INT J TUBERC LUNG DIS 22(2):151–157

http://dx.doi.org/10.5588/ijtld.17.0535
E-published ahead of print 20 December 2017

Treatment outcomes and tolerability of the revised WHO anti-tuberculosis drug dosages for children

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SUMMARY

BACKGROUND: In 2010, the World Health Organization (WHO) revised the paediatric dosages of anti-tuberculosis drugs, increasing rifampicin to 15 mg/kg, isoniazid to 10 mg/kg and pyrazinamide to 35 mg/kg. We assessed treatment outcomes, safety and adherence among children treated with the new recommended dosages.

METHODS: Prospective cohort of children started on anti-tuberculosis treatment in Uganda with 12 months of follow-up, including alanine aminotransferase (ALT) monitoring. Treatment intake was observed.

RESULTS: Of 144 treated children, 81 were male (56.3%), 106 (73.6%) were aged <5 years, 30 (22%) had moderate to severe malnutrition and 48 (33.3%) had human immunodeficiency virus infection. Treatment outcomes were as follows: 117 (81.3%) successes, 3 (2.1%) failures, 4 (2.8%) lost to follow-up, 19 (13.2%) deaths and 1 (0.7%) transferred out. There was no relapse. Severe malnutrition (adjusted hazard ratio 8.76, 95% confidence interval [CI] 1.59–48.25) was the only predictor of death. Two serious adverse events were attributed to treatment: one case of increased ALT and one with peripheral neuropathy. Median ALT values at baseline and at weeks 2, 4 and 8 were respectively 24 (interquartile range [IQR] 16–39), 26 (IQR 18–38), 28 (IQR 21–40) and 27 (IQR 19–38) international units/l. Treatment adherence was above 85% on all visits.

CONCLUSION: We confirm the good tolerability of and adherence to the new treatment recommendations. The increased risk of fatal outcome among severely malnourished children requires attention.

KEY WORDS: tuberculosis; treatment; children; mortality

FOR A LONG TIME, prescription of anti-tuberculosis treatment in childhood was based on adult dosages per kg.[1–4] However, a drug dose in mg/kg when administered to a child aged <5 years may not reach the same blood concentration as that in an adult; higher dosages may therefore be required in young children.[5] Based on pharmacokinetic studies in children and safety data, in 2010 the World Health Organization (WHO) recommended increasing the dosages of anti-tuberculosis drugs in children as follows: rifampicin (R, RMP) to 15 mg/kg, isoniazid (H, INH) to 10 mg/kg and pyrazinamide (Z, PZA) to 35 mg/kg.[1–4,6]

However, no published randomised clinical trial of efficacy and safety of the recently recommended TB drug dosages is available. In 2010, the WHO recommended conducting high-quality observational studies to evaluate the risk of hepatotoxicity of INH at the increased dose of 10 mg/kg.[4] Until recently, the available fixed-dose combinations (FDCs) of anti-tuberculosis drugs for children comprised RHZ 60:30:150 for the intensive phase and RH 60:30 for the continuation phase; these were considered suitable when using the previous dosage recommendations of RMP 10 mg/kg and INH 5 mg/kg because the ratio of R:H was 2:1.[7] However, after the revision, this ratio increased to 3:2, thereby creating programmatic challenges for its implementation, with potential risks of incorrect prescription and poor treatment adherence due to the high pill burden.

In the present study, we assessed treatment outcomes, safety—particularly hepatotoxicity—and treatment adherence among children treated with the new WHO anti-tuberculosis drug dosages in a low-resource setting with high human immunodeficiency virus (HIV) prevalence.

METHODS

Study design and population

The study was a nested prospective cohort of

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Article submitted 31 July 2017. Final version accepted 22 September 2017.

Table 1 Anti-tuberculosis drug dosage by weight bands

	Weight, kg		
	5–7	8–14	15–20
Intensive phase: 2HRZ ± E			
Tablet H 30 mg, R 60 mg, Z 150 mg +	1	2	3
Tablet H 60 mg, R 60 mg ±	1	1	2
Tablet E 100 mg	1	2	3
Continuation phase: 4HR			
Tablet H 30 mg, R 60 mg +	1	2	3
Tablet H 60 mg, R 60 mg	1	1	2

H = isoniazid; R = rifampicin; Z = pyrazinamide; E = ethambutol.

paediatric TB cases started on anti-tuberculosis treatment from a larger observational cohort of children with presumptive TB in Mbarara Regional Referral Hospital in Mbarara, Uganda. Consecutive children aged between 1 month and 14 years started on treatment for active TB were eligible for the nested cohort. Children who had completed a full course of anti-tuberculosis treatment in the past 6 months, who were already on treatment for 3 days or on INH prophylaxis and children living beyond a 20 km radius around Mbarara City were excluded.

Procedures

At initial assessment, the parent/guardian was interviewed about the child's medical history and household TB contact history with a smear- or culture-positive TB index case, followed by physical examination. A tuberculin skin test (TST) was performed using 5 and 10 mm cut-offs to define positive results in HIV-infected and non-infected children, respectively. Postero-anterior and lateral chest X-ray digital images were obtained for all children, read and recorded by the doctor onsite using pre-determined tick-sheets and classified according to a structured approach as follows: 'normal', 'abnormal, suggestive of TB' or 'abnormal, non-suggestive of TB'. Children were offered HIV testing using the nationally approved testing algorithm. Two sputum specimens were collected over 2 consecutive days using induced sputum for children unable to produce specimen and tested with the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), two Löwenstein-Jensen (LJ) cultures and one MGIT (BD, Sparks, MD, USA) culture from each sputum sample. Similar tests were performed on extra-pulmonary specimens collected according to the clinical presentation.

After initial assessment, children with any positive TB bacteriological test, chest X-ray or clinical presentation suggestive of TB disease according to an experienced paediatrician were started on anti-tuberculosis treatment using RMP (10–20 mg/kg), INH (10–15 mg/kg), PZA (30–40 mg/kg). FDCs (INH 30 mg, RMP 60 mg, PZA 150 mg and INH 60 mg, RMP 60 mg) were prescribed according to body weight. Ethambutol (E, EMB) (15–25 mg/kg) was added to the regimen during the intensive phase in the presence of extensive disease (excluding TB meningitis), smear-positive results, HIV infection and/or suspected INH drug resistance (Table 1).[8] Drugs were centrally procured using WHO pre-qualified manufacturing sources (Lupin Pharma Inc, Mumbai, India), and delivered every 2 weeks to the child's guardian/parent during the intensive phase and every 4 weeks during the continuation phase. Intake was directly observed at home, with each dose being recorded in a treatment card by the parent/guardian.

Newly diagnosed HIV-infected children were referred to the hospital HIV clinic for appropriate treatment. Children were followed monthly for 6 months, with a last visit at month 12 with symptom assessment and physical examination by the study clinician and adherence assessment by the study nurse using pill count and review of the TB DOT (directly observed treatment) cards. Alanine aminotransferase (ALT) levels were monitored at weeks 2, 4 and 8 of treatment.

Definitions

Treatment outcome definitions were adapted from adult definitions, as advised by the 2014 WHO paediatric guidelines.[9] Cure and treatment completion were taken as successful outcome, and death, loss to follow-up and failure were defined as unsuccessful outcome. Malnutrition was defined using the WHO weight-for-height *Z*-score standard deviation (SD):[10] normal, SD > -1; mild, SD -2 to $\leqslant -1$; moderate, SD -3 to $\leqslant -2$ and severe malnutrition, SD $\leqslant -3$. Events resulting in death; immediate life threatening, persistent or significant disability/incapacity; in-patient hospitalisation or prolongation of existing hospitalisation; and increase of ALT to 5 times the upper limit of normal (ULN), were defined as serious adverse events and notified to the ethics review committees.

Statistics

Of the 392 children with presumptive TB enrolled in the main cohort between April 2012 and January 2014, 144 were treated for TB and included in the nested cohort.[10] Data were entered using Voozanoo (Epiconcept, Paris, France) and were analysed using Stata® v13 software (Stata Corp, College Station, TX, USA). Patient characteristics were summarised using frequencies and percentages for categorical variables, and medians and interquartile ranges (IQRs) for continuous variables. Medians (IQR) of ALT levels were recorded at baseline and at weeks 2, 4 and 8 of treatment. Treatment adherence rates (number of pills given – pills remaining/pills given) were calculated for the period between two consecutive study visits in all patients still on treatment at the respective study visit. Survival analysis using Kaplan-Meier estimates was performed and presented by age group. Patients were censored at the date of

Table 2 Baseline characteristics of children initiated on anti-tuberculosis treatment

Characteristics	($n = 144$) *n/N* (%)
Female sex	63 (43.8)
Age, years	
<2	64 (44.4)
2–5	42 (29.2)
⩾5	38 (26.4)
Smoke exposure	108 (75.0)
Previously treated for TB	2 (1.4)
Received antibiotics 2 weeks before inclusion	81 (56.3)
HIV-positive	48/142 (33.8)
CD4 cell count, cells/mm^3, median [IQR] ($n = 12$)	415 [39–650]
On ART	21 (43.8)
TST-positive	67/134 (50.0)
Weight for height	
> −1 SD	59/142 (41.6)
⩽ −2 SD	35/142 (24.7)
< −2 to ⩽ −3 SD	18/142 (12.7)
> −3 SD	30/142 (21.1)
Clinical presentation (any sign)	
>2 weeks of cough	120/140 (85.7)
>7 days of reported fever	65/140 (46.4)
>2 weeks of night sweats	71/140 (50.7)
>2 weeks of unexplained fatigue	65/140 (49.3)
Peripheral adenopathy	13/140 (9.3)
Chest X-ray (any sign)	
Consolidation	35/135 (26)
Cavity	3/135 (2.2)
Mediastinal adenopathy	61/135 (45.2)
Broncho-pneumonic patterns	82/135 (60.7)
Microbiological confirmation of TB	18 (12.5)
Culture-positive sputum	14/125 (11.2)
Xpert *M. tuberculosis* detected	13/119 (11.0)

TB = tuberculosis; HIV = human immunodeficiency virus; IQR = interquartile range; ART = antiretroviral therapy; TST = tuberculin skin test; SD = standard deviation.

death or at study visit completion. Predictors of unsuccessful outcome among baseline characteristics were explored using univariate and multivariate logistic regression models. Covariates associated with a P value of <0.4 in univariate analysis were included in the initial multivariate model; a manual backward stepwise approach was used to obtain the final multivariate model. Statistical significance ($P < 0.05$) was assessed with the likelihood ratio test. The same analysis was repeated for death alone.

The study was approved by the Mbarara University Faculty of Medicine Research Committee, Mbarara University Institutional Review Board, Mbarara; the Uganda National Council for Science and Technology, Kampala, Uganda; and the Comité de Protection des Personnes of Ile de France XI, Saint Germain-en-Laye, France.

RESULTS

Baseline characteristics

Of the 144 children included, 81 (56.3%) were male, 106 (73.6%) were aged <5 years, 30 (22%) were severely malnourished and 48 (33.3%) were HIV-positive. Only 18/144 (12.5%) had microbiological confirmation of TB (Table 2).

Although more than 80% of the children were treated successfully, 19 (13.2%) died, 13 (68.4%) of whom were aged <2 years (Table 3). Most of the children lost to follow-up (3/4) were aged ⩾5 years. Although the difference was not significant, HIV-negative children tend to achieve higher treatment success than HIV-positive children (85.1% vs. 75.0%, $P = 0.14$), whereas twice as many HIV-infected as non-infected children died (18.8% vs. 9.6%, $P = 0.11$). Children without or with mild malnutrition had lower treatment success than those with moderate to severe malnutrition (73.5% vs. 87.1%, $P = 0.04$), which was mainly due to the higher mortality in the former group (22.4% vs. 7.5%, $P = 0.01$).

Of the children who were treated successfully, more than 93.2% (109/117) maintained success after

Table 3 End-of-treatment and post anti-tuberculosis treatment outcomes by age category, HIV status and nutritional status

		Age group, years				HIV status			Weight for height		
Outcomes	Overall ($n = 144$) *n* (%)	<2 ($n = 64$) *n* (%)	⩾2–5 ($n = 42$) *n* (%)	⩾5 ($n = 38$) *n* (%)	*P* value	Positive ($n = 48$) *n* (%)	Negative ($n = 94$) *n* (%)	*P* value	⩽ −2SD ($n = 49$) *n* (%)	> −2SD ($n = 93$) *n* (%)	*P* value
End of treatment					0.08			0.14			0.04
Success	117 (81.3)	48 (75.0)	37 (88.1)	32 (84.2)		36 (75.0)	80 (85.1)		36 (73.5)	81 (87.1)	
Failure	3 (2.1)	2 (3.1)	0	1 (2.6)		2 (4.2)	1 (1.1)		0	3 (3.2)	
Death	19 (13.2)	13 (20.3)	4 (9.5)	2 (5.3)		9 (18.8)	9 (9.6)		11 (22.4)	7 (7.5)	
Lost to follow-up	4 (2.8)	1 (1.6)	0	3 (7.9)		0	4 (4.3)		2 (4.1)	1 (1.1)	
Transfer out	1 (0.7)	0	1 (2.4)	0		1 (2.1)	0		0	1 (1.1)	
Post treatment					0.44			0.11			0.09
Success	109 (75.7)	44 (68.8)	35 (83.3)	30 (79.0)		33 (68.8)	76 (80.8)		36 (73.5)	72 (77.5)	
Relapse	0	0	0	0		0	0		0	0	
Death	21 (14.6)	14 (21.9)	4 (9.5)	3 (7.9)		10 (20.8)	10 (10.6)		11 (14.5)	9 (9.7)	
Lost to follow-up	10 (6.9)	4 (6.3)	2 (4.8)	4 (10.5)		2 (4.2)	7 (7.4)		2 (4.1)	9 (9.7)	
Withdrawal*	2 (1.4)	1 (1.6)	1 (2.4)	0		1 (2.1)	1 (1.1)		0	2 (2.1)	
Other†	2 (1.4)	1 (1.6)	0	1 (2.6)		2 (4.2)	0		0	1 (1.1)	

*1 patient transferred out during treatment and there was 1 voluntary withdrawal during post-treatment follow-up.
†2 patients who were started on retreatment due to failure and were still on treatment at the end of the study follow-up.
HIV = human immunodeficiency virus; SD = standard deviation.

Table 4 Predictors of unsuccessful TB treatment outcome (death + failure + loss to follow-up)

Factors	Unsuccessful outcome *n* (%)	OR (95%CI)	aOR (95%CI)
Sex			
Male	81 (18.5)	1	1
Female	63 (17.5)	0.93 (0.39–2.20)	0.72 (0.27–1.97)
Age, years			
<2	64 (25)	0.56 (0.14–2.16)	0.48 (0.11–2.15)
2–5	42 (9.5)	1.78 (0.63–5.03)	1.16 (0.33–4.10)
⩾5	38 (15.8)	1	1
Received antibiotics within last 2 weeks			
No	61 (9.8)	1	
Yes	81 (24.7)	3.00 (1.12–8.03)	3.78 (1.05–13.58)
Weight for height			
> −1 SD	59 (6.8)	1	1
⩽ −2 SD	35 (22.9)	4.07 (1.13–14.73)	3.83 (0.96–15.23)
< −2 to < −3 SD	18 (5.6)	0.81 (0.08–7.73)	0.33 (0.31–3.44)
< −3 SD	30 (36.7)	7.96 (2.26–28.00)	3.48 (0.85–14.41)
HIV status			
Negative	94 (14.9)	1	
Positive, on ART	21 (19.1)	1.34 (0.39–4.59)	
Positive, not on ART	27 (26.0)	2.00 (0.71–5.61)	
CXR suggestive of TB			
No	31 (9.7)	1	
Yes	113 (20.4)	2.38 (0.67–8.54)	
TB laboratory confirmation			
No	126 (19.8)	0.24 (0.30–1.87)	
Yes	18 (5.6)	1	

TB = tuberculosis; OR = odds ratio; CI = confidence interval; SD = standard deviation; HIV = human immunodeficiency virus; ART = antiretroviral therapy; CXR = chest X-ray.

6 months. However, there were two more deaths, one of whom was a treatment failure and was being retreated but died after enucleation due to right-sided retinoblastoma, and the other died due to unknown febrile illness at home. None of these children had microbiologically confirmed TB.

After adjusting for age and sex, children who had received a non-specific antibiotic trial were more likely to have an unsuccessful outcome (Table 4). When the same analysis was repeated using death as dependent variable, only severe malnutrition was independently associated with death (adjusted odds

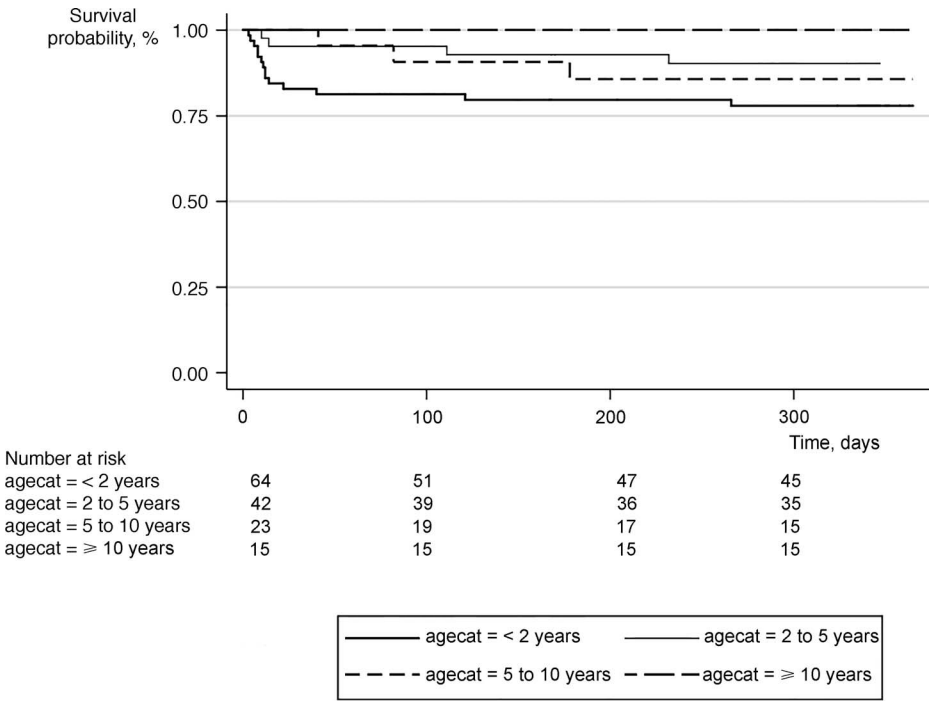

Figure 1 Survival analysis by age group.

Table 5 Frequency of each SAE among all children, by age group and HIV status

Type of SAE	All ($n = 144$) n (%)	Age group, years <2 ($n = 64$) n (%)	Age group, years ⩾2–5 ($n = 42$) n (%)	Age group, years ⩾5 ($n = 38$) n (%)	HIV status Positive ($n = 48$) n (%)	HIV status Negative ($n = 96$) n (%)
Respiratory infections	16 (11.1)	9 (14.1)	4 (9.5)	3 (7.9)	8 (16.7)	8 (8.3)
Malnutrition	4 (2.8)	4 (6.2)	0	0	2 (4.2)	2 (2.1)
Deteriorating unknown cause	3 (2.1)	1 (1.6)	1 (2.4)	1 (2.6)	1 (2.1)	2 (2.1)
Malaria	3 (2.1)	0	3 (7.1)	0	1 (2.1)	2 (2.1)
Increased ALT	1 (0.7)	0	1 (2.4)	0	1 (2.1)	0
Gastroenteritis	1 (0.7)	1 (1.6)	0	0	0	1 (1.0)
Haemoptysis	1 (0.7)	0	1 (2.4)	0	0	1 (1.0)
Demyelinating neuropathy	1 (0.7)	0	0	1 (2.6)	1 (2.1)	0
Hypovolemic shock	1 (0.7)	1 (1.6)	0	0	1 (2.1)	0
Weight loss	1 (0.7)	0	0	1 (2.6)	1 (2.1)	0
Viral encephalopathy	1 (0.7)	1 (1.6)	0	0	0	1 (1.0)
Retinoblastoma	1 (0.7)	1 (1.6)	0	0	0	1 (1.0)

SAE = serious adverse event; HIV = human immunodeficiency virus; ALT = alanine aminotransferase.

ratio [aOR] 8.76, 95% confidence interval [CI] 1.59–48.25). However, there was an interaction between age and malnutrition: severely malnourished children aged <2 years had a higher case fatality rate (9/32, 28.1%) than non-severely malnourished children aged <2 years (3/89, 3.4%, $P < 0.01$); there was no difference among children aged >2 years (1/14, 7.1% vs. 5/250, 2.3%, $P = 0.21$).

As shown on the Kaplan-Meier curve, most deaths occurred during the first weeks of treatment, and median time to death was 12 days (IQR 8–39) (Figure 1).

Tolerability and treatment adherence

Thirty (20.8%) children experienced 34 serious adverse events (SAEs); more than half of these were aged <2 years (Table 5). Respiratory tract infections and malnutrition were the most frequent causes of SAE, especially in children aged <2 years (14.1% and 6.2% of the children). These two SAEs were also more common among HIV-infected children (16.7% and 4.2%) than among non-HIV-infected children (8.3% and 2.1%). Of the 34 SAEs, only two, increased ALT and peripheral neuropathy (5.9%), may have been related to anti-tuberculosis treatment. Anti-tuberculosis treatment was well tolerated, as shown in Figure 2, which depicts ALT evolution throughout the intensive phase of treatment. Only one child experienced ALT levels more than 5 times the ULN, which normalised without the need for treatment interruption.

Treatment adherence was above 85% on all visits (Figure 3), despite the high pill burden: the median was three pills (IQR 2–5), but this could go up to eight in children receiving EMB.

DISCUSSION

This observation cohort conducted in programmatic conditions shows very good tolerability of the increased anti-tuberculosis drug dosage in children. Despite the high proportion of children who experience SAEs (20.8%), only one child had a major increase in ALT (5 × ULN) at week 8 that was likely to be drug-related and which resolved without treatment interruption. These results confirm reports

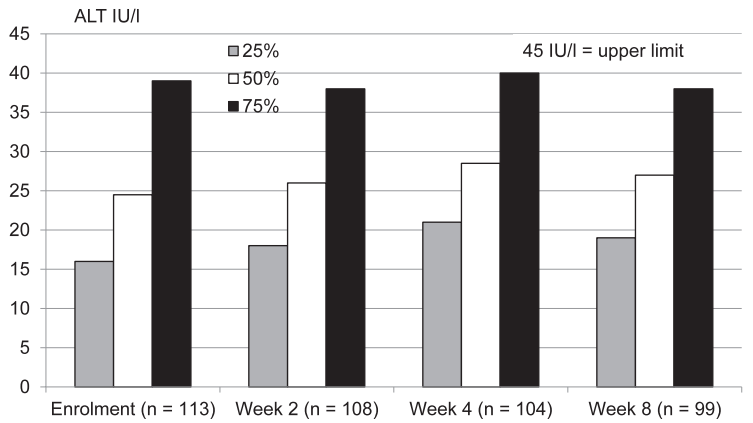

Figure 2 Median ALT values with interquartile ranges at treatment initiation and after 2, 4 and 8 weeks of anti-tuberculosis treatment. ALT = alanine aminotransferase transferase; IU = international unit.

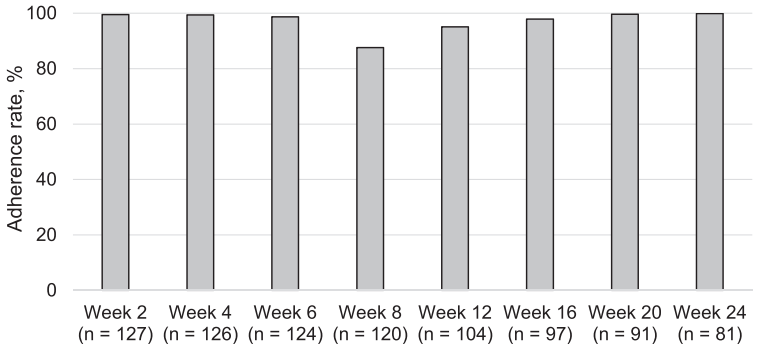

Figure 3 Treatment adherence rate calculated at each study visit during anti-tuberculosis treatment among children with treatment adherence assessed at study visit.

of the low incidence of anti-tuberculosis drug-induced hepatotoxicity in children when the previous dose recommendations were used, and are reassuring regarding the risk of hepatotoxicity when the dose is increased.[6] Mild increases in ALT levels are not uncommon during the first 2 months of anti-tuberculosis treatment, but it still remains unclear if this rise is a predictor of severe drug-induced hepatotoxicity. The ALT increases can also be due to granulomatous hepatitis caused by TB or paradoxical reaction to treatment.[6,11] The other SAE that seemed to be drug-related was a case of severe peripheral neuropathy, probably induced by INH despite co-administration of pyridoxine. Other SAEs were due to respiratory infections, other diseases (1 retinoblastoma, 1 viral encephalopathy and 3 malaria) or could be related to the presence of comorbities or TB disease severity. Half (53%) occurred in children aged <2 years.

Although our study yielded a high treatment success of 81.3%, it did not reach the WHO target of 85%, and mortality was also high (13.2%). However, these results are consistent with previous reports in sub-Saharan African countries, and can still be considered good given the context of high HIV prevalence (33.8%) and moderate-to-severe malnutrition (33.8%) in our study population.[12–16] Of note, these previous studies used the former anti-tuberculosis drug mg/kg dosing. Only three failures and no relapses were identified during the 6 months of post-treatment follow-up. The main reason for not reaching the 85% treatment success target was the high case fatality rate, especially among young children, as previously reported.[15–17] Contrary to previous reports in sub-Saharan Africa, we did not find a significant association with HIV infection, even when taking into account antiretroviral treatment prescription.[13,14,16] Mortality was particularly high among young children with severe malnutrition. The association between malnutrition and death is well known, as malnutrition affects cell-mediated immunity, the principle host defence against TB; in patients with TB, this leads to loss of appetite, nutrient and micronutrient malabsorption and altered metabolism, leading to wasting.[18–20]

Despite the high pill burden and the relative complexity of the treatment, requiring two different FDCs to be able to reach the targeted mg/kg dosage, there was good treatment adherence. Only three were lost to follow-up, and adherence remained above 85% throughout treatment. FDCs for anti-tuberculosis treatment have recognised advantages over the use of individual drugs, such as the limited risk of selective intake of some of the drugs and reduction of the pill burden.[21] To allow currently available FDCs to achieve the desirable bactericidal serum levels in children without increasing the pill burden more than required (there was supported evidence that a minimal INH dosage of 7 mg/kg could provide adequate levels in almost all children, even among those aged <2 years and/or those who are INH fast acetylators), the WHO increased the dosage of INH in 2014 from 10–15 mg/kg to 7–15 mg/kg, and adjusted the dosing charts.[3,22–24] In addition, the recent development of new child-friendly paediatric FDCs (RMP 75, INH 50, PZA 150 and RMP 75, INH 50) is expected to improve the uptake of the recent WHO drug dosing recommendations.[3,23]

The study had several limitations: 1) the high proportion of laboratory-unconfirmed TB (87.5%) in our cohort may call into question the reliability of TB diagnosis in our study setting. However, the number of children started on anti-tuberculosis treatment, 144 (37%), is in line with reports from previous studies (30–50%) in similar settings,[25–28] and highlights once again the extreme difficulty of diagnosing TB in young children; 2) the small numbers limited the analysis of predictors of unsuccessful outcomes; 3) given the high proportion of SAEs due to low respiratory tract infection, and in the absence of autopsy, it was very difficult to know how many deaths were due to TB; 4) the number lost to follow-up at the end of treatment may have led to an overestimation of maintained success; 5) treatment adherence may have been overestimated because DOT was administered by the parent or guardian

and assessed by counting the remaining pills and checking adherence cards; and 6) there was an absence of systematic ophthalmic examination during follow-up, with a potential underreporting of optic neuritis due to the use of EMB.

In conclusion, our study confirms the good tolerability of the WHO-recommended increased anti-tuberculosis drug dosage in children, especially with regard to the risk of hepatotoxicity, and the high rates of adherence to the new formulas. Programmatic implementation of this recommendation is expected to increase with access to the new child-friendly paediatric FDCs. Nevertheless, we would like to highlight the critical issue of high case fatality rates among young children with severe malnutrition. Case management of these highly vulnerable children deserves greater attention, and particularly earlier detection of TB.

Acknowledgements

The authors thank the study participants; the Epicentre (Paris, France) nurses and laboratory personnel who participated in data collection; Médecins Sans Frontières, which funded the research; and the Mbarara University (Mbarara, Uganda) and hospital colleagues who supported the study through constructive advice and patient referral to the study; and J Kiwanuka, for his technical expertise in the design of the study.

Conflicts of interest: none declared.

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RÉSUMÉ

CADRE : En 2010, l'Organisation mondiale de la Santé a modifié le dosage pédiatrique des médicaments antituberculeux en augmentant la rifampicine à 15 mg/kg, l'isoniazide à 10 mg/kg et le pyrazinamide à 35 mg/kg. Nous présentons les résultats, la tolérance et l'observance du traitement avec ces nouvelles recommandations.

MÉTHODES : Cohorte prospective d'enfants traités pour une tuberculose en Ouganda avec 12 mois de suivi incluant la surveillance du niveau d'alanine aminotransferase (ALT). La prise du traitement était observée.

RÉSULTATS : Sur 144 enfants traités, 81 étaient de sexe masculine (56,3%), 106 (73,6%) avaient moins de 5 ans, 30 (22%) présentaient une malnutrition modérée à sévère et 48 (33,3%) étaient infectés par le virus de l'immunodéficience humaine. Les résultats de traitement étaient comme suit : 117 (81,3%) succès, 3 (2,1%) échecs, 4 (2,8%) abandons, 19 (13,2%) décès et 1 (0,7%) transfert. Il n'y a pas eu de récidive. La malnutrition sévère (risque relative ajusté 8,76 ; IC95% 1,59–48,25) était le seul facteur prédictif de décès. Deux événements adverses sérieux ont été attribués au traitement : une augmentation des ALT et un cas de neuropathie périphérique. La médiane des ALT étaient de 24 (écart interquartile [IQR] 16–39), 26 (IQR 18–38), 28 (IQR 21–40) et 27 (IQR 19–38) unités internationales/l à l'inclusion et après 2, 4 et 8 semaines de suivi. Le taux d'observance du traitement était à plus de 85% à chacune des visites.

CONCLUSION : Nous confirmons la bonne tolérance et observance du traitement avec les nouvelles recommandations. L'augmentation du risque de décès chez les enfants avec une malnutrition sévère nécessite une attention particulière.

RESUMEN

MARCO DE REFERENCIA: En el 2010, la Organización Mundial de la Salud revisó la posología pediátrica del tratamiento de la tuberculosis con un aumento de la rifampicina a 15 mg/kg, de la isoniazida a 10 mg/kg y de la pirazinamida a 35 mg/kg. En el presente estudio se evaluaron los desenlaces terapéuticos, la seguridad toxicológica y el cumplimiento terapéutico en niños tratados con las nuevas recomendaciones.

MÉTODOS: Se inició el tratamiento antituberculoso en una cohorte prospectiva de niños en Uganda y se practicó un seguimiento durante 12 meses, que comportó la determinación de la alanina-transaminasa (ALT). La administración del tratamiento fue de tipo observado.

RESULTADOS: De los 144 niños tratados, 81 eran de sexo masculino (56,3%), 106 eran menores de 5 años de edad (73,6%), 30 presentaban malnutrición de moderada a grave (22%) y 48 sufrían infección por el virus de la inmunodeficiencia humana (33,3%). Los siguientes fueron los desenlaces terapéuticos observados: 117 éxitos (81,3%), 3 fracasos (2,1%), 4 abandonos (2,8%), 19 muertes (13,2%) y 1 transferencia a otro centro (0,7%). No se observaron recaídas. El único factor pronóstico de mortalidad fue la malnutrición grave (cociente de riesgos ajustado 8,76; IC95% 1,59–48,25). Se atribuyeron al tratamiento dos reacciones adversas graves, a saber: un aumento de la ALT y una neuropatía periférica. Las medianas de la concentración de ALT fueron: al comienzo, 24 unidades internacionales (UI)/l (amplitud intercuartílica [IQR] 16–39); a las 2 semanas, 26 UI/l (IQR 18–38); a las 4 semanas, 28 UI/l (IQR 21–40); y a las 8 semanas, 27 UI/l (IQR 19–38). El cumplimiento terapéutico fue superior al 85% en todas las consultas.

CONCLUSIÓN: Los resultados del presente estudio confirman la buena tolerabilidad y la observancia terapéutica con las nuevas recomendaciones de tratamiento. Es preciso prestar atención al aumento del riesgo de un desenlace fatal en los niños con malnutrición grave.