion,
239 although only the time to culture conversion reached statistical significance. Culture conversion
240 at two months has been shown to be a good predictor of eventual treatment outcome in MDR-
241 TB; the median time to culture conversion in our study is similar to that reported from a DOTS-
242 Plus programme in Latvia[32]. This study was unable to look in depth at the factors associated
243 with smear and culture conversion. We had no reliable data on extent of pulmonary disease
244 and cavitation which is likely to be a significant factor in the conversion times[32]. All cases were
245 by definition sensitive to kanamycin and ciprofloxacin but we had no data on susceptibility to

246 other second-line agents. Whilst differences in CD4 counts are unlikely to explain the
247 differences, the concurrent use of ART was more common in the CM group and this may
248 contribute to improved outcomes in co-infected patients. Further research is required to inform
249 the optimal strategy for co-infected patients with MDR-TB, in particular whether the benefit of
250 ART extends to those with CD4 counts above current treatment thresholds. We are working
251 towards the integrated delivery of TB/HIV care through the primary health care system, and
252 evidence from elsewhere suggests that this is feasible[33].
253
254 There are clear limitations to our study inherent to retrospective comparisons. In particular, the
255 TM cohort includes a period when staffing in local service was minimal and before the scale-up
256 of HIV programmes brought development of local laboratory facilities. This means that the
257 historical cohort suffers from incomplete data for important variables, for example CD4 counts,
258 that could confound results and the direction in which such a theoretical bias might act cannot
259 be known. We did consider alternative study designs for this work, for example the use of a
260 contemporary cohort from another hospital within the region. However, this too would be
261 subject to potential confounders including different referral systems, different TB programme
262 performance, different co-existing ART programmes. On balance, given the urgency and
263 necessity for data to inform policy we opted for the methods outlined above.
264
265 In conclusion, we have shown that a community-based treatment model can expedite
266 treatment and does not adversely affect early treatment outcomes. The data presented here
267 suggest that community-based treatment is both feasible and safe in rural South Africa and

that, where resources allow, programmes should be scaled up and, furthermore, should be integrated with HIV treatment and care programmes.

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Conflicts of interest

We declare that we have no conflicts of interest

Author contributions

TH & RL were responsible for study design, data acquisition, data analysis, and drafting the manuscript. CW, TB, GSC, MLN provided assistance with the data analysis, data interpretation, and revision of the manuscript. LM assisted with data acquisition from Hlabisa and revision of

290 the manuscript. IM was responsible for data acquisition from KGH and revision of the
291 manuscript. All authors approved the final version of the article.
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Table 1. Baseline characteristics of CM group (n=50) and TM group (n=57)

Patient characteristic		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	72.7% (8/11)	92.1% (35/38)	0.117
	<200	45.5% (5/11)	65.8% (25/38)	0.298
Antiretroviral therapy‡		30.0% (9/30)	61.5% (24/39)	0.015
***M.tuberculosis* resistance pattern, *n*, %§**	**RH**	15 (26.3%)	20 (40.0%)	0.003
	RHE	6 (10.5%)	1 (2.0%)	
	RHS	26 (45.6%)	29 (58.0%)	
	RHES	10 (17.5%)	-	

* χ^2 test

† Missing data from two patients (TM) and one patient (CM)

‡ Established on ART at time of MDR-TB treatment initiation

§ R=rifampicin, H=isoniazid, E=ethambutol, S=streptomycin

Table 2. Six-month treatment outcomes for both groups

Outcome	TM group (*n*=57)	CM group (*n*=46)*	*p*-Value†
Active & 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%)	

* 4 individuals excluded from CM group as not reached 6-month follow-up at time of analysis

† χ^2-test

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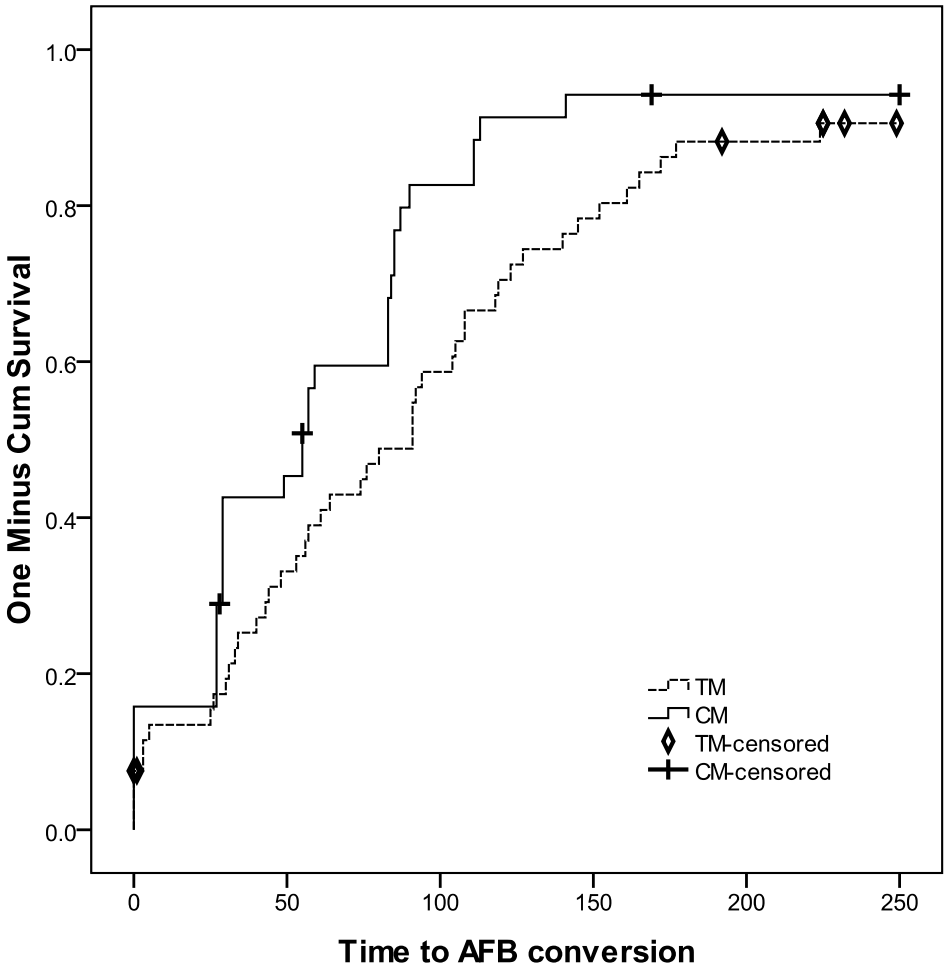

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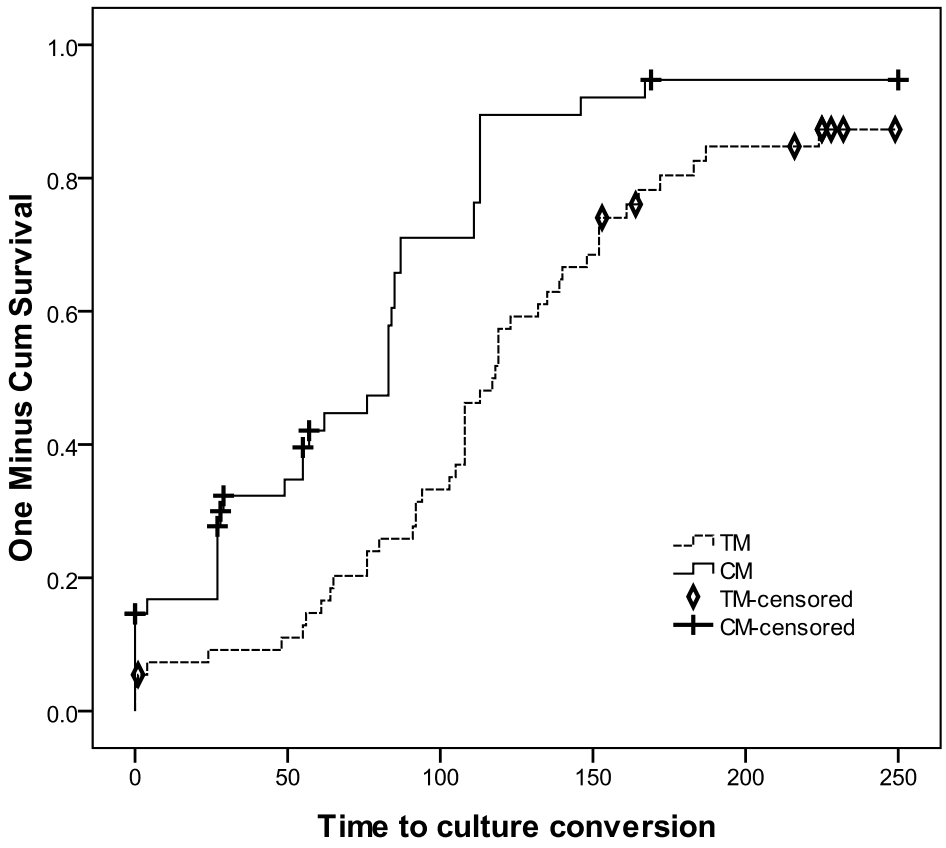

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400 ***Figure 1. Kaplan-Meier plots for time to a) sputum smear conversion and b) sputum culture***

401 ***conversion (TM group censored at 250 days, equivalent to the longest observation time in CM***

402 ***group)***

403