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ORIGINAL ARTICLE

ISONIAZID PREVENTIVE THERAPY UPTAKE AND COMPLETION AMONG HIV INFECTED CHILDREN IN TWO REFERRAL HOSPITALS, NORTHWEST ETHIOPIA

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ABSTRACT

Introduction: *Isoniazid prevention therapy alone can reduce the risk of tuberculosis in people with HIV regardless of CD4 count or antiretroviral treatment. In Ethiopia, there is scarcity of evidence on implementation of isoniazid prevention therapy and factors associated with its uptake.*

Objective*: The study aimed to assess isoniazid preventive therapy implementation and factors associated with isoniazid completion among human immunodeficiency virus infected children in Felege-Hiwot and Gondar University Referral Hospitals in Northwest Ethiopia.*

Methods: *A facility-based cross-sectional study using a combination of face-to-face interviews of caregivers/parents and retrieval of client records was conducted in May 2014. Trained nurses with experience in human immunodeficiency virus infection and tuberculosis care conducted the document review and interviews. Data were entered onto Epi Info version 3.5.4 for windows, cleaned and exported to Statistical Package for Social Sciences version 20.0 for windows for analysis.*

Results*: A total of 454 HIV infected children (51.8% females and 48.2% males) were studied. Nearly a third, 168 (37%),of children were provided isoniazid prevention therapy and 67.9% completed the full course. Isoniazid completion was associated with distance from hospital (p<0.005), explanation of the reasons to take isoniazid pills (p<0.001), thinking isoniazid may be dangerous to child's health (p<0.001), believing that the chance of getting sick from tuberculosis is high for the child (p<0.001), disclosure of human immunodeficiency virus infection status (p<0.04) and isoniazid preventive therapy disclosure status (p<0.001).*

Conclusions: *Uptake of isoniazid preventive therapy was low among human immunodeficiency virus infected children. In addition, isoniazid therapy completion was very low. The hospitals and Regional Health Bureau should avail isoniazid preventive therapy in the nearby health facilities and strengthen adequate counseling on the role of isoniazid preventive therapy for tuberculosis.*

Key words: *Tuberculosis; isoniazid preventive therapy; completion; children; Ethiopia.*

INTRODUCTION

Childhood tuberculosis (TB) is estimated to constitute between 9.6% and 11% out of all incident cases, the majority of which occur in high TB burden countries. Children can present with TB at any age, but the most common age is between one and four years (1)**.** A high TB and multidrug resistant (MDR) TB burden country, Ethiopia's TB prevalence including HIV infected is 572 cases per 1,000 population while its incidence is 359 cases per 1,000 population (2)**.**

In Ethiopian children, smear negative TB is the dominant type with a frequency of 56%-65% followed by extra pulmonary(24-45%) and smear positive TB (20%) (3,4). Persons infected with HIV are more likely to develop active TB disease, manifest with different clinical picture, and have higher mortality rates than persons without HIV(5-8). INH preventive therapy (IPT), intensified case finding for TB, and infection control are believed to reduce the burden of TB among people living with HIV and recommended to be implemented at all HIV services (5-9). Children living with HIV who do not have poor weight gain, fever or current cough, and a contact history with a TB case are eligible to receive IPT (8-10).

IPT can reduce the risk of TB in people with HIV regardless of CD4 count or antiretroviral treatment (ART). Taking a six-month course of IPT as directed reduces the risk of TB in people with HIV and latent TB by around 64%, and the risk of death by 26%. In high TB incidence areas, INH alone and combined with ART could reduce the risk of TB disease by 80 and 90%, respectively (11,12). Though IPT is safe and beneficial for most people, some of the problems linked to IPT include uncommon adverse effects such as neuropathy and hepatitis, and poor adherence (13,14).

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A study revealed that 19.3% of the surveyed physicians provided IPT and 34.5% of them did not do screening chest radiography for active TB mainly because their patients had no symptoms or signs of pulmonary TB, or due to the increased cost to their patients. The major reasons for not providing IPT were patient's poor adherence, fear of inducing INH-resistance, concern about side effects of INH, the need for prior chest X-rays, and feeling INH is not beneficial (15). In Addis Ababa, self-reported dose adherence within seven days recall period was 86.5%. Participants who developed IPT related adverse effects were 93% less likely to adhere to the prescribed doses (16). In Ethiopia, there is scarcity of evidence on implementation of IPT. There is also lack of studies evaluating IPT implementation in our settings. The present study was therefore conducted to assess the eligibility screening; INH completion and factors associated with INH completion among HIV infected children in two referral hospitals.

PATIENTS AND METHODS

***Study Design and Setting*:** A facility-based cross-sectional study among HIV infected children was conducted in May, 2014 at Gondar University Referral Hospital (GURH) and Felege-Hiwot (FHRH) Referral Hospital. The pediatric HIV care clinic of GURH serves more than 250 HIV infected children. FHRH is located in Bahir Dar city, and has a separate pediatric HIV clinic that offered HIV care.

Study Population: The source population for the study was all HIV infected children in Amhara Region while the study population was HIV infected children who were on chronic HIV care at FHRH and GURH. Children living with HIV and less than 15 years old were included the study. Children referred from other health facilities and those with incomplete follow-up were excluded.

Measurement: The primary outcome variable was INH completion while secondary outcome variables were adherence to IPT and proportion of tuberculosis. Explanatory variables were age, sex, family residence, education of caregiver, time taken to reach to hospital of the children and parents, and stage of HIV disease, duration of HIV infection, history of TB in the family, contact history with a TB patient, age at diagnosis of HIV infection, risk perception about TB, INH stock, information about benefits of INH, disclosure of IPT, and disclosure of ART status. Adherence was considered good if a child had $\geq$80% success in adhering to the treatment schedule and poor if the success was <80% (9). Completion of a course of IPT was considered complete if a full course of INH was taken in the last three years.

***Sample size calculation and sampling*:** The sample size was 454 children-parent pairs**.** This was calculated by the *Epi Info stat calc* program using the single population proportion formula and assuming one month IPT prevalence of adherence of 79.9% (16), 95% confidence level, margin of error of 4%, and a 15% non-response rate.

Data collection: A pre-tested structured questionnaire developed in English was used to collect data. A pre-test was conducted on 20 HIV infected children in Gondar Polyclinic and the questionnaire was reviewed accordingly. Data extraction formats were used to retrieve data from patients' charts on IPT, ART status and development of active TB. Data were collected by clinical nurses who received two days training on interview techniques and consent forms, and were familiarized with data collection tools. Investigators supervised the data collection process and completed questionnaires were checked for completeness and accuracy on daily basis.

Statistical analysis: Data were entered in to Epi Info version 3.5.4 software for windows, cleaned and exported to Statistical Package for Social Sciences (SPSS) version 20.0 for analysis. Descriptive statistics were computed to summarize the study data. Chi-square tests were computed to identify factors associated with INH completion. P-values less than 0.05 were considered statistically significant.

***Ethical Issues*:** The study was approved by the Institutional Review Board of Bahir Dar University and Amhara Region Health Bureau. Informed verbal consent was obtained from the caregivers who were the legal guardians. The questionnaires contained no personal identifiers; only unique ART numbers or medical record numbers were used. The data were kept locked in safe file cabinet.

RESULTS

***Socio-demographic characteristics*:** A total of 454 HIV infected children (51.8% females and 48.2% males) were studied. Nearly two-thirds (65.6%) were from GURH. The mean age was 82 ($\pm$63) months. More than half (58.4%) of them were 5 years of age and above. One-fifth (20.7%) of caregivers were unable to read and write and139 (44.5%) households were in the lowest or second income quintile (Table 1).

Table 1: Socio-demographic characteristics of HIV infected children and their caregivers, Northwest Ethiopia, May 2014

Characteristic	Number	Percent
Hospital		
Felege-Hiwot Referral Hospital	156	34.4
Gondar University Referral Hospital	298	65.6
Sex of child		
Male	219	48.2
Female	235	51.8
Age of child in months		
<6	18	4.0
6-11	78	17.2
12-23	64	14.1
24-35	2	0.4
36-47	11	2.4
48-59	16	3.5
>/=60	265	58.4
Education of Mother		
Unable to read and write	94	20.7
Read and write	48	10.6
Elementary	232	51.1
Secondary	66	14.5
College	14	3.1
Family Size		
<5	278	61.3
5-10	174	38.3
>10	2	0.4
Household Income Quintile		
Lowest	100	22.0
Second	93	20.5
Middle	57	12.6
Fourth	113	24.9
Highest	91	20.0

***Proportion of tuberculosis*:** Table 2 below summarizes the occurrence of tuberculosis. Eighty-five (18.7%) of the HIV infected children had active tuberculosis. The proportion of TB among children who took INH was 15.5% (95%CI: 10.7, 21.8) and it was 20.6% (95% CI: 16.3%, 25.7%) among children who did not receive INH. The hospital prevalence ratio of developing TB was 0.75 (i.e. children who took INH were 25% less likely to develop TB as compared to children who did not take INH) though this was not statistically significant (Table 2).

Eligibility assessment, uptake, and completion of isoniazid prevention therapy: The eligibility screening criteria used by the two hospitals for initiation of IPT were clinical examination and chest x-ray to rule out active TB, absence of cough or fever, no poor weight gain, and household contacts of an active TB case.

Clinicians explained the reasons for taking isoniazid preventive therapy to 128 children (76%), of which 168 were on IPT, 43(25.6%) from FHRH and 125 were from GURH (Table 3). A total of 168 children (37%) were provided IPT in the preceding three years. Adherence to IPT was good for 143 (86.1%) of the children. This was not assessed in 19 (11.3%) of the children. Two-thirds, 114 (67.9%), completed full IPT regimen (Table 3).

Table 2: Tuberculosis and Contributing Factors among HIV Infected children in two referral Hospitals, Northwest Ethiopia, May 2014

Character	Number of children	Percent
Anyone with cough in the household in the last three months		
No	394	86.8
Yes	60	13.2
Contact history with cases with tuberculosis		
No	300	66.1
Yes	154	33.9
Any illness history other than tuberculosis		
No	384	84.6
Yes	70	15.4
History of tuberculosis		
No	341	75.1
Yes	113	24.9
History of anti-tuberculosis treatment		
No	342	75.3
Yes	112	24.7
Adherence to antiretroviral therapy		
Good	364	80.2
Fair	5	1.1
Not assessed	85	18.7
Has active tuberculosis		
No	369	81.3
Yes	85	18.7

Table 3: Isoniazid Preventive Therapy Eligibility Assessment, Uptake and Completion among HIV Infected Children in two Referral Hospitals, Northwest Ethiopia, May 2014.

Character	Number	Percent
Criteria used for eligibility assessment (n=168)		
Absence of TB	168	100.00
No cough	168	100.00
No fever	168	100.00
No poor weight gain	168	100.00
Household contacts of active Cases with tuberculosis	168	100.00
Chest x-ray to rule out tuberculosis		
Done	188	41.4
Not done	266	58.6
Medical condition that increased the risk of tuberculosis checked		
Yes	119	26.2
No	335	73.8
Child took IPT in the last three years		
No	286	63.0
Yes	168	37.0
INH completed by child (n=168)		
No	54	32.1
Yes	114	67.9
Adherence to IPT(n=168)		
Good	143	86.1
Poor	6	3.6
Not assessed	19	11.3
Hospital the child was on isoniazid preventive therapy		
Felege-Hiwot Referral Hospital	43	25.6
Gondar University Referral Hospital	125	74.4

Barriers to implementation of isoniazid preventive therapy: Table 4 presents the barriers for the implementation. In 29 (20.9%) of the children, the caregivers could not afford to go to the clinic on schedule to collect drugs. One in five (20%) of the caregivers, believed that INH may be dangerous to the child's health. More than half (54.2%) of the caregivers disclosed that the child was on IPT.

Nearly two-fifth, 174 (38.3%), of the caregivers believed that the child's chance of getting TB without IPT is below average or no risk at all (Table 4).

Table 4: Barriers to implementation of isoniazid preventive therapy among care givers of HIV infected children in two referral hospitals, Northwest Ethiopia, May 2014.

Type of Barrier	Number of children	Percent
Clinician explained the reasons for taking isoniazid	128	76.0
Care taker not sure when to give isoniazid to the child	8	4.8
Cannot afford to get to clinic on schedule to collect drug	29	20.9
Care taker do not know why the child is supposed to take the drugs	11	6.6
Care taker forgets to give medication	15	8.9
INH may be dangerous	91	20.0
Disclosed human immunodeficiency virus infection status to any other body than family/caregiver (n=454)	171	37.7
Disclosed INH use	91	54.2
Chance of getting tuberculosis without isoniazid prevention therapy (n=454)		
Below average or no risk	174	38.3
Average risk	112	24.7
Above average risk	39	8.6
High risk	83	18.3
Do not know	46	10.1
Hospital runs out of medication	22	13.1
There are side effects of medication	10	5.9
Run out of medication due to longer appointment than the amount of drug	15	8.9

***Factors associated with INH completion*:** GURH had a much better INH completion rate than FHRH. Distance from hospital was associated with INH completion. Children taking less than half an hour travel to the hospitals were more likely to complete their INH as compared to children taking >1 hour (x^2=7.79, p<0.005). Explanation by the health worker about reasons for taking INH increased the completion rate (x^2=91, p<0.001).

Caregivers' who agreed to the question that INH may be dangerous were less likely to have a child completing the INH regimen (x^2=19, p<0.001). Disclosure of the HIV status(x^2=4.17, p<0.04) and IPT status (x^2= 54, p<0.001) were significantly associated with INH completion (Table 5).

Table-5: Factors Associated with Isoniazid Completion among Human Immuno Deficiency Virus Infected Children in two Referral Hospitals, Northwest Ethiopia, May 2014

Characters	Isoniazid completion status		Chi-square	P-value
	No	Yes		
Type of hospital				
Felege-Hiwot Referral Hospital	33	10	52.8	<0.001
Gondar University Referral Hospital	21	104		
Distance from hospital				
<Half hour	24	72		
Half to 2 hours	20	36	7.79	0.005
More than 2 hours	10	6		
Health worker explained reasons for taking isoniazid				
No	37	2	91	<0.001
Yes	17	112		
Isoniazid may be dangerous				
Agree	13	40		
Disagree	16	68	19	<0.001
Don't know	25	6		
Chance of getting sick from tuberculosis				
Average or below	16	24		
Above average or high	9	83	70	<0.001
Don't know	29	7		
Disclosed isoniazid preventive therapy status				
No	47	30	54	<0.001
Yes	7	84		
Disclosed HIV status				
No	15	52	4.17	0.04
Yes	37	62		
Clinic runs out of medication				
No	49	97	1.03	0.3
Yes	5	17		
Side effects from isoniazid				
No	50	108	0.3	0.58
Yes	4	6		
Caregiver cannot afford to go to clinic				
No	47	92	1.03	0.3
Yes	7	22		
Caregiver not sure when to give medication				
No	52	108	0.2	0.66
Yes	2	6		

DISCUSSION

The study assessed the uptake and completion of INH preventive therapy and associated factors among 454 HIV infected children in two teaching referral hospitals. Isoniazid uptake was 37%, and 67.9% completed the regimen. The type of hospital, distance from hospital, explanation of the benefit of IPT by health worker, belief on safety of INH, perception of risk of getting TB, disclosure of IPT use and HIV status were associated with completion of IPT. The proportion of active tuberculosis among HIV infected children was 18.7%. The occurrence of TB was common (56%) among those aged 5 years and older.

The distribution by age of TB in our series is in contrast to previous reports that showed TB was more common among the age groups one to four years of age (10). The reason could be because a larger proportion (58.4%) of children included in our study was above the age of 60 months. This might also be due to the higher rate (76%) of contact history with TB cases in children in the age group 60 months and above. In our series, IPT users were 25% less likely to develop TB as compared to non-users. This shows a higher reduction of TB burden among IPT users as compared to non-users. That this failed to achieve statistical significance could possibly be due to an uncontrolled effect of other independent variables. Our finding is much lower than that of others, which reported figures as high as 80% in reduction in TB occurrence (11-13).

Cognizant of the major challenge of diagnosing TB among children, chest x-ray coverage was very low, 188 (41.4%), in our study, which was due to clinician's fear of risk of repeated exposure to x-ray, absence of signs and symptoms of TB, and the workload and cost of radiology services. Other studies also found similar reasons for not ordering chest x-ray to screen active TB (15). In our study, coverage of IPT three years prior to the survey was very low (37%), while the intended target was provide it all HIV infected children without active TB (10). Shortage of INH, fear of drug burden and resistance were possible reasons. Low IPT coverage could eventually undermine its benefits of reducing the occurrence of, mortality from, and associated medical costs among HIV infected children in high TB burden countries like Ethiopia (12).

The level of adherence to IPT (86.1%) in our series was similar to a report from Addis Ababa (86.5%) and the non-adherence to IPT in our study may be due to fear of INH side effects, also suggested by the study in Addis Ababa (16). Other explanations for high non-adherence levels could be due to INH stock-outs, and long distances making it hard for caregivers to bring children to the facility on schedule. The INH completion rate of 67.9% in our study was low as compared to the intended target. Distance from hospital is a key determinant of INH completion, suggesting that the health system needs to task-shift IPT services to the nearby district hospitals or health centers to facilitate follow-up visits.

Health workers' explanation about the use of INH was a key determinant of INH completion. This would not only improve perception related to drug safety and increase adherence, but also build trust between clients and clinicians enhancing compliance with health care providers' recommendations. This has been reported by studies conducted elsewhere (15-18). We observed that caregivers' perception about INH safety impacted completion status. Caretakers who believed that INH may be dangerous tended to interrupt INH. This necessitates the need to exhaustively address the concerns of caregivers to effectively run the program. Similarly, persons who thought that the child's risk to acquire TB was high were more likely to complete the full course of INH. TB was perceived as a serious chronic disease and individuals with such a perception might intend to properly adhere to the IPT regimen.

Disclosure of IPT status was significantly associated with INH completion in our series. Those who disclosed their HIV status already were more comfortable to give/ take the INH pills in front of people and complete their regimen (16). HIV status disclosure has also an important role in improving IPT adherence and completion of regimen. Those disclosing HIV status are more comfortable to take their INH pills in the presence of a person, which minimizes missed doses of INH and enhances their adherence.

In conclusion, the proportion of TB among HIV infected children in Northwest Ethiopia was high. Chest X-ray was not used optimally to screen for active TB. Uptake of IPT to HIV infected children was very low. INH completion was low and major determinants included distance from hospital, inadequate explanation by health workers, safety of INH use, and perception related to acquiring TB. There is a need for availing pediatric INH regimens, adequately educating caregivers on use of IPT, improving pediatrics clinical services, improving referral to nearby health facilities, and encouraging disclosure of both IPT and HIV status of HIV infected children.

Competing Interest **:** The authors declare that they have no competing interests.

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