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ADHERENCE TO ISONAZID PREVENTIVE THERAPY AMONG HIV INFECTED CHILDREN AT AMPATH CLINIC IN MOI TEACHING AND REFERRAL HOSPITAL, ELDORET
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ADHERENCE TO ISONAZID PREVENTIVE THERAPY AMONG HIV INFECTED CHILDREN AT AMPATH CLINIC IN MOI TEACHING AND REFERRAL HOSPITAL, ELDORET

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ABSTRACT

***Background*: Tuberculosis is the most common cause of infectious disease related to mortality worldwide. Children infected with Human Immunodeficiency virus are at risk of developing tuberculosis hence Isoniazid preventive therapy is recommended to reduce tuberculosis burden. Isoniazid preventive therapy is new and non-adherence may lead to isoniazid resistance and treatment failure.**

***Objective*: To determine level of adherence and describe factors associated with adherence to isoniazid preventive therapy among human immunodeficiency virus infected children.**

***Design*: Prospective study.**

***Setting*: AMPATH of Moi Teaching and Referral hospital**

***Participants*: Two hundred and fifty one children were consecutively sampled. Interventions: Participants were followed up monthly until completion of isoniazid preventive therapy.**

***Outcome measures*: Adherence was assessed using validated AMPATH adherence tool.**

Results: Median age was 11.0 (IQR: 8.0, 13.0) years, 129(51.4%) were female, 229(92%) were virally suppressed. Caregiver median age was 40years (IQR 35.0, 44.0), 215 (87.7%) were female, 135 (53.8%) had primary level of education. Adherence to isoniazid preventive therapy was 80.8%. Two hundred and thirty-six (94%) completed 6months of isoniazid preventive therapy. Good viral suppression OR 25.68 (95%CI: 6.22, 105.96) and regular follow up OR 30.86 (95% CI: 8.57, 111.07) for month 6, were associated with good adherence while children whose caregivers had secondary/tertiary level of education were non-adherent AOR: 0.36(95%CI:0.14,0.95).

Conclusion: **Adherence to isoniazid preventive therapy was good with 8 in 10 being adherent. Completion rate was 94%. Participants with good viral suppression, regular follow up were associated with good adherence while participants whose caregiver had secondary level of education were non-adherent.**

INTRODUCTION

Tuberculosis is one of the causes of morbidity and mortality among people living with Human Immunodeficiency Virus. Mycobacterium tuberculosis is the causative agent and humans are the only reservoir. TB may develop in certain instances as of age or defects in cell mediated immune response for instance HIV infection, malnutrition, prolonged steroid use and administration of chemotherapy. HIV infected children have a lifelong risk of developing tuberculosis (TB).HIV infection causes an increase in the risk of progression of tuberculosis infection and reactivation of latent tuberculosis infection by 5-15% annually.(Final-TB-Prevalence-Survey-Report,n.d.).Tuberculosis progress more rapidly to severe disease with high mortality while TB/HIV co-infection causes more rapid progression of HIV disease.

Isoniazid preventive therapy is a key public health intervention for prevention of tuberculosis among people living with Human Immunodeficiency Virus and has been recommended by world health organization as part of comprehensive HIV/AIDS care strategy. In Kenya, ministry of health recommends Isoniazid preventive therapy for six months for all eligible people living with Human Immunodeficiency Virus. However IPT implementation in Kenya has been slow since its official roll out in March 2015.(IPT_for_PLHIV_Operational_Guidelines_Sept_2015. n.d.)

Isoniazid preventive therapy is provided using intensified case findings (ICF) tool for high-risk children who have no signs and symptoms of tuberculosis disease. The categories who receive isoniazid preventive therapy includes all HIV infected children and all children under 5 years with contact with persons with sputum positive. Isoniazid preventive therapy should be given at a dose of 10mg/kg for duration of six months. Adherence is the extent to which the patient's history of therapeutic drug-taking coincides with the prescribed treatment. The significance of adherence to treatment is important in optimizing the patient's response to treatment. Non-adherence may lead to treatment failure, waste of medications, disease progression, increase use of medical resources and development of drug resistance(Jimmy & Jose, 2011). The World Health Organization proposes that adherence is affected by the following factors, health care system or provider-patient relationship factors, disease and treatment factors, patient related factors, Socio-economic factors.(Alsaddig, Pharm, & Pharm, 2014). In a qualitative study looking at the barriers to the treatment of childhood tuberculosis in Peru, barriers included poor adherence to IPT, dosing errors and provider concern that IPT generates isoniazid resistance. (Chiang et al., 2017). Mwangi et al in a hospital based study in Kenya reported adherence level of 82.4% and completion rate to be 88% and the reason cited for non-completion were pill burden and health care

provider instigating due to poor adherence(Mwangi, 2016). Previous studies done in Eastern province, Kenya showed 91.7% completion rate 0.7% loss to follow up and 0.3% developed adverse reactions while 3% developed TB.(Masini, Sitienei, & Weyeinga, 2013).

METHODOLOGY

Study Design

Prospective cohort, hospital based study was conducted at module four pediatric HIV clinics and Adolescent Rafiki Centre at the AMPATH clinic in Moi Teaching and Referral Hospital (MTRH).The study population was HIV infected children aged 14 years and below initiated on isoniazid preventive therapy during the study period.

Sample Size

Fisher's formula was used to calculate the sample size

$$N_0 = \left(\frac{Z^2 p(1-p)}{e^2} \right)$$

$$= \frac{(1.96)^2 \times 0.82 \times 0.18}{(0.05)^2}$$

$$= 226$$

$Z^2 = 1.96$ is the quintile of the standard normal distribution.

p = 0.82 is proportion adherent to IPT, e = 0.05 is the margin of error.

P is 82.4% proportion of patients who were adherent to IPT in 6 months. (Mwangi, 2016)

We anticipate a drop out of 10 % so in order to cushion against insufficient sample size we adjust for loss to follow up as follows;

$$\frac{\mathbf{N}_o}{\mathbf{1-r}} = \frac{\mathbf{226}}{\mathbf{0.90}} = 251,$$

Where r is the dropout rate.

Sampling Technique

Consecutive sampling technique was done and all HIV infected children initiated on IPT were included and we excluded severely ill participants initiated on IPT during the study period.

Data Collection, Entry, and Analysis

Data was collected using an interviewer administered structured questionnaire and entered into an electronic database.

Descriptive statistics were used to summarize continuous and categorical variables. Continuous variables were summarized using the median and the corresponding interquartile range (IQR). Categorical variables were summarized using frequencies and the corresponding percentages. Factors associated with child adherence were assessed using logistic regression model for binary outcomes. The odds ratios (OR) and the corresponding 95% confidence intervals (95% CI) were reported.

Ethical Consideration

Approval to carry out the study was sought from the MTRH and Moi University Institutional Research and Ethics Committee (IREC), and AMPATH.

RESULTS

There were 251 children and caregivers recruited.

Table 1

Child clinical characteristics at enrollment

Characteristic	**N**	**Median (IQR) or n (%)**
Age (years), Median (IQR)	251	11.0 (8.0, 13.0)
Range (Min. – Max.)		2.0 – 14.0
≤ 5 Years		37 (14.7%)
5-10 Years		85 (33.9%)
> 10 Years		129 (51.4%)
Sex, n (%)		
Female	251	129 (51.4%)
Male		122 (48.6%)
INH dose (mg), n (%)		
100 mg		4 (1.6%)
200 mg	251	43 (17.1%)
300 mg		204 (81.3%)
Pyridoxine administered, n (%)		
No	251	20 (8.0%)
Yes		231 (92.0%)
Pyridoxine administration appropriate for age/weight, n (%)		
No	231	0 (0.0%)
Yes		231 (100.0%)
WHO clinical stage, n (%)		
I		103 (41.0%)
II	251	64 (25.5%)
III		72 (28.7%)
IV		12 (4.8%)
Viral load (log base 10), Median (IQR)	251	
Range (Min. – Max.)		22(8.0%)
VLS (VL<1000)	251	229 (92.0%)
ART regimen, n (%)		
First line	251	200 (80.0%)
Second line		51 (20.0%)

IQR – Inter quartile range, N – Number of children with characteristic measured and analyzed, VL – Viral load, VLS – Viral load suppression (VL<1000 copies per mL), ART – Antiretroviral therapy

Table 2

Caregiver characteristics

Characteristic	N	Median (IQR) or n (%)
Age (years), Median (IQR)	251	40.0 (35.0, 44.0)
Range (Min. – Max.)		19.0 – 74.0
Gender		
Female	251	215 (85.7%)
Male		36 (14.3%)
Marital status		
Single		34 (13.6%)
Separated		9 (3.6%)
Married	251	197 (78.5%)
Widow		10 (4.0%)
Widower		1 (0.4%)
Level of Education		
None		12 (4.8%)
Primary		135 (53.8%)
Secondary	251	78 (31.1%)
Tertiary		26 (10.4%)
Caregiver-child relationship		
Mother		174 (69.3%)
Father		30 (12.0%)
Grandfather		2 (0.8%)
Grandmother		9 (3.6%)
Sibling	251	7 (2.8%)
Guardian		6 (2.4%)
Aunt		17 (6.8%)
Uncle		6 (2.4%)
Caregiver aware of IPT		
No		39 (15.5%)
Yes	251	212 (84.5%)

N – Number of caregivers who responded or with the characteristic measured and analyzed

IPT Outcome

Up to 236(94.0%) of the children managed to complete the IPT and 10(4.0%) discontinued. Of those who discontinued, 4(40.0%) had adverse drug reactions and 6(60.0%) had poor adherence to treatment.

Adherence Score

Adherence scoring using AMPATH validated adherence tool. Good adherence implies a score of 0 out of 4, fair adherence implies a score of 1 or 2 out of 4, and poor adherence implies a score of 3 or 4 out of 4

The overall adherence scoring was 80.8%.

Table 3

Baseline factors associated with child adherence to IPT use

Characteristic	UOR (95% CI)	AOR (95% CI)
Child characteristics		
Age (Years)		
≤ 5 years	Reference	Reference
5 – 10 years	4.68 (1.23, 17.76)	3.68 (0.82, 16.46)
> 10 years	1.79 (0.54, 5.92)	1.31 (0.34, 5.00)
Gender		
Male	Reference	Reference
Female	1.55 (0.59, 4.06)	1.75 (0.65, 4.71)
VLS (VL<1000 cells per mL)		
No	Reference	Reference
Yes	24.90 (7.36, 84.26)	25.68 (6.22, 105.96)
Follow up time		
Month 1	Reference	Reference
Month 2	2.63 (1.35, 5.09)	2.54 (1.30, 4.97)
Month 3	4,61 (2.11, 10.07)	4.42 (2.01, 9.70)
Month 4	9.36 (3.77, 23.28)	8.99 (3.59, 22.51)
Month 5	24.29 (7.33, 80.57)	23.30 (7.05, 76.97)
Month 6	32.21 (8.96, 115.75)	30.86 (8.57, 111.07)
Caregiver education level		
None/Primary	Reference	Reference
Secondary/Tertiary	0.36 (0.14, 0.95)	0.37 (0.14, 1.00)

UOR – Unadjusted Odds Ratio, AOR: Adjusted Odds Ratio, CI – Confidence interval

The results indicate that a higher proportion of children aged 5 – 10 years were adherent compared to children aged five years or less, OR: 4.68 (95% CI: 1.23, 17.76). The data also show that a higher proportion of children aged above ten years were adherent compared to children aged five years or less though the difference was not statistically significant, OR: 1.79 (95% CI: 0.54, 5.92).

Children who were virally suppressed at baseline were more likely to be adherent to IPT use compared to those who were not virally suppressed, OR: 24.90 (95% CI: 7.36, 84.26).

Follow up time was strongly associated with adherence demonstrating an increasing proportion of children who were becoming adherent to IPT use over time, OR: 2.63 (95% CI: 1.35, 5.09) for month 2, 4.61 (95% CI: 2.11, 10.07) for month 3, 9.36 (95% CI: 3.77, 23.28) for month 4, 24.29 (95% CI: 7.33, 80.57) for month five and 32.21 (95% CI: 8.96, 115.75) compared to month 1.

Table 4

Association between caregiver characteristics and child adherence to IPT use

Characteristic	N	UOR (95% CI)
Caregiver characteristics		
Age (years)		
≤ 30		Reference
30 – 40	251	0.87 (0.21, 3.57)
> 40		1.53 (0.34, 6.92)
Gender		
Male	251	Reference
Female		2.13 (0.67, 6.81)
Married		
No (single, Separated, Widow, Widower)		Reference
Yes	251	1.08 (0.34, 3.39)
Education level		
None/Primary		Reference
Secondary/Tertiary	251	0.36 (0.14, 0.95)
Relationship with child		
*Other		Reference
Parent(Father/Mother)	251	0.41 (0.11, 1.60)

**Other = Grandfather, grandmother, Sibling, Aunt, Uncle, Neighbor, UOR – Unadjusted Odds Ratio, CI – Confidence interval, N – Number of caregivers who responded or with the characteristic measured and analyzed*

The caregiver age, gender, and marital status were not associated with child adherence to IPT use.

The children of the caregivers who had secondary or tertiary level of education were less likely to be adherent to IPT use compared to children whose caregivers had no formal education or had primary level or education only, OR: 0.36 (95% CI: 0.14, 0.95).

DISCUSSION

Completion rate of IPT

Majority of the children managed to complete the IPT with only 4.0% being discontinued. The high completion rate in this study was because most participants were virally suppressed, most being in WHO-HIV clinical stage I or II and caregiver awareness of IPT.

Masini et al in Eastern province of Kenya found high completion rate of 91.7 % among HIV infected children due to integration in HIV clinics with pre-existing patient retention mechanism.(Masini et al., 2013)

A prospective Study done in Nigeria on adherence to IPT among children in close contact adult PTB patient found that 49.6% of children initiated on IPT completed the six month of INH(Paul & Gabriel-Job, 2019).The difference from our study could be due to low age of participants{< 5 years} hence challenges in drug administration; care giver factors where they felt their children were not sick and tired of taking the drugs.

Adherence to IPT

The overall adherence rate to IPT was 80.8%. This study used AMPATH validated adherence tool and it has been shown to be working well in assessing ART adherence among HIV infected children(Vreeman et al., 2014).The increasing higher adherence rate was due to regular visits which constituted

guidance and counseling session on importance of adherence and reasons for the medications by the health care providers. The good level of adherence is explained by that most participants were virally suppressed which means most of these children are stable clinically as opposed to children with high viral load who are likely to have opportunistic infection with possibility of being on multiple medication hence low pill burden. We attribute the good adherence to the behavior habits of good ART adherence.

Similarly, a pilot study on Isoniazid preventive therapy in HIV-infected children on antiretroviral therapy whereby adherence was 97%. (Gray et al., 2014).The reason for high adherence rate was reported that most of the HIV infected children taking IPT already had excellent adherence to ART medication. A prospective descriptive study on adherence to IPT among children in close contact adult PTB patients, reported low adherence rate of 49.6%.(Paul & Gabriel-Job, 2019).The low adherence rate in this study was the caregivers felt that their children were not sick and the children were tired of medications.

Factors associated to adherence to IPT

The data showed higher proportion of children aged above five years were adherent compared to children aged five year and below. The reason for good adherence was due to disclosed HIV status and better understanding of reasons for IPT treatment. Similar to a randomized control trial in cape town south Africa, where better adherence was noted in children older than four years. (le Roux et al., 2009)

Participants with good viral load suppression at baseline were more likely to be adherent to IPT use compared to those who were not virally suppressed. Virally suppressed participants were stable clinically as opposed to children with high viral load who are likely to have opportunistic infection with possibility of being on multiple medications. Participants with good adherence to ART had undetectable viral load levels. Their behavior habits of good adherence to ART could explain the likelihood of being adherent to IPT.

Regular follow up time was strongly associated with good adherence demonstrating an increasing proportion of children who were becoming adherent to IPT use over time. The increasing monthly adherence rate was due to monthly adherence session by the health care providers who would encourage and educate participants on importance and benefits of good adherence to medications. The sessions featured encouragement and reinforcement of adherence hence positive impact on adherence.

In a study by Mwayuma et al, there were no factors (individual characteristics of index cases, households and or health facility characteristics) found to be significantly associated with IPT adherence. In the qualitative analysis, identified factors relating to parents/caregivers, disease, household and health-care providers as major themes determining IPT adherence (Mwayuma et al., 2019)

The caregiver age and gender was not associated with child adherence to IPT use. These findings were similar to a study done in Nairobi, Kenya on implementation of IPT among HIV infected children where the age of the caregiver was not statistically significant.(Mwangi, 2016)

Children under the caregivers who had secondary or tertiary level of education were more likely to be non-adherent. The reason that could explain the above finding is that caregiver with higher level of education

would seek other opinion before administering medication while the caregiver with primary level of education are more likely to follow health care provider instructions without doubt. These findings were similar to a study done in Nairobi, Kenya on implementation of IPT among HIV infected children where children whose caregiver had attained secondary school level of education were less likely to have IPT compared to those who had lower level of education.(Mwangi, 2016).The reason for similar findings could be due to similar study setting which are both referral facility.

Awareness of IPT was reported by 84.5% of the caregivers. The high rate of awareness of isoniazid preventive therapy was because most of the caregivers were either the father or the mother who had prior history of use of isoniazid as the primary caretaker. Similar to a mixed method study done in Rwanda on Adherence to isoniazid preventive therapy among child contacts where caregivers' knowledge about the benefit of IPT and beliefs about the threat of TB disease were reported as a facilitator of IPT adherence (Mwayuma et al., 2019).

CONCLUSIONS

Adherence to isoniazid preventive therapy among HIV infected children at AMPATH in MTRH was good with 8 in 10 being adherent and high completion rate with 9 in 10 being able to complete six months period of taking IPT.

Participants with good viral suppression and regular follow up were associated with good adherence while participants whose caregivers had secondary level of education were likely to be non-adherent.

RECOMMENDATIONS

Provision of isoniazid preventive therapy should be continued.

Further qualitative studies are needed to explore on reasons why human immunodeficiency virus infected children whose caregivers with secondary/tertiary level of education were non-adherent.

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