



## Tuberculosis in HIV-infected South African children with complicated severe acute malnutrition

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1 **Tuberculosis in HIV-infected South African children with complicated severe acute**  
2 **malnutrition**

3 Running head: TB in children with HIV & severe malnutrition

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26 All authors had a role in the design of this study. H Adler, M Archary and P Mahabeer  
27 collected the data. H Adler performed statistical analyses and wrote the first draft of the  
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## 37 SUMMARY

38 Setting: Academic tertiary referral hospital in Durban, South Africa

39 Objective: To describe the incidence and diagnostic challenges of TB in HIV-infected children  
40 with severe acute malnutrition (SAM)

41 Design: Post-hoc analysis of a randomised controlled trial that enrolled ART-naïve, HIV-  
42 infected children with SAM. Trial records and hospital laboratory results were explored for  
43 clinical diagnoses and bacteriologically confirmed cases of TB. Negative binomial regression  
44 was used to explore associations with confirmed cases of TB, excluding cases where the  
45 clinical diagnosis was not supported by microbiological confirmation.

46 Results: Of 82 children enrolled in the study, 21 (25.6%) were diagnosed with TB, with  
47 bacteriological confirmation in 8 cases. Sputum sampling (as opposed to gastric washings)  
48 was associated with an increased risk of subsequent diagnosis of TB (adjusted relative risk  
49 1.134, 95% CI 2.1%—26%). A culture-proven bacterial infection during the admission was  
50 associated with a reduced risk of TB (aRR 0.856, 0.748—0.979), which may reflect false  
51 negative microbiologic tests secondary to empiric broad spectrum antibiotics.

52 Conclusion: TB is common in HIV-infected children with SAM. While microbiological  
53 confirmation of the diagnosis is feasible, empiric treatment remains common, possibly  
54 influenced by suboptimal testing and false negative TB diagnostics. **Rigorous microbiological**  
55 TB investigation should be integrated into the programmatic management of HIV and SAM.

56

## 57 INTRODUCTION

58 Tuberculosis (TB), HIV infection and severe acute malnutrition (SAM) are individually  
59 responsible for high levels of morbidity and mortality among children across sub-Saharan  
60 Africa. Research is ongoing into how these three interact, although the potency of the  
61 combination has been recognised for some time.<sup>1</sup>

62 Over 650,000 cases of paediatric TB occur annually in the 22 highest-burden countries,<sup>2</sup>  
63 resulting in an estimated 140,000 annual deaths.<sup>3</sup> Over 2.6 million children across the world  
64 are living with HIV, with 90% of these living in sub-Saharan Africa.<sup>4</sup> HIV was responsible for  
65 150,000 childhood deaths in 2014. SAM—incorporating marasmus, kwashiorkor and  
66 marasmic kwashiorkor—is responsible for as much as 10% of all global mortality in children  
67 aged <5 years,<sup>5</sup> with marasmus alone accounting for over 500,000 deaths annually in this  
68 age group.<sup>6</sup>

69 In South Africa, over 36,000 cases of childhood TB occur annually, one quarter of which are  
70 believed to be HIV co-infected.<sup>7,8</sup> HIV is responsible for 17% of all deaths in South African  
71 children aged under 5 years.<sup>8</sup> One study found that 10% of children initiating antiretroviral  
72 therapy (ART) in rural South Africa also had SAM.<sup>9</sup>

73 While SAM combined with HIV has already been recognised as a challenging clinical entity,  
74 associated with increased mortality,<sup>10,11</sup> the contribution of TB in this scenario is uncertain.  
75 Malnutrition is associated with increased mortality in paediatric TB,<sup>12</sup> particularly with HIV  
76 co-infection<sup>13</sup>. TB causes cachexia and wasting, and may itself be impacted by poor  
77 nutritional status.<sup>14,15</sup> HIV is an independent risk factor for both TB and malnutrition,  
78 worsening the outcomes of either condition.<sup>10,16</sup> The spectrum of TB in a cohort of  
79 paediatric patients who all have the specific combination of both HIV and SAM has not yet  
80 been studied. A randomised controlled trial (Malnutrition and Antiretroviral Timing in  
81 Children with HIV, MATCH) assessing the clinical and pharmacokinetic responses to early  
82 versus delayed ART in HIV-infected children with SAM was conducted in Durban, South  
83 Africa.<sup>17</sup> We present a post-hoc analysis of TB diagnoses in these patients.

84

85

## 86 STUDY POPULATION AND METHODS

### 87 Setting

88 King Edward VIII Hospital (KEH) in Durban, South Africa has a 100-bed paediatric ward,  
89 including 10 nutritional rehabilitation beds, providing regional tertiary-level care.

### 90 Recruitment and eligibility

91 All children presenting with SAM and newly diagnosed with HIV were eligible for inclusion in  
92 the trial, and randomised either to early (within ten days of admission) or delayed (at four  
93 weeks or at protocol-defined nutritional recovery) ART.<sup>17</sup> Recruitment was carried out  
94 between 2012 and 2014. All children eligible for inclusion in the MATCH trial were eligible  
95 for inclusion in this retrospective analysis.

96 SAM was defined as weight-for-height z score below -3 standard deviations from the World  
97 Health Organisation (WHO) median or a mid-upper-arm circumference of <115mm, with or  
98 without bilateral oedema<sup>18</sup> and was managed according to the latest WHO guidelines.<sup>19</sup>

99 Patients were classified as bacteriologically confirmed TB (based on positive sputum smear  
100 microscopy, mycobacterial culture or nucleic acid amplification), clinically diagnosed  
101 (empirically treated) TB, or no TB, as per the WHO.<sup>20</sup> A more detailed classification of  
102 clinically-diagnosed cases was not possible, as patients' original files and radiographs were  
103 frequently unavailable.

### 104 Data collection

105 We retrospectively searched the National Health Laboratory Service's laboratory  
106 information management system for TB diagnostic test results from all patients in the  
107 MATCH trial, from the date of admission with SAM to any hospital in Durban, through to  
108 one month after transfer to KEH and enrolment in the study. We also recorded routine  
109 biochemical, haematological and immunological laboratory results from the day of  
110 admission. Clinical parameters and tuberculin skin test results at admission were not  
111 captured routinely, as children were only enrolled after admission and a positive HIV test.

112

113 As per the local standard of care, investigations for pulmonary TB were performed on at  
114 least three samples of induced sputum or gastric washings, at the discretion of the treating  
115 clinician. Patients were also investigated for other concurrent infections according to local  
116 standard protocols.<sup>21</sup> Fluorescent microscopy was performed on sputum smears, followed  
117 by culture in mycobacterial growth indicator tubes. Specimens that were smear positive  
118 and cultures that flagged positive were further subjected to polymerase chain reaction by  
119 line-probe assay (LPA; MTBDRplus, Hain Lifescience, Germany). In-vitro drug sensitivity  
120 testing was performed for both first and second line anti-tuberculosis drugs. The Xpert MTB-  
121 RIF platform (hereafter referred to as Xpert) was introduced in late 2013, replacing sputum  
122 smear microscopy.

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124

#### 125 Statistical analysis

126 We present a descriptive analysis of all TB diagnoses in the MATCH study. TB-negative  
127 patients, bacteriologically-confirmed TB cases and clinically-diagnosed cases were compared  
128 using ANOVA (for continuously-distributed data) or chi-square (for categorical variables). In  
129 addition, we assessed associations between patient characteristics (including laboratory  
130 results, TB sampling method and ART strategy) and the diagnosis of TB using a negative  
131 binomial logistic regression model comparing children with and without a confirmed  
132 diagnosis of TB; empirically-treated children were excluded from this model, as were any  
133 children with missing data. We hypothesised that anaemia (Hb <10g/dL), leukocytosis  
134 (white cell count >12 x 10<sup>9</sup>), thrombocytosis (platelets >400 x 10<sup>9</sup>) and hypoalbuminaemia  
135 (<25g/L) might, as surrogate markers of inflammation, be associated with a diagnosis of TB  
136 (ESR and CRP levels were infrequently measured, and therefore were not included in the  
137 model). Following univariate analysis, all variables were included in a fully-adjusted  
138 multivariate model. A parsimonious adjusted model was then reached via a backward  
139 stepwise approach, sequentially excluding variables whose p value was >0.1 and selecting a  
140 final model that minimised the Akaike information criterion. Results are presented as  
141 adjusted relative risks (aRR) with 95% confidence intervals (CI), and p values <0.05 were  
142 considered significant. All analyses were performed using SPSS version 22 (IBM).

143

144 Ethics

145 Written informed consent was obtained from the caregivers of all children enrolled in the  
146 MATCH study. The trial was approved by the Biomedical Research Ethics Committee of the  
147 University of KwaZulu Natal and King Edward VIII Hospital.

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## 150 RESULTS

151 Descriptive analysis

152 We enrolled 82 children in the MATCH trial. Figure 1 outlines the recruitment and TB  
153 diagnostic process, while Table 1 outlines the patients' baseline characteristics and sites of  
154 TB. The mean age at admission was 23 months, 46.3% (n = 38) were girls, the mean CD4  
155 percentage was 17.46% and 21.95% (n = 18) presented with oedematous malnutrition.

156 Seventy five children were investigated for TB and 21/82 (25.6%) were determined to have  
157 TB. Eight (10.9%) had bacteriologically confirmed pulmonary TB (one of whom died before  
158 the culture flagged positive) while thirteen were clinically diagnosed. Eight were treated  
159 empirically after admission, while five were on treatment at enrolment but had no positive  
160 TB results on record. All six culture-positive TB isolates were fully sensitive in vitro.

161 62 patients had sputum samples, while the remaining 13 had gastric aspirates. The mean  
162 ages of those with sputum or gastric aspirate samples did not differ significantly (25 versus  
163 21 months, p = 0.7). No gastric aspirate samples tested positive for TB; two empirically-  
164 treated patients had had gastric aspirate samples tested. Xpert was employed in 45  
165 patients, but was only positive in two, both of whom were subsequently culture positive. Of  
166 the 37 patients enrolled before Xpert was widely available, five had confirmed TB and seven  
167 were empirically treated, versus three confirmed and six empirically treated after Xpert was  
168 introduced (p=0.199). Thus, the introduction of Xpert did not appear to affect the rates of  
169 empiric treatment for TB in smear-negative patients, though it should be underlined that  
170 this study was carried out while local clinicians were still familiarising themselves with Xpert.

171 One empirically-treated child was suspected of having TB meningitis clinically and on  
172 cerebrospinal fluid analysis (leukocytosis and elevated protein levels), but was TB culture  
173 negative from all specimens. The remainder of those commenced on empiric treatment at  
174 our centre were suspected of having pulmonary TB. Prior to their admission to KEH, two  
175 children were on treatment for suspected pulmonary TB, two for suspected disseminated  
176 TB, and one for suspected abdominal TB. **In addition, one child underwent an axillary lymph  
177 node biopsy which led to a diagnosis of Bacille Calmette-Guérin (BCG) IRIS; this child was not  
178 classified as having TB in this study.**



179 Regression analysis

180 Fifty-three children had sufficient data for inclusion in the multivariate analysis, including 7  
181 of those with proven TB (the eighth child, who was smear-positive but culture-negative, was  
182 excluded for lack of a full blood count result). Results of the regression analysis are  
183 presented in Table 2. While leukocytosis was associated with a slight increased risk of TB in  
184 the final model (aRR 1.81, 95% CI 1.067—1.308), thrombocytosis was unexpectedly  
185 associated with a reduced risk (aRR 0.868, 95% CI 0.774—0.974). The diagnosis of a culture-  
186 proven bacterial infection during the admission was associated with a reduced risk of TB  
187 (aRR 0.856, 0.748—0.979). Sputum sampling (as opposed to gastric washings) was  
188 associated with a 13.4% increased risk of subsequent diagnosis of TB (95% CI 2.1%—26%).  
189 While allocation to the “delayed ART” group was associated with a 13.8% increased risk of  
190 TB in the full model, this association disappeared when the parsimonious model was  
191 created and it was omitted from the final model. There was a small reduction in risk for  
192 children with CD4 percentages between 20—25% (aRR 0.864, 95% CI 0.765—0.976 with CD4  
193 percentage >25% used as the reference category), but no other CD4 values were associated  
194 with either increased or decreased risk.

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196

## 197 DISCUSSION

198 In our prospective cohort of 82 HIV-infected South African children, admitted to a university  
199 teaching hospital for the management of complicated SAM, we found a 25.6% incidence of  
200 TB **within the first month of admission**, with bacteriological confirmation in 38% of cases (n  
201 = 8/21).

202 Children with HIV often present with paucibacillary TB disease that defies culturing, sample  
203 acquisition is difficult (particularly in the case of extrapulmonary TB) and malnutrition is a  
204 component of most clinical diagnostic scoring systems, rendering these less reliable in a  
205 population of malnourished children.<sup>22</sup> We found few associations between routine  
206 laboratory parameters and culture-proven TB. Ultimately our best regression model was  
207 still not a particularly good fit for the data, likely due to unmeasured confounders and a lack  
208 of clinical and radiological details, and the associations we identified were not strong  
209 enough to be useful in a predictive model. Further studies are required to identify  
210 biomarkers of active TB that are reliable in severely-malnourished, HIV-infected children.<sup>23</sup>

211 In the regression model, sputum sampling was associated with a diagnosis of TB when  
212 compared with gastric aspirates, which is consistent with previous studies showing superior  
213 sensitivity of sputum sampling.<sup>24</sup> Some of the other associations that we identified require  
214 a nuanced interpretation. The association of delayed ART and TB was seen in the fully  
215 adjusted model but not the final parsimonious model, and is not likely to be a true  
216 association, as all but one positive sputum sample were acquired during the first week of  
217 admission—i.e. early ART would not have prevented these diagnoses of TB. In addition,  
218 randomisation was stratified by TB status at enrolment. Possibly this finding indicates  
219 sampling bias by clinicians in this open-label study. The strongest conclusion one could  
220 draw is that the lack of increased risk of TB following early ART allays concerns regarding  
221 immune reconstitution inflammatory syndrome (IRIS) reactions in these children.

222 Culture-proven bacterial infection was associated with a 14.4% reduced risk of culture-  
223 proven TB—not only is it exceedingly unlikely that bacterial infections are protective against  
224 mycobacterial infections, but multiple simultaneous opportunistic infections are in fact  
225 expected in severely immunosuppressed children. It is more likely that treatment for  
226 bacterial infections led to false-negative TB samples, or that treatment for TB resulted in

227 false-negative bacterial cultures. Broad-spectrum antibacterials—empiric or otherwise—  
228 were frequently administered to the children in this study, as SAM is frequently associated  
229 with infections at time of presentation, and hospital-acquired infections are also common in  
230 this patient group.<sup>21</sup> While the local formulary dictates that quinolones only be prescribed if  
231 indicated by antibiotic susceptibility profiles or on the advice of the infectious diseases  
232 service, aminoglycosides are frequently employed (benzylpenicillin and gentamicin are first-  
233 line empiric therapy for severely unwell children in this institution), as were carbapenems,<sup>21</sup>  
234 both of which have activity against TB.<sup>25</sup> We were unable to access the original charts for  
235 most patients, meaning that we could not correlate actual antibiotic prescriptions with the  
236 likelihood of a TB diagnosis. However, it is reasonable to assume that TB diagnoses could be  
237 masked by the treatment of other infections (or vice versa) in severely unwell children with  
238 HIV and SAM, or not considered when a child with SAM presents to hospital with a sepsis-  
239 like syndrome and therefore it would be advisable to include TB investigation as part of the  
240 standard admission workup in order to minimize the risk of false negatives in the acute phase  
241 of malnutrition management.

242 This is, to our knowledge, the first study describing TB in children who all have both HIV and  
243 SAM. Looking beyond the multivariate model in a subset of patients, there were 13  
244 additional patients in this study who were empirically treated for TB. The true rate of TB in  
245 children with SAM and HIV remains unquantifiable as long as so many cases remain  
246 unconfirmed. Table 3 summarises a sample of studies of such populations<sup>26,27</sup>: while the  
247 rate of confirmed TB in children with SAM appears to rise in parallel with increasing rates of  
248 HIV (allowing for local variation in baseline TB rates), rates of empiric treatment vary  
249 substantially. Thus, it is impossible to assess the separate contributions of HIV and SAM to  
250 the pathogenesis of TB in children, though Table 3 does suggest that HIV is a key risk factor  
251 for TB in SAM—with increasing numbers of malnourished children now having HIV as an  
252 underlying cause, it is important for clinicians to particularly consider TB in such cases. Our  
253 own study shows that, despite the inherent challenges, microbiological confirmation of  
254 suspected pulmonary TB is possible in severely malnourished children with HIV.

255 Other studies in Africa have started with a diagnosis of TB and looked backwards for  
256 associations with malnutrition and/or HIV, usually finding strong and independent  
257 associations with both of these risk factors and TB mortality.<sup>12,13,28</sup> The only other studies

258 that we can find that began with malnourished children and looked for associations with TB  
259 were carried out in South Asia, where paediatric HIV prevalence is far lower, and differ in  
260 many important methodological factors from our study.<sup>29,30</sup> One such study examined 405  
261 severely malnourished Bangladeshi children with respiratory symptoms and radiographic  
262 pulmonary infiltrates: 7% had confirmed TB and a further 16% were treated based on  
263 clinical suspicion.<sup>30</sup> HIV prevalence was not determined, but was known to be rare in that  
264 locale. While this study is important in raising awareness of TB mimicking acute pneumonia  
265 in children with SAM, the TB prevalence in a select population with radiologic changes will  
266 obviously be higher than the TB prevalence in malnourished children in general.

267 Strengths of our study include prospective recruitment of patients and access to tertiary-  
268 level diagnostic facilities. Limitations include the relatively small number of patients,  
269 missing data, practice changes during the course of the trial (eg. the introduction of Xpert)  
270 and the single-centre setting, limiting the generalisability to other settings in sub-Saharan  
271 Africa and beyond. Poor availability of patients' original hospital files meant that we lacked  
272 data regarding clinical findings, radiographs and tuberculin skin tests, which would have  
273 been a useful addition to our analysis. We considered our two patients who were smear-  
274 positive but culture negative to have confirmed TB, in keeping with the WHO classification,<sup>20</sup>  
275 but these may have been false positives due to non-tuberculous mycobacteria—equally, we  
276 considered patients who started treatment in other centres to be empirically-treated, when  
277 they may in fact have had a confirmed diagnosis which was not identifiable on the national  
278 laboratory online system.

279

280

## 281 CONCLUSIONS

282 TB is **very** common in HIV-infected children with severe acute malnutrition. While  
283 microbiological confirmation of the diagnosis is feasible, **numerous diagnostic challenges—**  
284 **including suboptimal testing (gastric aspirates as opposed to induced sputum) and false**  
285 **negative TB diagnostics (with prior antibacterial therapy)—mean that** empiric treatment  
286 remains common in this patient group. Future studies should focus on diagnostic strategies  
287 that are sufficiently robust for this important, vulnerable population of children in resource-  
288 poor settings. With SAM being increasingly seen in conjunction with HIV in sub-Saharan  
289 Africa, it is important that TB diagnosis and treatment be integrated into the programmatic  
290 management of these conditions.

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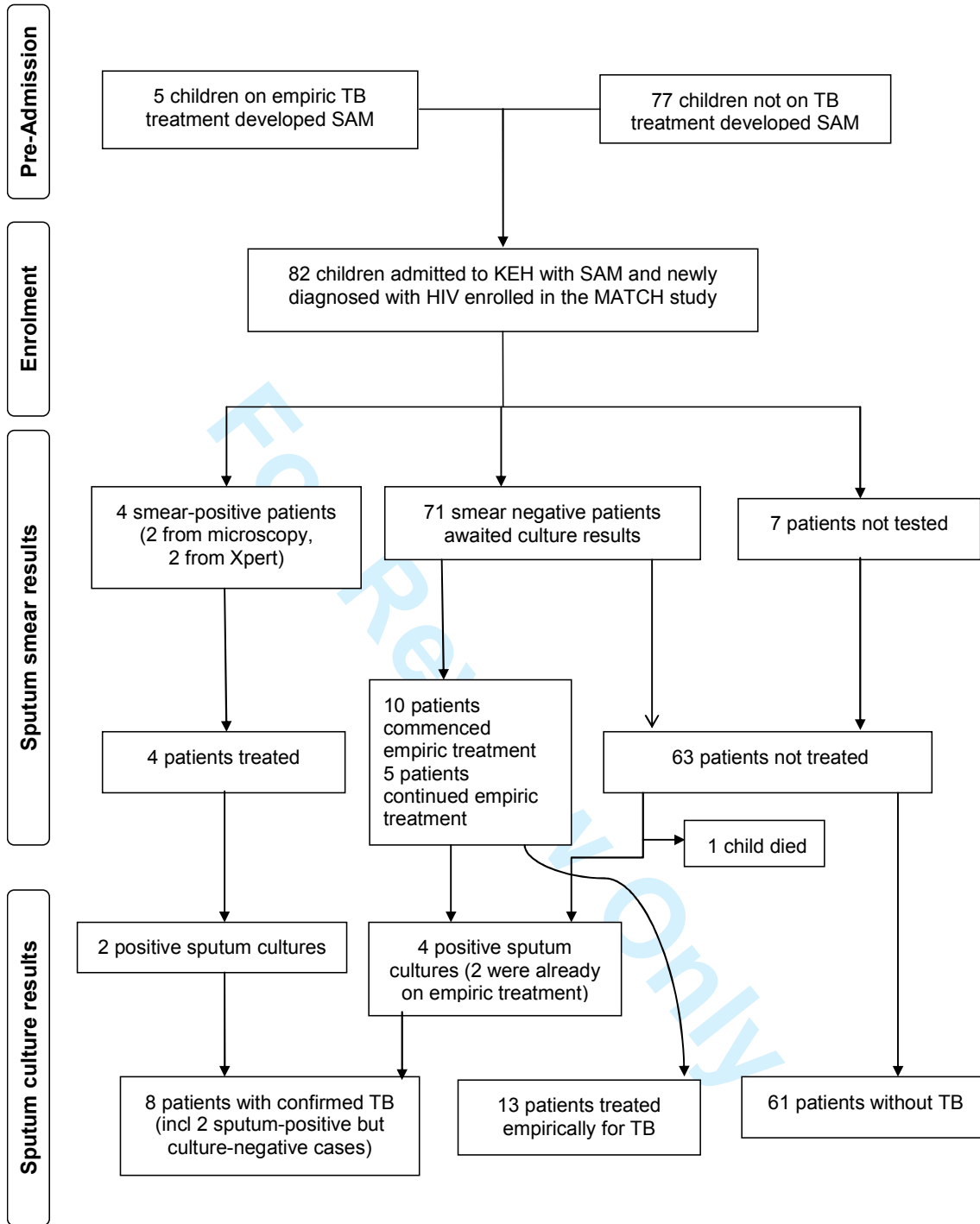
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387 Figure 1: Recruitment and diagnostic process

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|                                  | TB negative (n = 61) | Bacteriologically confirmed (n = 8) | Clinically diagnosed (n = 13) | p    |
|----------------------------------|----------------------|-------------------------------------|-------------------------------|------|
| <b>BASELINE CHARACTERISTICS</b>  |                      |                                     |                               |      |
| Age (months)                     | 19 ± 22              | 29 ± 41                             | 36 ± 40                       | 0.1  |
| Female                           | 28 (45.9%)           | 5 (62.5%)                           | 5 (38.5%)                     | 0.56 |
| Oedema present                   | 12 (19.7%)           | 4 (50%)                             | 2 (15.4%)                     | 0.12 |
| Early ART (<2 weeks)             | 29 (47.5%)           | 3 (37.5%)                           | 6 (46.2%)                     | 0.87 |
| Other bacterial infection        | 33 (54.1%)           | 3 (37.5%)                           | 3 (23.1%)                     | 0.1  |
| CD4 (cells/μL) (n = 73)          | 945 ± 807            | 874 ± 309                           | 721 ± 214                     | 0.49 |
| CD4 percentage (n = 73)          | 18.35 ± 9.1%         | 15.5 ± 9.83%                        | 14.5 ± 11.4%                  | 0.4  |
| Haemoglobin (g/dL)               | 8.65 ± 2.0           | 8.7 ± 3.8                           | 8.4 ± 1.7                     | 0.73 |
| Haemoglobin <7                   | 9 (14.8%)            | 3 (37.5%)                           | 2 (15.4%)                     | 0.27 |
| Platelets (x 10 <sup>9</sup> /L) | 336 ± 208            | 336 ± 215                           | 297 ± 131                     | 0.81 |
| Platelets >400                   | 20 (32.8%)           | 1 (12.5%)                           | 4 (30.8%)                     | 0.6  |
| Albumin (g/L)                    | 24 ± 8               | 21 ± 5                              | 23 ± 6                        | 0.56 |
| Albumin <25                      | 30 (29.2%)           | 6 (75%)                             | 8 (61.5%)                     | 0.35 |
| CRP (mg/L) (n = 37)              | 38 ± 49              | 38 ± 41                             | 57 ± 35                       | 0.68 |
| CRP >10 (n = 37)                 | 16                   | 5                                   | 5                             | 0.17 |
| <b>SITE OF TB</b>                |                      |                                     |                               |      |
| Pulmonary                        | -                    | 7                                   | 8                             | -    |
| Pulmonary + Disseminated         | -                    | 1                                   | 3                             | -    |
| Meningitis                       | -                    | 0                                   | 1                             | -    |
| Abdominal                        | -                    | 0                                   | 1                             | -    |
| <b>DIAGNOSIS</b>                 |                      |                                     |                               |      |
| Smear microscopy                 | -                    | 2*                                  | -                             | -    |
| Xpert                            | -                    | 2†                                  | -                             | -    |
| Culture                          | -                    | 6                                   | -                             | -    |

389 Table 1: Baseline characteristics of the patients in this study.

390 Values are given as mean ± SD or n (%) as appropriate. P values are for a three-way  
391 comparison. Bacterial infection refers to any positive blood/sputum/urine culture for  
392 pathogenic bacteria within the first month of admission.

393 \*Both were smear positive but culture negative

394 †Both were culture positive

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For Review Only

| Risk factor                                   | TB        | No TB        | Unadjusted <sup>c</sup> | p (Wald) | Fully adjusted <sup>c</sup> | p (Wald) | Parsimonious adjusted <sup>c</sup> | p (Wald) |
|---|-----------|--------------|-------------------------|----------|-----------------------------|----------|------------------------------------|----------|
| Total (n = 53)                                | 7         | 46           |                         |          |                             |          |                                    |          |
| Sex <sup>a</sup> : Male                       | 3 (42.9%) | 24 (52.2%)   | 0.963 (0.82—1.131)      | 0.645    | 1.041 (0.933—1.162)         | 0.467    | -                                  | -        |
| Female  | 4 (57.1%) | 22 (47.8%)   | 1                       | -        | 1                           | -        | -                                  | -        |
| Delayed ART <sup>a</sup>                      | 5 (71.4%) | 22 (47.8%)   | 1.101 (0.942—1.286)     | 0.229    | 1.138 (1.003—1.291)         | 0.044    | -                                  | -        |
| Early ART                                     | 2 (28.6%) | 24 (52.2%)   | 1                       | -        | 1                           | -        | -                                  | -        |
| Oedema present <sup>a</sup>                   | 3 (42.9%) | 11 (23.9%)   | 1.101 (0.904—1.341)     | 0.337    | 1.052 (0.904—1.247)         | 0.464    | -                                  | -        |
| No oedema                                     | 4 (57.1%) | 35 (76.1%)   | 1                       | -        | 1                           | -        | -                                  | -        |
| Hb <10g/dL <sup>a</sup>                       | 3 (42.9%) | 12 (26.1%)   | 0.921 (0.761—1.114)     | 0.397    | 0.870 (0.740—1.023)         | 0.092    | 0.875 (0.756—1.014)                | 0.075    |
| Hb ≥10g/dL                                    | 4 (57.1%) | 34 (73.9%)   | 1                       | -        | 1                           | -        | 1                                  | -        |
| WBC >12 x 10 <sup>9</sup> <sup>a</sup>        | 7 (100%)  | 29 (63%)     | 1.194 (1.072—1.331)     | 0.001    | 1.199 (1.057—1.359)         | 0.005    | 1.181 (1.067—1.308)                | 0.001    |
| WBC ≤12 x 10 <sup>9</sup>                     | 0         | 17 (37%)     | 1                       | -        | 1                           | -        | 1                                  | -        |
| Platelets ≥400 x 10 <sup>9</sup> <sup>a</sup> | 1 (14.3%) | 14 (30.4%)   | 0.921 (0.789—1.076)     | 0.299    | 0.825 (0.730—0.932)         | 0.002    | 0.868 (0.774—0.974)                | 0.016    |
| Platelets <400 x 10 <sup>9</sup>              | 6 (85.7%) | 32 (69.6%)   | 1                       | -        | 1                           | -        | 1                                  | -        |
| Albumin <25g/L <sup>a</sup>                   | 5 (71.4%) | 26 (56.5%)   | 1.065 (0.91—1.245)      | 0.434    | 0.940 (0.788—1.120)         | 0.486    | -                                  | -        |
| Albumin ≥25g/L                                | 2 (28.6%) | 20 (43.5%)   | 1                       | -        | 1                           | -        | -                                  | -        |
| CD4 <15% <sup>a</sup>                         | 4 (57.1%) | 18 (39.1%)   | 1.064 (0.845—1.338)     | 0.599    | 1.039 (0.899—1.201)         | 0.604    | 1.082 (0.927—1.264)                | 0.317    |
| CD4 15—20%                                    | 2 (28.6%) | 12 (26.1%)   | 1.029 (0.805—1.314)     | 0.821    | 0.914 (0.760—1.100)         | 0.343    | 0.985 (0.822—1.181)                | 0.87     |
| CD4 20-25%                                    | 0         | 8 (17.4%)    | 0.900 (0.748—1.083)     | 0.264    | 0.806 (0.690—0.942)         | 0.007    | 0.864 (0.765—0.976)                | 0.019    |
| CD4 >25%                                      | 1 (14.3%) | 8 (17.4%)    | 1                       | -        | 1                           | -        | 1                                  | -        |
| Any positive bacterial culture <sup>a</sup>   | 2 (28.3%) | 24 (52.2%)   | 0.909 (0.777—1.062)     | 0.229    | 0.844 (0.752—0.948)         | 0.004    | 0.856 (0.748—0.979)                | 0.024    |
| No positive bacterial culture                 | 5 (71.7%) | 22 (47.8%)   | 1                       | -        | 1                           | -        | 1                                  | -        |
| Sampling site: Sputum <sup>a</sup>            | 7 (100%)  | 37 (80.4%)   | 1.159 (1.056—1.272)     | 0.002    | 1.115 (0.989—1.256)         | 0.076    | 1.134 (1.021—1.260)                | 0.019    |
| Gastric washings                              | 0         | 9 (19.6%)    | 1                       | -        | 1                           | -        | 1                                  | -        |
| Age (months) (Median, IQR) <sup>b</sup>       | 15 (8—42) | 18 (6.75—27) | 1.001 (0.998—1.005)     | 0.463    | 1.002 (0.999—1.005)         | 0.151    | -                                  | -        |

400 Table 2: Results of regression analysis. Data are presented as: (a) n (%); (b) median (IQR); (c) RR (95% CI)

| Study                           | Year | Setting                    | Number with SAM | Prevalence of HIV <sup>a</sup> | Prevalence of confirmed TB <sup>a</sup> | Prevalence of empiric TB treatment <sup>a</sup> | Overall rate of TB treatment <sup>a</sup> |
|---------------------------------|------|----------------------------|-----------------|--------------------------------|---|---|---|
| Cartmell (Part 1) <sup>26</sup> | 1983 | Maputo, Mozambique         | 833             | 0                              | 53 (6.4%)                               | 29 (3.5%)                                       | 81 (9.7%)                                 |
| Cartmell (Part 2) <sup>26</sup> | 2001 | Maputo, Mozambique         | 558             | 65 (29.3%)*                    | 78 (14%)                                | 14 (2.5%)                                       | 92 (16.5%)                                |
| De Maayer <sup>27</sup>         | 2011 | Johannesburg, South Africa | 113             | 58 (51%)                       | 3 (2.6%)                                | 29 (25.7%)                                      | 32 (28.3%)                                |
| This study                      | 2016 | Durban, South Africa       | 82              | 82 (100%)                      | 8 (9.8%)                                | 13 (15.9%)                                      | 21 (25.6%)                                |

401 Table 3: Examples of other studies of children admitted for the management of SAM in different sub-Saharan African settings. These data suggest that, as  
 402 rates of HIV increase, so too do rates of bacteriologically confirmed TB in children with SAM—however, rates of empiric treatment differ markedly between  
 403 studies and confound accurate assessment.

404 (a) n (%)

405 \*51 with an AIDS-defining-illness, 14 with confirmed HIV. An additional 30 had suspected HIV but this was not confirmed (not included in this table)

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