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1 **Community-based treatment for multidrug-resistant tuberculosis in rural**

2 **KwaZulu-Natal, South Africa**

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28 **SUMMARY**29 **Setting** Hlabisa health sub-district in KwaZulu-Natal, South Africa

30

31 **Objective** To describe the establishment of a community-based MDR-TB treatment programme
32 embedded in the district TB control programme and to evaluate whether early outcomes are
33 comparable to those in the traditional hospital-based model of care.

34

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

40

41 **Results** 50 CM cases and 57 TM cases were included. 39/50 CM cases (78.0%) were HIV
42 positive. The median time to initiation of treatment was 84 days for CM and 106.5 days for TM
43 ($p = 0.002$). Median time to sputum smear conversion was shorter for CM than TM (59 days vs.
44 92 days; $p = 0.055$) as was time to sputum culture conversion (85 days vs. 119 days; $p = 0.002$)

45

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

48

49 **Keywords:** TB, drug resistance, HIV

50 INTRODUCTION

51

52 The past few years have seen the escalation of combined epidemics of tuberculosis (TB) and
53 HIV infection in Southern Africa^{1,2}. Compounding this has been the emergence of multidrug-
54 resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB)³⁻⁵. KwaZulu-Natal (KZN) in
55 South Africa is at the epicentre of these intertwined epidemics with high HIV prevalence and
56 incidence⁶⁻⁸ and TB incidence of 1,094 per 100,000 person years⁹. Over 2,000 laboratory
57 confirmed cases of MDR-TB were identified per year in KZN in 2006 and 2007¹⁰.

58

59 The management of MDR-TB in South Africa has historically involved centralised treatment
60 including admission to specialist provincial hospitals for at least the intensive phase of
61 treatment¹¹. The rationale for this has been to monitor complex drug regimens, optimise
62 adherence, and to limit community transmission. However, there is no evidence that
63 hospitalisation actually limits community transmission and it is likely that most patients have
64 been infectious for several months before hospitalisation given the delays in diagnosis and
65 treatment under routine programme conditions¹². Moreover the risk of nosocomial
66 transmission, both to other patients and to health care workers, is high¹³⁻¹⁵. There are also
67 economic and social costs to keeping patients isolated in hospitals often far from home and this
68 can lead to default from treatment programmes¹⁶. The estimated cost of MDR-TB hospitals
69 accounts for half of the national TB programme (NTP) budget in South Africa¹⁷. The centralised
70 model of care currently lacks the capacity to deal with the burden of MDR-TB in South Africa
71 and there is an urgent need to scale-up and evaluate community-based treatment models^{18,19}.

72

73 Community-based treatment for drug-resistant TB is not a new concept and successful
74 outcomes have been reported elsewhere, most notably from Peru^{20,21}. However, most cases in
75 these studies were HIV negative and the high rate of HIV co-infection in Southern Africa
76 presents additional programmatic challenges^{4,5}. Public-private partnerships and non-
77 governmental organisations (NGO) have developed community-based treatment projects in
78 Southern Africa but the sustainability of such programmes is always a concern^{22,23}. We describe
79 experience in Hlabisa sub-district in the province of KwaZulu-Natal, South Africa, with the
80 establishment of a community-based MDR-TB treatment model within the existing Department
81 of Health TB programme.

82

83

84 **METHODS**

85

86 **Setting**

87 In KwaZulu-Natal the majority of MDR-TB and XDR-TB patients are treated at a single site: King
88 George V Hospital (KGH), Durban (160 beds). Patients are referred with culture-proven MDR-TB
89 or XDR-TB and individualised drug regimens are prescribed according to national guidelines¹¹.
90 The most common MDR-TB regimen involves 6 months of kanamycin (Km), ofloxacin (Ofx),
91 ethionamide (Eto), cycloserine (Cs), ethambutol (E) and pyrazinamide (Z) followed by 12 to 18
92 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 HIV²⁴. 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 TB²⁵.

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

115 for 4 weeks in Hlabisa hospital. If no complications were observed then directly-observed
116 treatment (DOT) was continued in the PHC clinic nearest to the patient's home. Patients were
117 sent for monthly follow-up visits at KGH and could be admitted to Hlabisa hospital at any time if
118 complications arose.

119

120 **Analysis**

121 Cases were included if pulmonary MDR-TB treatment was commenced between March and
122 December 2008 within the community-based treatment model (CM). All patients who received
123 MDR-TB treatment under the traditional hospital-based model of care between 2001 and
124 February 2008 were included as a control arm (TM). Routine DST in our programme included
125 susceptibility to rifampicin, isoniazid, ethambutol, streptomycin, ciprofloxacin, and kanamycin.
126 MDR-TB was defined for the purpose of this analysis as *M. tuberculosis* resistant to rifampicin
127 and isoniazid but sensitive to ciprofloxacin and kanamycin. Patients were excluded from the
128 analysis if they had other patterns of drug resistance (XDR-TB, pre-XDR-TB, or mono-resistance),
129 missing DST results, or had transferred in from another facility. Demographic, clinical, and
130 laboratory data were extracted from the routine TB programme databases at Hlabisa hospital
131 and KGH. Further information for the CM cases regarding CD4 cell counts and antiretroviral
132 therapy was obtained from the Hlabisa HIV Treatment and Care Programme database. The
133 baseline characteristics of the two groups were compared using χ^2 test.

134

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

137 time to sputum smear and culture conversion (number of days between commencement of
138 treatment and collection of first of two consecutive negative sputum smears or culture²⁶).

139 Patients without a date assigned to their diagnostic sputum culture were excluded from the
140 time to initiation analysis ($n=13$). Patients with a negative sputum smear prior to initiation of
141 treatment ($n=23$) or no sputum smear data after initiation of treatment ($n=4$) were excluded
142 from the smear conversion analysis. Patients with a negative sputum culture prior to the
143 initiation of treatment ($n=11$) or no sputum culture data after initiation of treatment ($n=4$) were
144 excluded from the culture conversion analysis. The time to initiation of treatment for the two
145 groups was compared using the Mann-Whitney U test. Time to sputum smear conversion and
146 time to culture conversion were compared for the two groups in Kaplan-Meier survival analysis
147 and using the Mantel-Cox log rank test. Cox regressions of time to sputum smear conversion
148 and time to culture conversion were performed with group category (TM vs. CM), sex, HIV
149 status, and TB drug resistance pattern as independent variables. Three additional patients were
150 excluded in these regressions because data on baseline weight were missing. In order to avoid
151 overestimating the duration of time to smear or culture conversion in the TM group relative to
152 the CM group, observation time in the TM group was censored at the longest observation
153 period in the CM group (250 days) both in the Kaplan-Meier and the Cox regression analyses. All
154 analyses were performed using SPSS 15.0 (SPSS inc., Chicago, Illinois) and STATA version 10
155 (StataCorp, College Station, Texas). The study was approved by the Hlabisa Hospital Ethics
156 Committee and the KwaZulu-Natal Department of Health.

157

158

159 **RESULTS**

160

161 134 patients were identified as receiving treatment for drug-resistant pulmonary TB between
162 2001 and 2008 in Hlabisa health sub-district (57 CM; 77 TM). Seven patients were excluded
163 from the CM group (three transferred in from another facility; two treated as XDR-TB; and two
164 with rifampicin mono-resistance). Twenty cases were excluded from the TM arm (16 missing
165 resistance data; three treated as XDR-TB; and one with rifampicin mono-resistance). Thus 50
166 CM cases and 57 TM cases were available for analysis.

167

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

175

176 The median time to initiation of MDR-TB treatment was 84 days (95%CI 78.7-93.3) for CM
177 ($n=48$) and 106.5 days (95%CI 88.6-151.1) for TM ($n=46$) ($p=0.002$). The median time to smear
178 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
179 ($n=48$) ($p=0.055$). The median time to culture conversion was 85 days (95%CI 68.0-102.0) for

180 CM ($n=39$) and 119 days (95%CI 106.1-131.9) for TM ($n=53$) ($p=0.002$). Kaplan-Meier plots for
181 time to sputum smear and culture conversion are shown in Figure 1.

182

183 When controlling for sex, weight, HIV status, and resistance pattern in multiple Cox regression,
184 time to sputum smear conversion was longer for the TM group compared to the patients in the
185 CM group (adjusted hazard ratio (aHR) = 1.78, $p=0.062$) as was the time to culture conversion
186 (aHR = 1.82, $p=0.026$).

187

188 The 6-month outcomes for the two groups are shown in Table 2. Of the four deaths in the CM
189 group, one occurred during the first month in hospital and was attributed to disease severity;
190 the other three occurred after hospital discharge and no further details were available
191 regarding the circumstances of these deaths. The final outcomes for the TM group (excluding
192 16 patients still receiving treatment) were as follows: cured 23 (56.1%), failed 2 (4.9%),
193 defaulted 8 (19.5%), died 8 (19.5%).

194

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

200

201

202 DISCUSSION

203

204 The growth of the drug-resistant TB epidemic in association with the HIV epidemic in South
205 Africa has presented unique challenges to the national TB control programme. The
206 infrastructure of hospitals designed to deal with relatively small numbers of drug-resistant TB
207 cases has been stretched and this has driven the consideration of community-based treatment
208 models. The emergence of MDR-TB in Hlabisa was reported many years ago but recent years
209 have seen the rapid growth of the HIV/TB co-epidemic in this area²⁷. Our results suggest that it
210 is feasible to develop a community-based treatment programme and that patients can be
211 managed safely within the existing infrastructure of the TB programme with specialist expertise
212 available on an outpatient basis.

213

214 The main arguments in favour of hospitalisation for drug-resistant TB relate to the need to
215 administer and monitor complex, toxic drug regimens and to limit the community spread of
216 drug resistant-TB. Expertise in the administration of drugs used for treatment of drug-resistant
217 TB can be achieved with focused training and adequate exposure to clinical cases. Most adverse
218 drug reactions are well characterised (e.g. psychosis with cycloserine) and our study shows that
219 these can be managed at a district hospital level²⁸. Transmission of drug-resistant TB can occur
220 both in the community and in health care facilities and there needs to be increased focus on
221 infection control strategies at all levels²⁹. The majority of our patients remain sputum smear
222 positive at the end of the first month of treatment and therefore transmission could occur after
223 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 contacts³⁰.

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 days³¹. 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 Latvia³². 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 times³². 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 feasible³³.

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

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

270

271

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276

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282

283 **Conflicts of interest**

284 We declare that we have no conflicts of interest

285

286 **Author contributions**

287 TH & RL were responsible for study design, data acquisition, data analysis, and drafting the
288 manuscript. CW, TB, GSC, MLN provided assistance with the data analysis, data interpretation,
289 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.

292

293

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377

378 **Table 1. Baseline characteristics of CM group (n=50) and TM group (n=57)**

379

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
<i>M.tuberculosis</i> 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%)	-	

380 * χ^2 test

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

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

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

384

385 **Table 2. Six-month treatment outcomes for both groups**

386

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%)	

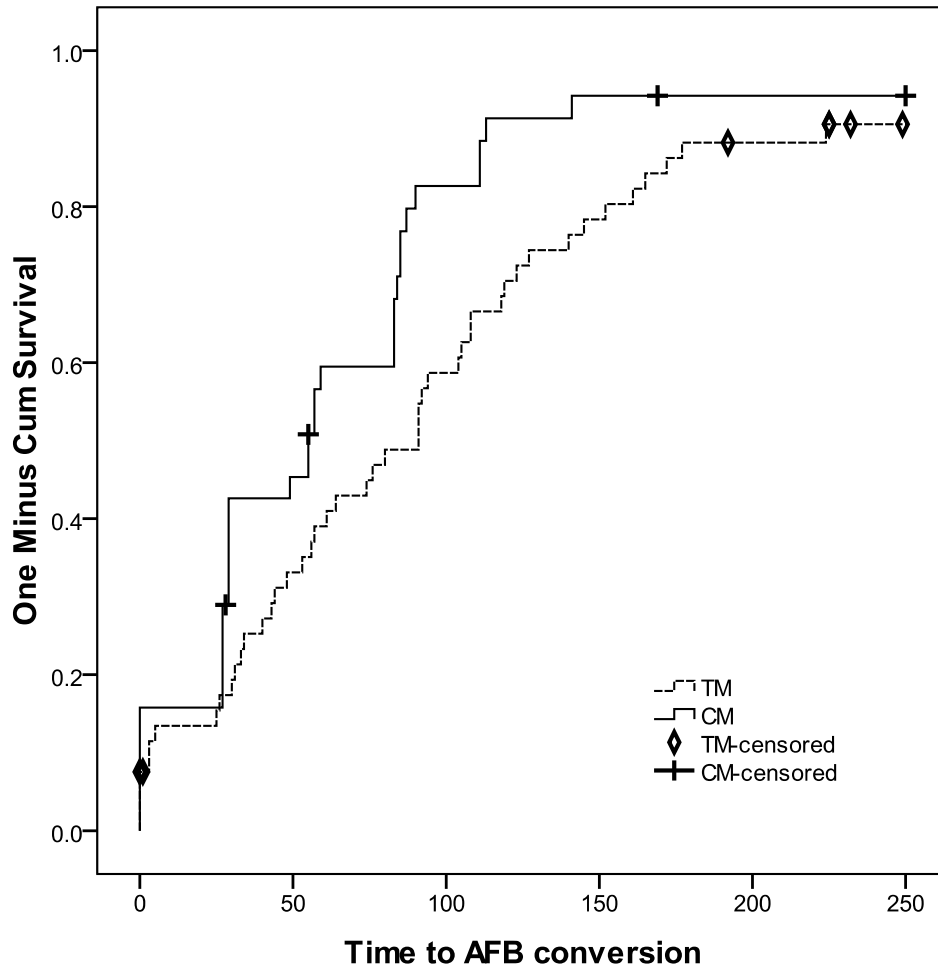
387

388 * 4 individuals excluded from CM group as not reached 6-month follow-up at time of analysis

389 † χ^2 -test

390

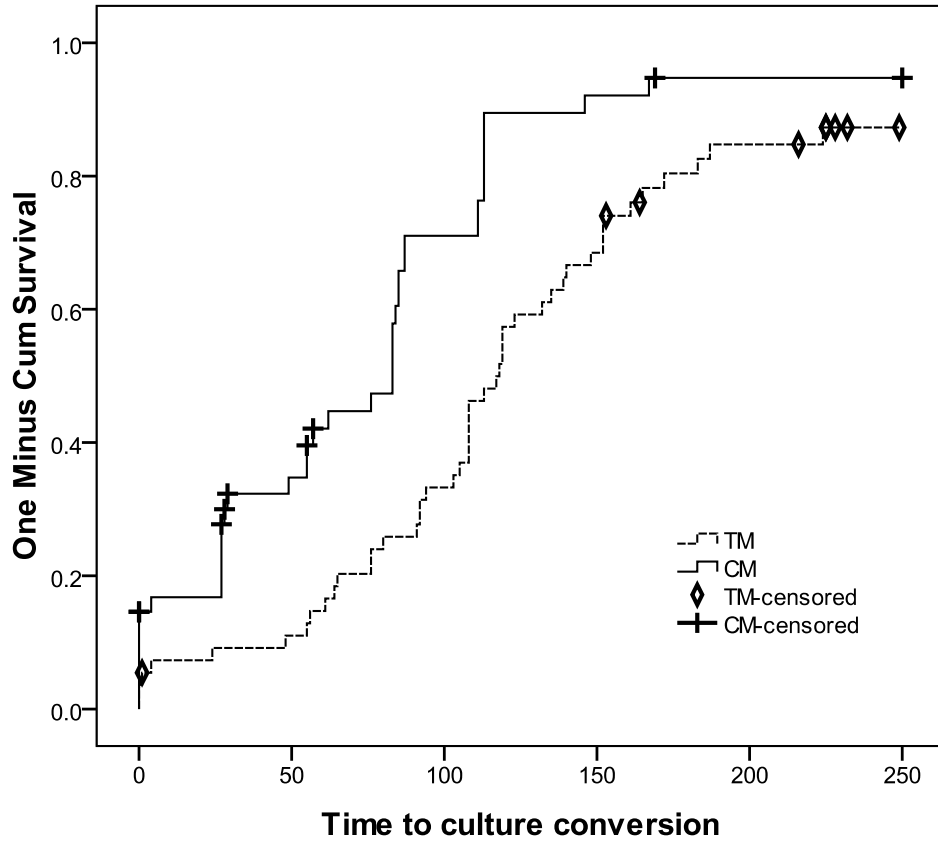
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400 **Figure 1. Kaplan-Meier plots for time to a) sputum smear conversion and b) sputum culture**
401 **conversion (TM group censored at 250 days, equivalent to the longest observation time in CM**
402 **group)**
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