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Research Article

Determinants of Adherence to Anti-Tuberculosis Treatment among Paediatric Patients in A Kenyan Tertiary Referral Hospital

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Background: Non-adherence to anti-tuberculosis treatment increases the risk for development of drug resistance, TB recurrence and mortality.

Objectives: This study was designed to determine the rate and predictors of adherence to anti-tuberculosis treatment in paediatric TB patients.

Methodology: This was a cross sectional study carried out at the Kenyatta National Hospital TB clinic. Caregivers of children were interviewed and the patients requested to provide a urine sample which was tested for the presence of isoniazid to verify adherence to medication.

Results: Adherence to anti-TB medications measured by urine testing and self-report, was 91.8% and 44.9% respectively. Patients who administered medication at 24 hour intervals were more likely to adhere to medication (OR = 7.70 [1.85 - 33.33], 95% CI). There was no significant association between adherence and regimen complexity factors, relationship between health care provider and caregiver or the pattern of healthcare delivery. The results suggested a slight agreement between self-reported adherence and the isoniazid urine test (κ= 0.20).

Conclusion: Adherence to anti-TB medication in this population of children was relatively high, and could be attributed to the structures that have been put in place to ensure that TB patients have access to treatment services at the community level.

Keywords: Adherence, tuberculosis in children, anti-tuberculosis treatment, isoniazid

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1. Introduction

Tuberculosis (TB) is a major cause of morbidity and mortality in Kenya. The country is ranked 13th among the 22 high burden TB countries in the world, and the 5th highest country in TB burden in Africa (WHO, 2013).

According to the World Health Organization's Global TB control report, Kenya had approximately 120,000 new TB cases in 2012. Children formed about 3 % of the new cases of smear-positive pulmonary tuberculosis in Kenya for the same year (WHO, 2013).

The therapeutic regimens recommended by WHO have been shown to be highly effective for both preventing and treating TB, but poor adherence to anti-TB medication is major barrier to its global goal (WHO, 2003). Diverse factors have been associated with adherence to TB treatment such as patient characteristics, the relationship between healthcare provider and the patient, the treatment regimen and the health care setting. Factors that constitute barriers to adherence to TB treatment can further be classified as economic factors, patient related factors, regimen complexity, supportive relationship between the health

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care provider and the patient and the pattern of health care delivery (WHO, 2003).

Adherence to childhood tuberculosis treatment requires the active participation of the caregiver in the management and co-operation between the caregiver or patient and the health care provider. TB therapy requires a high compliance rate of over 90% to facilitate cure (Awofeso, 2008). This study was designed to determine the rate and predictors of adherence to anti-tuberculosis treatment in paediatric TB patients.

2. Methods

2.1 Study site and Study Design

This was a hospital based cross sectional study which was carried out at the Kenyatta National Hospital (KNH) TB clinic to determine the rate and predictors of adherence to anti-tuberculosis treatment in paediatric TB patients. Kenyatta National Hospital (KNH) located in Nairobi, Kenya, is the largest national referral hospital in Kenya. KNH has a TB clinic that offers care and anti-tuberculosis treatment to adults and children with Mycobacterium tuberculosis disease.

Two methods were used to elucidate determinants of adherence: (i) A questionnaire based face-to-face interview using patient self-report; and (ii) Detection of isonicotinyl hydrazide (INH) and its metabolites in urine using INH urine strips.

Patients were defined as non-adherent to medication if they had missed one or more doses of anti-tuberculosis drugs at some point in their course of treatment. Those who tested negative with the INH urine test strips were also termed non-adherent.

2.2 Inclusion and Exclusion criteria

Both male and female patients were eligible for inclusion in the study if they were children aged 0-15 years and had been receiving anti-tuberculosis treatment for at least two months in the out-patient clinic. Patients were excluded if they were over 15 years of age, enrolled in clinical trials, or were in-patients.

2.3 Sampling and Patient Recruitment

A sample size of 45 patients was calculated to be sufficient to detect adherence rate of 97 % in patients on anti-tuberculosis treatment at a two sided level of significance of 5 % and 95 % level of confidence. All children aged 0-15 years, diagnosed with TB, and who were on treatment with anti-TB drugs and had been on treatment for more than two months were eligible for the study. Caregivers of the children who met the inclusion criteria were interviewed consecutively as they were seen at the KNH TB clinic.

2.4 Data Collection

Adherence was assessed using two tools of measurement. Self-reported adherence was measured using a standardized questionnaire administered in face-to-face interviews with the caregivers of the children on TB treatment from May to July 2010 at the TB clinic.

The presence of INH and its metabolites in urine was tested using BBL Taxo® INH test strips (Taxo INH test trips) using the manufacturer's protocol. Briefly, during the visit to the clinic, fresh untimed urine specimens were collected in sterile leak resistant polypropylene containers without preservatives. A positive control for the test was prepared by placing a Taxo INH test control disc in 2 ml of deionized water in a test tube, and shaken three times over a 15 minute period to assure extraction of the INH into the water. INH test strip was dipped in urine specimen for 15-30 minutes followed by observations. The same test was performed using the Taxo INH test control which had been prepared in the test tube parallel with the urine sample. INH and its metabolites are detectable in the specimen within 24 hours after the last intake of isoniazid.

The results obtained from the urine test were used as a measure of adherence whereby a patient with a positive test result was termed as adherent and a patient with a negative test result was termed as non-adherent.

2.5 Outcomes

The primary outcome variable was adherence. Adherence was defined as the consistency and accuracy with which a patient followed the prescribed regimen. Patients were considered non-adherent to medication if they had missed one or more doses of anti-tuberculosis drugs at some point in their course of treatment. Those who tested negative with the INH urine test strips were also termed non-adherent.

2.6 Statistical analysis

Qualitative variables were described in frequencies or percentages and compared between groups using the Chi square ($\chi 2$) test. The independent sample t-test was used to analyze the continuous variables, such as age of child and duration of treatment with anti-TB drugs. Pearson's Chi-square test was used to test for the strength of association between categorical variables. Multivariate logistic regression model was developed for variables previously tested individually and confirmed to relate significantly with non-adherence to treatment at bivariate analysis.

Level of significance was set at 0.05 ($p<0.05$) with a 95% confidence interval. Cohen's kappa (κ) was used to assess the strength of agreement between self-reported adherence and isoniazid urine test. $\kappa < 0$ indicated poor agreement; <0.2=slight agreement; 0.21-0.4=fair agreement; 0.4-0.6=moderate agreement; 0.6-0.8=substantial agreement and 0.8-1.0=almost perfect agreement (Landis and Koch, 1977). Statistical analyses were performed using SPSS software, version 13 (SPSS Inc. Chicago, USA).

2.7 Ethical considerations

Permission to carry out the study was granted by the Kenyatta National Hospital and University of Nairobi Ethics and Research Review Committee (KNH/UoN ERC, Approval Reference No. **P8/01/2010**). Consent from the caregivers of the children who met the inclusion

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criteria was sought and consent forms were signed by the caregivers before inclusion into the study.

Table 1: Baseline characteristics of the study participants

Characteristics	N (%)
Gender	
Male	22 (44.9)
Female	27 (55.1)
Age	
<5 years	28 (57.1)
≥5 years	21 (42.9)
Weight	
<20 Kg	32 (65.3)
≥20 Kg	17 (34.7)
Caregiver characteristics	
Education	
Tertiary	11 (22.4)
Secondary	23 (46.9)
Primary	15 (30.6)
Marital status	
Currently married	38 (77.6)
Not married	11 (22.4)
Family Average Monthly Income (KSh)	
>20,000	13 (26.5)
10,001 - 20,000	13 (26.5)
5,000 - 10,000	11 (22.4)
<5,000	8 (16.3)
Residence	
Rural	16 (32.7)
Urban	33 (67.3)

3. Results

3.1 Characteristics of the study population

A total of 55 patients who met the inclusion criteria were recruited to participate in the study, however 6 patients were unable to provide a urine sample and were excluded. 49 patients and their caregivers were therefore included in this study. Socio-demographic characteristics of the study participants are presented in **Table 1**. The median age of the patients who participated in this study was 3.5 years. The inter-quartile ranges were 2 to 7.8 years. Majority of the patients were below 5 years, 28 (57.1%) and the rest were 5years and above, 21(42.9%). Female patients accounted for 55.1% (n = 27) of the study participants while male patients accounted for 44.9% (n = 22).

A total of 13 (26.5%) of the care-givers had received primary school education. 23 (46.9%) had received secondary school education and 11 (22.4%) had received tertiary education (either diploma or degree courses). A small number of the participants 2 (4.1%) had not received any formal education. Most of the care-givers (77.6%) who participated in the study were married.

The average monthly income of the families ranged from less than KSH 5,000 to more than KSH 20,000. A total of 8 (16.3%) earned less than 5,000 shillings a month and 11 (22.4%) earned 5,000-10,000 shillings a month. The income ranges 10,000-20,000 KSH a month and over 20,000 KSH a month were each earned by 13 (26.5%) families respectively. 8.2% either declined to disclose how much they earned or were unemployed and being supported by relatives and therefore did not have this information.

3.2 Adherence to anti-tuberculosis treatment measured by urine tests

The rate of adherence to TB medication was determined using the Taxo INH urine test strips. Urine isoniazid (INH) was detected in 45 (91.8%) of the 49 patients who took part in the study (**Table 2**).

3.3 Self-reported adherence to anti-tuberculosis treatment

Adherence to anti-TB medication throughout the course of treatment was determined using self-report from the care-givers. 44.9% of the patients had missed taking their medication at some point during the treatment period.

3.4 Relationship between adherence to TB treatment and baseline characteristics

There was no significant association between the baseline characteristics and adherence to TB medication (P> 0.05). However, adherence to TB medication was 1.21 [95% CI= 0.39-3.78] times more in female patients aged < 5 years (57.1%) compared to those aged ≥ 5 years (52.4%). Adherence was 1.45 times more in females (59.3%) compared to males (50.0%) and 1.64 times more in those weighing less than 20kgs (59.4%) compared to those weighing 20 Kg or more (47.1%).

However, there was a statistically significant association between marital status and adherence to TB medication (P= 0.046). Patients with married caregivers (63.2%) were 4.57 times more likely to adhere to TB treatment compared to those whose caregivers were not married (27.3%).

There was no statistically significant relationship between level of education, family's average monthly income, area of residence and adherence to TB medication.

No association was found between the patient/caregiver factors including knowledge on TB and community's perception towards TB patients, and adherence to TB medication. However, patients whose caregivers had adequate knowledge on TB were 2.04

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times more likely to adhere to medication compared to those who had inadequate knowledge.

With regard to timing of administration of medication, there was a statistically significant association between administering medication at 24 hour intervals and adherence to TB medication (P = 0.003). Patients whose caregivers administered medication at 24 hour intervals were 7.70 times more likely to adhere to medication compared to those who did not administer at 24 hour intervals.

There was no statistically significant association between adherence to TB medication and duration of treatment, administration of drug with regards to meals, child's refusal to take medicine, experience of side effects, administration of medication in the morning or evening and employing means of remembering to administer medication.

Table 2: Adherence to anti-tuberculosis treatment measured by urine tests INH urine test (n=49)

Characteristics	INH positive, N (%) (Adherent)	INH negative, N (%) (Non-adherent)	P value
Gender			
Male	21 (95.5)	1 (4.5)	0.740
Female	24 (88.8)	3 (1.2)	
Age group			
<5 years	25 (89.2)	3 (10.8)	0.517
≥5 years	20 (95.2)	1 (4.8)	
Weight			
<20 Kg	29 (90.6)	3 (9.4)	0.409
≥20 Kg	16 (94.1)	1 (5.9)	

Table 3: Relationship between adherence to anti-TB medication and regimen complexity factors

Medication characteristics	Adherent (n=27) n (%)	Not adherent (n=22) n (%)	OR [95% CI]	P value
Number of tablets patient is taking				
One	11 (61.1)	7 (38.9)	1.47 [0.45, 4.8]	0.519
More than one	16 (51.6)	15 (48.4)	1 [0.45, 4.8]	
Type of drug formulation				
Dispersible tablets	16 (59.3)	11 (40.7)	1.45 [0.47, 4.52]	0.517
Tablet	11 (50)	11 (50)	1 [0.47, 4.52]	
Problems when administering				
Did not experience	19 (61.3)	12 (38.7)	1.98 [0.61, 6.43]	0.253
Experienced problems	8 (44.4)	10 (55.6)	1 [0.47, 4.52]	

Table 4: Relationship of marital status and timing of medicine administration with adherence

Predictors	Bivariate analysis				Multivariate analysis	
	Adherent N (%)	Non-adherent N (%)	OR (95% CI)	P value	Adj. OR (95% CI)	P value
Marital status: Currently married	24 (63.2)	14 (36.8)	4.57 (1.04 – 20.11)	0.046	3.06 (0.61 – 15.37)	0.173
Medicine administration: 24 hrs. interval	24 (68.6)	11 (31.4)	8.00 (1.85 – 34.54)	0.003	6.47 (1.44 – 29.10)	0.015

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3.5 Relationship between adherence to anti-TB medication and regimen complexity

There was no statistically significant relationship between adherence to TB medication and regimen complexity factors. However patients who were taking one tablet were 1.47 times more likely to adhere than those who were taking more than one tablet. Patients who were taking the dispersible tablets were also 1.45 times more likely to adhere than those who were taking the tablets. The patients whose caregivers did not experience any problems when administering the medication were twice as likely to adhere to medication compared to those who experienced problems when administering the medication (**Table 3**).

Various healthcare delivery pattern factors were also explored to determine whether they influenced adherence to TB medication. They included waiting time at the clinic, availability of drugs at the clinic, suitability of clinic operating days and time of attending the clinic.

There was no significant association between the pattern of healthcare delivery and adherence to TB medication. Adherence was relatively the same among those who found the waiting time at the clinic to be long and those who did not find the waiting time long (OR= 1.01). Those who found the clinic operation days not suitable were 1.90 times more likely to adhere to TB medication, compared to those who found the days suitable.

Binary logistic regression was used to model adherence to TB treatment using two candidate predictive factors, namely: marital status and medicine administration at 24 hour dosing intervals.

These factors were significantly associated with adherence to TB treatment at bivariate analysis. Upon adjustment in multivariate analysis, the resulting model is as shown in **Table 4**.

Adjusting for interval of administration of medicine, marital status emerged not significantly associated with adherence to TB treatment (P=0.173). However, a child raised by a married couple was 3.06 times more likely to adhere to treatment compared to one raised by a single caregiver.

Upon adjusting for marital status, administration of medicine at 24 hours interval was significantly associated with adherence to TB treatment (P=0.015). A child given medication at 24 hour interval was 6.47 times more likely to adhere to treatment compared to one given at a shorter interval.

3.6 Agreement of measurement methods

The results suggest that there is a slight agreement (κ = 0.20) between self-reported adherence and isoniazid urine test. Although isoniazid urine test reliably predicts non-adherence in patients who have not recently ingested anti-TB medicines, it is less reliant in detecting patients who are non-adherent outside 24 hr preceding the test.

4. Discussion

This study was conducted in children receiving anti-tuberculosis treatment primarily to determine adherence to treatment in an urban setting in Kenya's largest referral hospital.

The adherence to anti-tuberculosis treatment in this population was high at 91.8% from INH urine tests. This finding is comparable to studies in adult populations in Kenya. Raguenaud et al (2008) found an adherence of 96.5% using an INH urine test in Kibera, a low socio-economic setting in Nairobi, while Nackers et al (2012) estimated an adherence of 92.5 - 97.6 % in adult TB patients in Homabay county, Kenya.

Studies in Uganda have however reported adherence of 72- 80 % (Amuha et al., 2009; Lugada et al., 2002; Meissner P. et al., 2002; Pekovic et al., 1998).

Age, sex and weight of the patients had no statistically significant association with adherence to medication. These results were consistent with the findings in other studies which similarly concluded that age and sex of the patient had no significant association with adherence (Amuha et al., 2009; Caylà et al., 2009; McDonnell et al., 2001; Naing et al., 2001; Nuwaha, 1999; Wares et al., 2003; Xu et al., 2009). This could be attributed to the fact that in paediatric patients, adherence is highly dependent on the caregivers of the children therefore the baseline characteristics of the patients may fail to reflect their association with patient's adherence to medication.

Marital status of the caregiver showed a statistically significant association with adherence to medication (P = 0.046) in the bivariate analysis. However when adjusted for in the multi-variate analysis, it was not statistically significant. The trend that emerged showed that a child whose caregiver was married was 3.06 times more likely to adhere to medication compared to one whose caregivers was not married. However, other studies did not find a significant association between marital status and adherence to medication (Amuha et al., 2009; McDonnell et al., 2001; Nuwaha, 1999; Wares et al., 2003). It is possible that marriage offers good structural support which promotes adherence.

Although the level of education did not have a statistically significant relationship with adherence, the rate of adherence seemed to increase with the level of education. Secondary or tertiary education was 1.49 or twice as likely to predict adherence compared to primary education. The findings were in line with those of a Chinese study (Xu et al., 2009) and an Egyptian study (Gad et al., 1997) which also found no significant association between the level of education and adherence to medication. The trend observed could be attributed to a better understanding of the nature of disease, the treatment requirements and the consequences of poor adherence in those with higher levels of education.

The family's average monthly income had no statistically significant relationship with adherence to medication. This was consistent with the findings of a Malaysian study (Nuwaha, 1999). However in a study carried out in China (Xu et al., 2009), the average income of the patient was significantly associated with adherence. This was because TB treatment had many

additional costs which where unaffordable to low income earners. In Kenya, TB treatment is free and therefore readily accessible to all. This could explain why there was no significant relationship between the average family income and adherence to medication.

There was no significant association between the rate of adherence and the area of residence of the patients. This was in line with the findings in a Ugandan study (Amuha et al., 2009) which also found no significant association. However, other studies (Jaiswal et al., 2003; Meissner P. et al., 2002; Naing et al., 2001; Wares et al., 2003) found the area of residence to significantly affect adherence since the distance to the healthcare facility depended on the patient's area of residence. In these studies, patients who lived far from the health facility had significantly higher odds of being non-adherent. In Kenya, TB treatment is delivered through 2,318 healthcare facilities which are spread out and are located at the community level. This may play a major role in improving adherence to anti-TB medication.

The caregiver's knowledge on TB had no significant association with adherence to medication. The findings were similar to the findings of Naing et al (2001). However, other studies found a significant association (Amuha et al., 2009; Kaona et al., 2004; Wares et al., 2003). In a Ugandan study (Amuha et al., 2009), knowledge of TB was associated with adherence at bivariate analysis however there was no significant association at multivariate analysis. In a study carried out in Eastern Nepal (Wares et al., 2003), majority of the non-adherents were not well informed about their disease, effects and treatment. In our study, 95.9% of the caregivers reported that they knew about TB. Most of them were able to describe it but the extent of the description varied from poor to very well. All of the caregivers knew that TB is curable and most of them quoted an advertisement in Kiswahili which states that "TB ina tiba" which translates into "TB is curable."

Most of the caregivers (95.9%) understood the importance of completing TB treatment. The national TB program by Division of Leprosy, TB and lung diseases (DLTLD) has laid emphasis on patient education at the TB clinics to ensure that they are informed abou the disease and the nature of treatment. The advertisements on the curability of TB seemed to have reached many people and had improved the perception people had of TB, and could explain why the findings on the association between knowledge on TB and adherence were not significant.

Disclosure to family and friends about the TB status of the child had no significant association with adherence. Presence of friends or relatives interfering with drug administration and how people in the patient's area of residence related to TB patients also had no significant association with adherence. These factors were picked as indicators for stigmatization in TB patients therefore stigmatization was not significantly associated with adherence to medication. However in a study that was carried out in China (Xu et al., 2009), there was a lot of stigma attached to TB and this lead to patients hiding their diagnosis from others and defaulting on their medication. Failure to find a significant association between stigma and adherence to medication could be attributed to reduced stigmatization of TB patients in our study setting.

There was no statistically significant relationship between side-effects to medication and adherence to anti-TB medication. The findings were similar to those of a Ugandan study (Amuha et al., 2009) and a South African study (Szakacs et al., 2006). Other studies however found a significant association between the occurrence of side-effects or adverse reactions and adherence (Ngamvithayapong et al., 1997; Shukla et al., 2002; Wares et al., 2003; Xu et al., 2009). The findings could be attributed to the fact that the side-effects that were experienced were minor and the caregivers had come up with ways of managing them.

Medicine administration at 24 hour intervals had a statistically significant association with adherence to medication both at bivariate and multivariate analysis. Children whose caregivers had a specific time for administering medication were 6.47 times more likely to adhere to medication compared to those whose caregivers did not administer the medication at 24 hour intervals. Caregivers who had a specific time for administering medication were less likely to forget to administer the medication since they used alarm clocks and other people to remind them. Adherence to medication can be improved by advising all the caregivers to pick the most suitable time for them to administer medication and to employ various methods of reminding them that it is time to administer the medication.

There was no statistically significant association between the pill burden and adherence to medication. These findings support those of a Ugandan study (Amuha et al., 2009) with similar findings. The type of drug formulation had no significant association with adherence to medication. However a trend emerged which showed that those patients who were taking dispersible tablets were more likely to adhere than those who were taking tablets. This could be attributed to the fact that the dispersible tablets were easy to administer compared to the tablets. Some of the children who were receiving tablets experienced some difficulty in swallowing the tablets and this could have had an impact on adherence.

Study limitations

There was only slight agreement between the two study instruments, with adherence to anti-TB medications determined as 91.8 % by urine testing vs 44.9 % by self-reported adherence. Although the INH urine test is an objective measure of adherence to anti-TB treatment, it has the limitation that it only measures a relatively recent ingestion of medicines. As such it may overestimate adherence where patients have a propensity to take their medicines before visiting the clinic. The methodology is also constrained by the costs of the tests, and is therefore challenging to implement in public health programmes of resource poor countries.

5. Conclusion

This study provides empirical evidence that adherence rate to anti-TB medication by paediatric patients is satisfactory. The high rate of adherence was probably

due to structures that have been put in place to ensure that TB patients have access to TB treatment services even at the community level.

Conflict of Interest declaration

The authors declare no conflict of interest

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