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

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

Running head: TB in children with HIV & severe malnutrition

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All authors had a role in the design of this study. H Adler, M Archary and P Mahabeer collected the data. H Adler performed statistical analyses and wrote the first draft of the paper, which was revised with contributions from all authors. All authors have approved the final version

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SUMMARY

Setting: Academic tertiary referral hospital in Durban, South Africa

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

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

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

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

INTRODUCTION

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

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

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

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

STUDY POPULATION AND METHODS

Setting

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

Recruitment and eligibility

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

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

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

Data collection

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

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

Statistical analysis

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

Ethics

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

RESULTS

Descriptive analysis

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

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

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

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

Regression analysis

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

DISCUSSION

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

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

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

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

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

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

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

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

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

CONCLUSIONS

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

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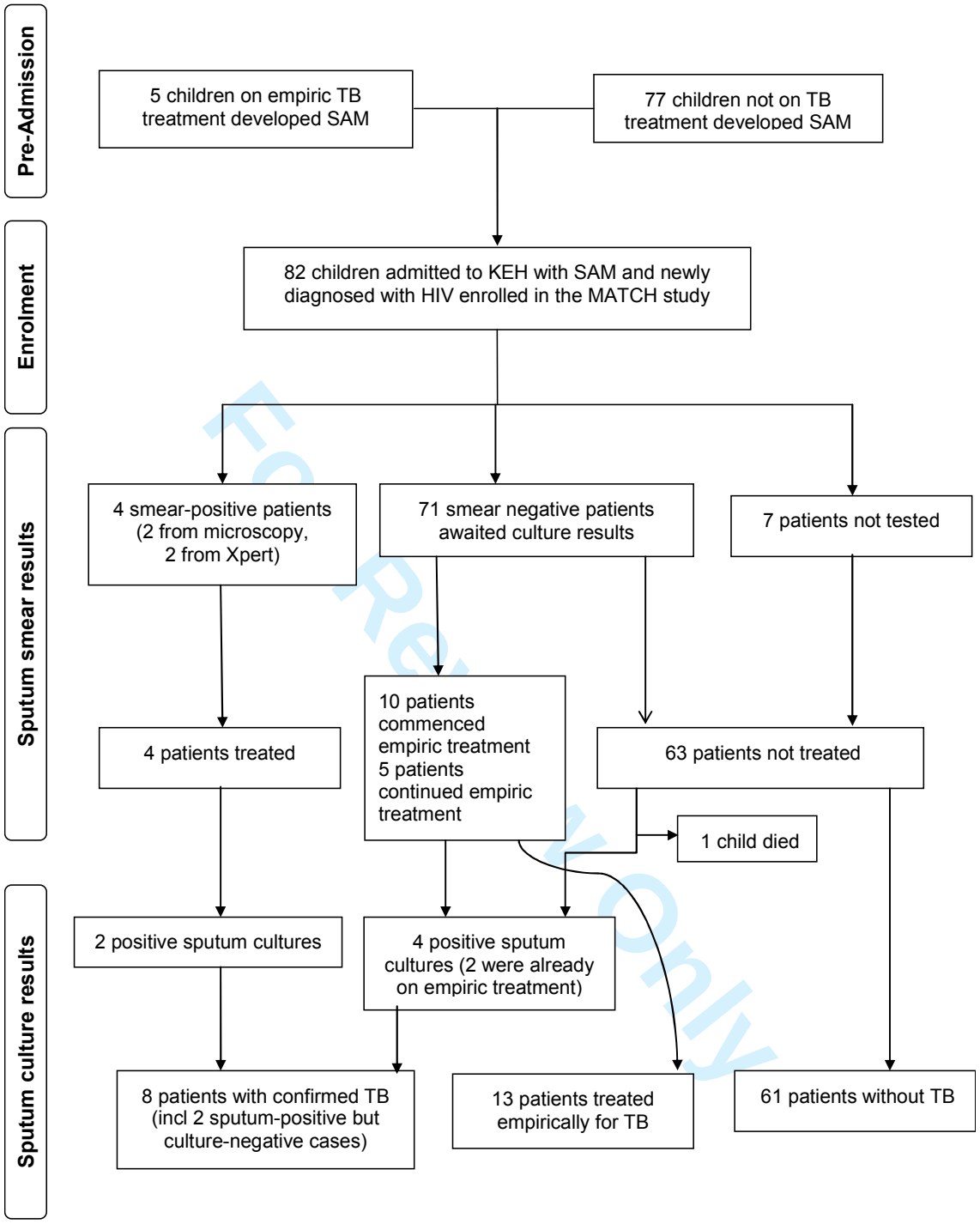

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387 Figure 1: Recruitment and diagnostic process

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	TB negative (n = 61)	Bacteriologically confirmed (n = 8)	Clinically diagnosed (n = 13)	p
BASELINE CHARACTERISTICS				
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 10^9/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
SITE OF TB				
Pulmonary	-	7	8	-
Pulmonary + Disseminated	-	1	3	-
Meningitis	-	0	1	-
Abdominal	-	0	1	-
DIAGNOSIS				
Smear microscopy	-	2*	-	-
Xpert	-	2†	-	-
Culture	-	6	-	-

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

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

*Both were smear positive but culture negative

†Both were culture positive

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Risk factor	TB	No TB	Unadjusted[c]	p (Wald)	Fully adjusted[c]	p (Wald)	Parsimonious adjusted[c]	p (Wald)
Total (n = 53)	7	46						
Sex[a]: 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[a]	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[a]	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[a]	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 10^9 [a]	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 10^9	0	17 (37%)	1	-	1	-	1	-
Platelets ≥400 x 10^9 [a]	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 10^9	6 (85.7%)	32 (69.6%)	1	-	1	-	1	-
Albumin <25g/L[a]	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%[a]	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[a]	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[a]	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)[b]	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[a]	Prevalence of confirmed TB[a]	Prevalence of empiric TB treatment[a]	Overall rate of TB treatment[a]
Cartmell (Part 1)[26]	1983	Maputo, Mozambique	833	0	53 (6.4%)	29 (3.5%)	81 (9.7%)
Cartmell (Part 2)[26]	2001	Maputo, Mozambique	558	65 (29.3%)*	78 (14%)	14 (2.5%)	92 (16.5%)
De Maayer[27]	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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