TITLE PAGE

Title: Adherence to Childhood Tuberculosis Treatment in Mozambique

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SUMMARY

Background: There is limited literature regarding adherence rates for the treatment of TB in children. We aimed to describe TB treatment outcomes and adherence as well as to evaluate associated factors to poor adherence in Mozambican children.

Methods: This is a sub-study of a community TB incidence study among children <3years of age... Incomplete adherence included the sum of lost to follow-up cases plus those with a delay of >3 weeks to treatment completion.

Results: Fifty TB treatments were assessed. Forty-four (88.0%) patients completed treatment, 2(4.0%) died during treatment and 4(8.0%) were lost to follow up.Incomplete adherence was observed in 31.3%(15/48) of cases and was associated with malnutrition or history of a migrant mother.

Conclusion: Although treatment outcome is overall good, there is still a significant proportion of incomplete adherence. Further larger paediatric TB cohorts and qualitative approaches are needed to assess and confirm potential factors for non-adherence

TEXT

BACKGROUND:

According to studies performed in the smear positive adult population, tuberculosis (TB) therapy requires a high adherence rate of over 90% to facilitate cure(1,2). In adults, poor adherence has proven to increase the risk of morbidity, mortality and drug resistance at an individual and population level (3,4). Incomplete adherence to long term therapy is one of the greatest challenges towards implementing the World Health Organization (WHO) End TB strategy, especially in Africa where the treatment success rate (81% in 2013) has not reached the Stop TB 90% target (5,6).

Children could account for 20-40% of all TB cases in high burden settings (7). Young children are at highest risk of developing TB disease as well as rapid disease progression and mortality if diagnosis and treatment are delayed(8). Adherence to TB treatment in children is complex and is influenced by patient nd healthcare system factors, among others(9). It depends on the understanding and motivation of caretakers, who frequently have limited awareness of the disease (3,10).

Studies on therapy for latent TB infection in children have shown low completion rates ranging from 44-78%(11). Treatment outcomes for pediatric TB disease in the African region have also shown high rates of poor outcomes (deaths, treatment failures and lost to follow-up) ranging from 10-19%(12–17). However, there are few studies which report adherence and treatment duration(11). In addition, there is very limited data on

associated barriers to anti-TB treatment in young children (11,18–20). Therefore, the aim of this study was to describe the treatment outcomes and adherence to TB treatment and to evaluate factors associated with poor adherence in Mozambican children aged less than 3 years of age.

METHODOLOGY

Settings

This study was conducted at the Manhiça District, Southern Mozambique, where the Manhiça Health Research Center runs a health and demographic surveillance system (HDSS) (21) . This setting has a high incidence of both TB and HIV with an estimated community-based incidence rate of TB among children < 3yr of 470/100,000 person-years(22–24) and an estimated case detection rate of 41%(25). TB treatment is offered free at no cost to the patient at the health units and pediatric fixed-dose combinations are available following WHO 2010 dose recommendations(26). At the time of the study implementation, pediatric TB treatment for smear negative pulmonary cases and non-severe forms of extrapulmonary TB, included an intensive phase of 2 months of daily Isoniazid, Rifampicin and Pyrazinamide, followed by 4 months of daily Isoniazid and Rifampicin , with weekly and monthly clinical checks and drug collection respectively (27). All TB cases co-infected with HIV are managed in an integrated manner with the provision of cotrimoxazole preventive therapy and anti-retroviral therapy at TB clinics.

Study Design

This is a sub-study of a larger prospective cohort study that assessed the minimum community incidence of TB among young children (<3 years of age) over a 1-year period (October 2011- 2012), whose detailed methodology and findings have previously been published(22). Briefly, all presumptive TB cases were evaluated through physical and radiological examination, HIV and tuberculin skin testing, as well as smear microscopy and culture of both induced sputum and gastric aspirate samples. All participants had at least one follow up visit arranged within six months of recruitment. All TB cases were registered with the National Tuberculosis Program (NTP) and managed according to established national clinical guidelines. Treatment was always initiated at the Manhiça District Hospital (MDH) and patients 'care was then transferred to their corresponding peripheral health unit, if applicable. For the purpose of this analysis, TB cases were defined as any case registered to initiate TB treatment at the NTP during the study period. In the incidence study, TB cases followed the National Institute of Health (NIH) case definition for childhood TB (28) (See Box1).

Data Collection and analysis

Demographic and clinical data were obtained at the initial visit, and follow-up clinical data were recorded at every subsequent visit. Other socio-demographic data was obtained through the HDSS 2012 data. Information on the WHO treatment category, follow up visits, treatment outcome and adherence were retrospectively extracted from registers of

the NTP into a structured data collection tool. Delays in treatment completion were calculated based on the registered date of treatment initiation and treatment completion.

Proportions were compared using the Fisher´s exact chi-squared test. Prevalence ratio (PR) and its 95% confidence intervals (CI) were calculated from poison regression with robust standard errors to measure the strength of the association between clinical and demographic factors and adherence categories. Programmatic data from the NTP at the MDH for other age groups during the same period was used for comparison. Statistical software for analysis was Stata 11.2 (StataCorp. 2013. Stata: Release 11, StataCorp LP, Statistical Software, College Station, TX).

Ethical considerations

This study was approved by the Mozambican National Bioethics Committee (Ref.15/CNBS/2010). Written informed consent was obtained from the parents/caregivers of all children.

RESULTS

Fifty children under the age of three years consented to participate and initiated TB treatment in the district of Manhiça **(Table 1)**. All were treated for drug susceptible TB, 9

cases were microbiologically confirmed on the basis of culture, although none of them was smear positive on microscopy for acid-fast bacilli. Of all children starting treatment, 26 (52.0%) were male and 24 (48.0%) were HIV-infected. Although patients were followed-up in ten different peripheral health care centers, over 64.0% of cases were managed by two single health centers, one of which was the MDH (30.0%).

All 50 cases had documented treatment outcomes: 44(88.0%) children successfully completed treatment, 2 (4.0%) died prior to treatment completion and 4 (8.0%) were lost to follow up (LTFU) . There were no treatment failures nor transferred cases. Among treatment success cases, 11 (25.0%) had a delay in treatment completion, 8 of which were males, over half HIV infected and one microbiologically confirmed TB case. Among the LTFU, 3 were males, all lived more than 2 km distance from the MDH, none fulfilled the study TB case definition and all were HIV-infected. Overall incomplete adherence (delayed plus LTFU) was reported in 31.3% (15 among the 48 patients who did not die) (**Table 2).** **Figure 1** shows the distribution of the number of days from treatment initiation to treatment completion. Eleven cases finished treatment before the expected date, 8 of them 1-2 days earlier. One patient had a 74-day delay in treatment completion.

Compared to other age groups registered at the MDH NTP during the same time period, we found a higher treatment success rate in children under 3 (88% versus 68,1% and 72,5% among patients aged 3-15 years and >15 years respectively). However, incomplete adherence was similar in all groups. Figure2 shows adherence results for these three age categories (final numbers exclude deaths) .

Being malnourished at enrollment and having a mother with a history of migration in the previous 2 years to TB diagnosis were shown to be potential risk factors for incomplete adherence (PR 2.9 ; 95%CI:1.4-6.1 and PR 2.9; 95%CI:1.4-6.0 respectively, p-value<0.05) **(Table 2).**

DISCUSSION

Data on adherence to TB treatment in children is scarce. To our knowledge, this is the first study describing the profile and treatment outcomes among pediatric TB cases in Mozambique and one of the few reporting adherence and treatment outcomes in a well characterized cohort of young children. Although the overall treatment success rate(88%) was close to the 90% Stop TB target (6) there were still a significant proportion of pediatric TB cases with incomplete adherence (31.3%). Being malnourished and having a migrant mother were potential risk factors for incomplete adherence.

We have previously reported a treatment success rate of 67.3% among children <3 years in Manhiça during 2006-2010 (25). The significant improvement observed in the current study compared to the previous years can be due to several reasons. Firstly, to the substantial recent decrease in mortality as improved TB/HIV care and treatment services are available at the health facilities. The proportion of patients who die during TB treatment has decreased from 17% during 2006-2010 to 4% in this study(29). Secondly,

168 improved outcomes may be due to a slight decrease in the number of LTFU (from 9.6% in
169 2006-2010 to 8%) that could be influenced by the fact of being included in the
170 epidemiological incidence study. Although the study had active follow up visits which
171 could have positively influenced treatment adherence, the univariate analysis did not
172 show an association.

173 The treatment success rate reported in this study is similar to the 87% estimated by WHO
174 for all new cases in 2012 for Mozambique (5). It decreased, however, in other age groups
175 during the same period, reaching 68,1% and 72,5% in patients aged 3-15 year and >15
176 year, respectively. While other authors have also found higher success rates with younger
177 ages (11), Hailu et al. found that being above 5 years of age was a predictor of treatment
178 success (18).

179 Comparing TB treatment adherence results among different studies is difficult due to the
180 large variations in the definitions of adherence found in the literature, particularly for
181 childhood TB (11,19,17,30–33). As stated by Chang et al, it seems reasonable to consider
182 LTFU and incomplete adherence as part of the same problem, with different levels of
183 severity (34). Thus, for the purpose of this study we used a definition of incomplete
184 adherence that includes LTFU plus delayed completion. Despite the differences in the
185 definitions, the results in this study are similar to other pediatric reports from high burden
186 countries (17,32,33,35). Unpublished results from a recent meta-analysis show a
187 treatment success rate of 81% with 3% mortality, with large variations among the studies
188 included (12).

We have identified several factors associated with incomplete adherence, many of them were expected and have been previously cited by other authors as predictors of poor outcome(13,36,37). Evidence of chronic or acute malnutrition at diagnosis was associated with incomplete adherence. Several studies have also reported poor TB outcomes among malnourished children (36,37) but in this study malnutrition was associated both with LTFU and death as well as with a delay in treatment completion. This suggests that beyond the deleterious immunological impact of malnutrition on TB progression, other aspects such as tolerance to drugs or, more importantly, the social context, have an impact on adherence and outcome. The importance of the caregiver child relationship has been shown to impact overall child survival and thus, the history of migration of the mother seems to impact treatment adherence and outcomes(38). Malnutrition was significantly associated with a history of a migrant mother, hospitalization at the time of diagnosis, and TB case definition, and thus the specific impact of these other variables on adherence is difficult to interpret.

HIV co-infection is also a well-known risk factor for incomplete adherence in adults (2,39–42), and children(19,36),partly due to the increased pill burden and secondary effects. Because of the high treatment compliance rate (90%) required to facilitate cure and reduce the risk of rapid disease progression in children, the poor adherence observed among HIV-TB co-infected cases is cause for concern as it could lead to increased mortality. Given the inherent difficulties in diagnosing pediatric TB, caregivers may sometimes reflect their uncertainty in the diagnosis by not fulfilling the treatment recommendations. This may be the underlying cause of the poorer adherence observed among cases not fulfilling the study TB definition. Moreover, TB diagnostic algorithms do not perform well among HIV co-infected children(28). Given the HIV co-infection rate observed

among confirmed and non-confirmed TB cases (10% and 51%, respectively), this may have played a role in hesitance of diagnosis and adherence to treatment. The gender difference observed in the current study was not statistically significant and needs to be further evaluated with larger sample sizes. Some adult studies have also noted a higher rate of incomplete adherence among males although this association needs to be further evaluated and may not be necessarily extrapolated to the pediatric population (42–45).

There are several limitations to this study. Firstly, the small sample size of the cohort limits the ability to reach statistical significance for several potential associations (no multivariable logistic regression analysis was possible). Secondly, the analysis of adherence was performed using data measured indirectly with a retrospective design. In addition, the fact that most children starting treatment were part of a research study could have had a potential positive influence on adherence, although the study was focusing on case detection. Moreover, we did not register other common factors reported to influence adherence such as major side effects, who the main caregiver for the child was or the exact phase of the treatment where the main delay occurred. Furthermore, the results may be biased given that TB under-reporting is more common in severe forms of the disease which die before treatment initiation. Finally, we did not capture common system failures such as drug stock rupture or health personnel absenteeism, which might lead to non-patient originated poor adherence.

In conclusion, although pediatric treatment outcome is overall good, there is still a significant proportion of incomplete adherence cases. This study setting may have represented an improved health system scenario, so the true program performance may show worse indicators. Reinforcing the importance of timely treatment completion should remain a high priority. Successful treatment of pediatric TB requires the commitment and involvement of the corresponding caregiver. Further larger pediatric TB cohorts and qualitative research are needed to assess and eventually address potential risk factors for non-adherence.

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LEGENDS TO FIGURES

Figure 1. Duration of treatment among patients with treatment completion

Definitions: Days of delay in treatment completion were calculated based on a standard treatment duration of 180 days for retreatment cases, final day was adjusted)

Number of days in X axis are not in scale .

Figure 2. Treatment and adherence outcomes among different age groups (2011-2012)

This figure shows treatment outcome (treatment success vs. LTFU [lost to follow-up]) among patients who did not die and adherence results (full vs. incomplete adherence) among all age groups initiating TB treatment at the National Tuberculosis Program of the Manhiça Health Center (n= 867 to ≥ 15 yr; n= 82 to < 15 – 3 yr; n=56 to < 3yr). Excluded from this analysis are: dead and transferred cases as well as TB cases with number of treatment days missing.

TABLES

BOX1: Relevant study definitions

TB case: Any child registered to initiate TB treatment at the NTP during the study period.
Study TB case: Includes microbiologically confirmed plus probable cases (adapted from the standardized NIH case definition for childhood TB (28), full details on the classification are described elsewhere(22)). Confirmed TB case: compatible symptoms plus a positive culture with *Mycobacterium Tuberculosis*. Probable TB case: fulfilling the following 3 criteria: (1) compatible symptoms unresolved at last clinical follow up visit (prior to any TB treatment initiation) (2) compatible chest radiograph: ≥1 of the following radiographic abnormalities: airway compression, lymphadenopathy, opacification, nodular picture, effusion, cavities, spondylitis or Ghon focus (46) (3) at least one of the following: TB exposure, positive TST (induration >5 mm for HIV or malnourished children and >10 mm for the rest of participants) or positive response to TB treatment.
HIV infection: positive antibody test in children>18 months (Determine, Abbott Laboratories and confirmed with Unigold, Trinity Biotech); or positive HIV PCR in those <18 months; or a strong clinical suspicion with positive antibody test in the absence of a PCR result.
Treatment outcomes for drug susceptible TB patients (5,47): **Treatment success:** the sum of patients: 1. Cured: A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion) AND 2. Treatment completed: A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

Treatment failed: A TB patient whose sputum smear or culture is positive at month 5 or later during treatment. **Died:** A TB patient who dies for any reason before starting or during the course of treatment. **Lost to follow up:** A TB patient whose treatment was interrupted for 2 consecutive months or more. **Not evaluated:** A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Adherence categories were defined as: **Incomplete adherence.** The sum of the following two exclusive categories and calculated over those patients who did not die: 1. **Lost to follow-up** (patients whose treatment was interrupted for 2 consecutive months or more) AND 2. **Delayed completion (**patients with a delay of 3 or more weeksbeyond the expected date (calculated as 6 months after treatment initiation)) **Full adherence**. All treatment success cases with no delay in treatment completion.

434 * NIH: National Institute of Health; NTP: National TB Program; TB: Tuberculosis; TST:
435 tuberculin skin test
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438 **Table 1.- Clinical and Socio-demographic characteristics of TB cases <3yr at the time of**
439 **TB diagnosis**

Table 1A. Clinical and sociodemographic characteristics of TB cases <3yr at the time of TB diagnosis (N=50)

Clnical		**n**	**(%)**
Sex (male)	male	26	(52)
	female	24	(48)
Age in months, (Median [IQR])		19.8	[14.6-26.1]
Age at diagnosis (months)			
	< 12	10	(20)
	12 - 24	23	(46)
	> 24	17	(34)
BCG Scar [†]	*present*	43	(87.8)
	absent	6	(12.2)
HIV-coinfected	yes	24	(48)
	no	26	(52)
TST [α]	positive	21	(43.8)
	negative	27	(56.2)
Hospitalizations in previous year to TB diagnosis	yes	20	(40)
	no	30	(60)
Nº outpatient consultations in previous year to TB diagnosis	<10	36	(72.0)
	≥10	14	(28)
Study TB cases definition	*Confirmed*	9	(18)
	Probable	25	(50)
	Possible	13	(26)
	MTB infection/TB unlikely	3	(6)
TB Compatible CXR	yes	18	(36)
	no	32	(64)
Symptoms			
Cough >2 weeks	yes	14	(28)
	no	36	(72)
Fever>2 weeks	yes	6	(12)
	no	44	(88)
Wheeze	yes	3	(6)
	no	47	(94)
Chronic or Acute Malnutrition	yes	11	(22)
	no	39	(78)
Adenopathy	yes	1	(2)
	no	49	(98)
Contact of Pulmonary TB case (documented or reported)	yes	14	(28)
	no	36	(72)
Hospitalized at time of enrolment [β]	yes	9	(18)
	no	41	(82)
Number of follow-up visits to the cohort study during course of TB treatment			
	< 2	11	(22)
	≥ 2	39	(78)

Denominator is n=50 except for α (n=48) and † (n=49)

BCG= Bacille Calmette Guerin; HIV= human immunodeficiency virus; IQR= interquartilic range; CXR= Chest X ray; TST= Tuberculine Skin Test;
Definitions: Positive TST was defined as an induration >5 mm for HIV or malnourished children and >10 mm for the rest of participants. HIV infection was defined as positive antibody test in children >18 months (Determine, Abbott Laboratories and confirmed with Unigold, Trinity Biotech); or positive HIV polymerase chain reaction in those <18 months; or a strong clinical suspicion with positive antibody test in the absence of a polymerase chain reaction result. CXR were classified as compatible if presented ≥1 of the following radiographic abnormalities: airway compression, lymphadenopathy, opacification, nodular picture, effusion, cavities, spondylitis or Ghon focus.

Sociodemographic	**n**	**(%)**
Distance to Peripheral Health Care Centers in Km (Median [IQR])	1,68	[1.18-2.50]
Distance to Peripheral Health Care Centers		
< 1	30	(60)
2-5	15	(30)
> 5	5	(10)
Distance to Manhiça Health Center Km (Median [IQR])	12,46	[3.9-17.4]
Distance to Manhiça Health Center		
< 5km	16	(32)
≥ 5 km	34	(68)
Nº of people living in the house (median [IQR])	6	[4-9]
Nº of people living in the house		
< 6	21	(42)
≥ 6	29	(58)
Number of children <15y living in the house‡		
1 a 3	35	(80)
≥ 4	9	(20)
Children's birth order ‡		
1th o 2nd	30	(68.2)
≥ 3rd	14	(31.8)
Children <15 yr at home ‡		
1 a 4	26	(59.1)
≥ 5	18	(40.9)
Orphan (death of mother)	1	(2.0)
Orphan (death of father)	4	(8)
Death in the household in the previous year	14	(28)
Migration of the mother in previous 2 yr	8	(16)
Migration of the father in previous 2 yr	16	(32.0)
Migration in the household member	20	(40)
SES†		
Poorest	15	(30)
Less Poor	20	(40)

Denominator is n=50 except for ‡ (n=44) and † (n=35)
IQR= interquartilic range ; SES: Socio Economic Status
Definitions: A household asset-based wealth index was used to categorize the household socio-economic status (SES) into 5 wealth quintiles. The 2 lowest quintiles were grouped as "poorest" and the remaining 3 quintiles were renamed "less poor"

446 **Table 2. Univariate analysis of predictor factors for incomplete adherence.**

	Full Adherence†		Incomplete Adherence‡			
	n	**(%)**	**n**	**(%)**	**PR (95%CI)**	***p* value**
Total	**33**	**(68.8)**	**15**	**(31.3)**		
*Sex **						
Female	19	(82.6)	4	(17.4)	Reference	
Male	14	(56)	11	(44)	2.5 (0.9-6.9)	0.065
HIV-coinfected						
No	20	(80.0)	5	(20.0)	Reference	
Yes	13	(56.6)	10	(43.5)	1.9 (0.8-4.4)	0.080
Study TB case definition						
Possible-Unlikely	7	(50.0)	7	(50.0)	Reference	
Confirmed-Probable	26	(76.5)	8	(23.5)	0.5 (0.1-1.1)	0.072
*Nº outpatient consultations in previous year **						
0 - 9	21	(61.8)	13	(38.2)	Reference	
≥ 10	12	(85.7)	2	(14.3)	0.4 (0.1-1.5)	0.171
*Hospitalized at time of enrolment **						
No	30	(75.0)	10	(25.0)	Reference	
Yes	3	(37.5)	5	(62.5)	2.5 (1.2-5.4)	0.088
*Symptom at enrolment: malnutrition**						
No	30	(76.9)	9	(23.1)	Reference	
Yes	3	(33.3)	6	(66.7)	2.9 (1.4-6.1)	0.018
*Migration of the mother in previous 2 yr **						
No	31	(75.6)	10	(24.4)	Reference	
Yes	2	(28.6)	5	(71.4)	2.9 (1.4-6.0)	0.024
*Death in the household in the previous year **						
No	22	(61.1)	14	(38.9)	Reference	
Yes	11	(91.7)	1	(8.3)	0.2 (0.1-1.5)	0.073
Nº of people living in the house						
< 6	11	(55.0)	9	(45.0)	Reference	
≥ 6	22	(78.6)	6	(21.4)	0.5 (0.2-1.1)	0.082
Distance to the nearest Health Care Center						
< 2 km	23	(76.7)	7	(23.3)	Reference	
≥ 2 km	10	(55.6)	8	(44.4)	1.9 (0.8-4.4)	0.127

CI= confidence intervals; PR= prevalence ratio; HIV= human immunodeficiency virus; TB= tuberculosis

† =Full adherence: treatment completed on time with full adherence
‡ = Incomplete adjerence includes a) delayed treatment completion plus b) treatment non completion;

p values obtained through chi-squared test or Fisher´s exact test (when applicable)*

Only those variables with p-values < 0.2 are shown
A significant association was found between the variable malnutrition and hospitalization (p=0.02, migration of the mother (p=0.001) and TB case definition (P=0.002)

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