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Adherence to Isoniazid Preventive Therapy (IPT) among Children in Close Contact with Adult Pulmonary Tuberculosis (PTB) Patients

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Authors' contributions

This work was carried out in collaboration between both authors. Author NGJ designed the study, collected the data and performed the statistical analysis, Author NIP wrote the protocol, managed the literature searches and the first draft of the manuscript. Both authors read and approved the final manuscript

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ABSTRACT

Introduction: Tuberculosis (TB) is among the top ten leading cause of morbidity and mortality globally, and studies have shown that adherence to a six Month course of Isoniazid Preventive Therapy (IPT) reduces the incidence of TB disease in HIV-negative/positive populations at risk of developing active TB disease.
Objective: This study was carried out to identify active TB cases among children aged 0-5 years who are in close contact with adult cases of pulmonary TB (PTB), to determine the adherence rate to IPT among these close contacts that do not have active TB and to identify factors associated with non adherence if any.
Methodology: This study was a prospective descriptive study carried out in Rivers state, Nigeria in two health facilities that offers services for TB diagnosis and treatment. Ethical approval for the study was obtained from the Rivers State Ministry of Health while verbal consent was obtained from the parents/caregivers of the children. Children aged 0-5 years who were in close contact with

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newly diagnosed PTB cases were recruited for the study. They were screened for HIV and evaluated for TB using clinical features and standard laboratory investigations. Those without active TB disease were commenced on isoniazid preventive therapy (IPT) for six months at a daily dose of 5mg/kg after adherence counselling and followed up at the health centres. Obtained data was analysed using Epi Info Version 7.2.3.1 statistical software. Descriptive statistics was used while the test for association between variables was done with chi-square test at $p \leq 0.05$ level of significance. Frequency tables were used for presentation of results.

Results: A total of Sixty three children were recruited for the study 37 (58.7%) were males while 26 (41.3%) were females. Thirty two (50.8%) were children of index PTB patients while 29 (46.1%) belonged to lower socio-economic class. Their age ranged from 4 months to 4 years with a mean age of 2.84years ±1.27years. Six (16.2%) out of the 37 males and 2 (7.7%) out of the 26 females were confirmed to have active TB, giving a TB prevalence of 12.7%. The gender difference was not statistically significant (p= 0.32). Of the fifty five children that commenced INH in the first Month, only twenty four of them completed the six Month course of INH, giving an IPT adherence rate of 49.6%. Identified reasons for non adherence includes 'My child is not sick', 'No transport Money', 'My child is writing exams". "My child is tired of the drugs", "the Health workers are not friendly' and 'long waiting time before collecting medications".

Conclusion: Early contact tracing is important for early detection of TB cases in children. Adherence to IPT in this study is low and strategies like community tracing of defaulters using trained social workers and community nurses as well as use of well-supervised and convenient ambulatory treatment centres that are manned by trained lower cadre health staff can improve adherence.

Keywords: Pulmonary tuberculosis; Mycobacterium tuberculosis; preventive therapy; TB-HIV.

1. INTRODUCTION

Mycobacterium tuberculosis (TB) is the most common cause of chronic bacterial infection in humans [1–3] and is globally among the top ten leading cause of morbidity and mortality, especially in developing countries [4]. Human Immunodeficiency Virus (HIV)/Acquired immunodeficiency syndrome (AIDS) infection which has become an epidemic is the greatest risk factor for TB and over 4 million people are co-infected with both organisms, the majority of whom reside in Africa [5]. This HIV/AIDS epidemic increases the risk of reactivation of latent TB and a framework of TB/HIV/AIDS collaborative activities to prevent the occurrence of TB-HIV disease had been proposed by the World Health Organization (WHO).

Isoniazid preventive therapy (IPT), intensified TB case finding, infection prevention, Short course drug therapy and directly observed therapy are the major strategies to control TB in HIV-positive/negative individuals [6]. The Nigerian national TB program has adopted these activities including IPT and the guideline recommends that Isoniazid (INH) should be given to patients daily at a dose of 5 mg/kg, a maximum dose of 300 mg/day for a period of 6 months in eligible patients once active TB disease has been excluded.

Studies have shown that a course of Isoniazid Preventive Therapy reduces the incidence of TB disease in HIV-negative populations at risk of developing active TB disease [7]. IPT also reduced reactivation of latent TB infection, in HIV infected patients both in developing countries [8–10] and industrialized countries [11–13]. IPT is indicated in HIV positive patients, and persons in close contact with confirmed pulmonary TB (PTB) cases who have no evidence of active TB disease.

Despite proven efficacy and cost effectiveness of IPT, a major drawback in its use has been poor adherence [14]. Numerous concerns have been raised regarding the implementation of IPT in resource-poor settings, including the identification of large numbers of HIV-infected persons, the need to exclude active TB at screening and follow-up to prevent emergence of drug resistance, the supervision of preventive therapy, and the monitoring of adverse effects [14,15]. Defining strategies to maintain good adherence underlies these issues, both to ensure that individuals benefit from the intervention and to minimize the potential public health risks [16]. This study was carried out to identify active TB cases among children who are in close contact with adult cases of PTB, to determine the adherence rate to IPT among these close contacts who do not have active TB and to

identify factors associated with non adherence if any.

2. METHODOLOGY

This study was a prospective descriptive study carried out in Rivers state, Nigeria over a six Month period in 2017 (July 2017 – December 2017) in two health facilities that offers TB diagnosis and treatment services. Contact tracing was done for all newly diagnosed TB cases. However, children aged 0-5 years who were in close contact with newly diagnosed PTB cases were recruited for the study. A contact is said to be close when he/she lives in the same household with the index TB case or is in regular contact with an index case [17]. Newly diagnosed cases of Pulmonary Tuberculosis were identified at the DOTs clinics and were interviewed about their close contacts. Those with contacts who were 5 years and below were counselled on the need to evaluate these children for active TB disease or for commencement of IPT. Parents or care givers who gave consent were requested to bring their children for evaluation. Evaluation for TB included obtaining a history of chronic cough of at least 2 weeks, poor weight gain or weight loss, fever or excessive night sweats, Xpert MTB/RIF test using Sputum or gastric Aspirate and a Tuberculin skin test (TST) using the Mantoux method (intradermal injection of 0.1ml of 5 tuberculin units of purified protein derivative) and read off in 48–72 hours. A repeat TST was done 2 weeks later for all children who tested negative to the initial test. An induration of 10 mm or more was regarded as positive TST. Chest radiograph and HIV screening was requested for all the child TB contacts. Any child contact that was diagnosed with TB was commenced on first line anti TB drugs and those found to be HIV positive were eventually commenced on Highly Active Anti-Retroviral Therapy (HAART). For those without TB disease an IPT card was opened for each of them and they were commenced on isoniazid prophylaxis for six months at a daily dose of 5 mg/kg. Adherence counselling was done for the care givers/or the parents prior to commencement of IPT and at each follow up visit to ensure completion of treatment. Telephone numbers of the parents/caregivers were obtained for easy follow up and tracking. Children were followed up at the DOTs clinic on a monthly basis for clinical evaluation and refill of their drugs. Patients received 2 follow up calls on monthly basis one week and 48 hours before their next visit to remind them of their clinic visits while defaulters received another call to ascertain the reason for failure to visit the clinic and to encourage them to come for follow up and drug refill. Obtained data was analysed using Epi Info Version 7.2.3.1 statistical software. Descriptive statistics was used while the test for association between variables was done with chi-square test at $p \leq 0.05$ level of significance. Frequency tables were used for presentation of results.

3. RESULTS

3.1 Demographic Characteristic of Child Contacts

Sixty three children who had close contact with adults with PTB were reviewed for the commencement of IPT. Thirty seven (58.7%) were males, 32 (50.8%) were children of index TB patients while 29 (46.1%) belonged to lower socio-economic class. Their age ranged from 4 months to 4 years with a mean age of 2.84years ±1.27years. The mean age for males was 2.84 years ±1.30 years while that of females was 2.85 years ±1.26 years, there was no significant gender difference in age ($t= 0.03$, $p = 0.98$). Table 1.

3.2 Laboratory/Clinical Features of the Participants

Table 2 shows that of all the study participants, six (9.5%) were TST positive, 13 (20.6%) were HIV positive while 5 (8.0%) had suggestive chest radiographic features. MTB was detected in only one (1.6%) child using XpertMTB/RIF while 3 (4.8%) of the patients were symptomatic of TB disease. A total of six (Five had radiographic features, three of whom were symptomatic and one had MTB detected by XpertMTB/RIF) were diagnosed with active TB disease and they were all TST positive.

3.3 Prevalence of TB by Gender among the Study Participants

Six (16.2%) out of the 37 males and 2 (7.7%) out of the 26 females were confirmed to have active TB, giving the overall prevalence of TB of 12.7%. The gender difference was not statistically significant with a p value of 0.32 as shown in Table 3. Fifty five (87.3%) of the participants did not have active TB disease and were commenced on INH.

Table 1. Demographic characteristic of child contacts

Characteristics	Frequency (no)	Percentage (%)
Gender		
Male	37	58.7
Female	26	41,3
Relationship with index Patient		
Child	32	50.8
Sibling	16	25.4
Other relatives	11	17.5
Non relatives	4	6.3
Social Class		
Upper	10	15.9
Middle	24	38.1
Lower	29	46.1
Age in years		
<1	9	14.3
1-2	32	50.8
3-4	22	34.9

Table 2. Laboratory/Clinical features of the participants

Clinical features	Frequency (n)	Percentage (%)
Mantoux test (TST)		
< 10mm	56	88.9
≥ 10mm	6	9.5
Not done	1	1.6
HIV status		
Positive	13	20.6
Negative	48	76.2
Not done	2	3.2
Chest X ray		
Suggestive	5	8.0
Not suggestive	54	85.7
Not done	4	6.3
XpertMTB/RIF		
MTB detected	1	1.6
MTB not detected	47	74.6
Not done	15	23.8
Symptomatic		
Yes	3	4.8
No	60	95.2

Table 3. Prevalence of TB by gender among the study participants

TB cases identified	Gender		Total (%)
	Males (%)	Females (%)	
Yes	6 (16.2%)	2 (7.7%)	8 (12.7%)
No	31 (83.8%)	24 (92.3%)	55 (87.3%
Total	**37 (100.0%)**	**26 (100.0%)**	**63 (100.0%)**

$\chi 2 = 0.98$, DF= 1, p-value = 0.32

Table 4. Adherence to INH by gender

Month	Gender (N=55)		Total (%)
	Males (%)	Females (%)	
1.	31(56.4)	24 (43.6)	55(100.0)
2.	28(54.9)	23(45.1)	51(92.7)
3.	27(56.3)	21(43.7)	48(87.3)
4.	21(55.3)	17(44.7)	38(69.1)
5.	14(48.3)	15 (51.7)	29 (52.7)
6.	13 (54.2)	11(45.8)	24(49.6)

3.4 Adherence to INH by Gender

Table 4 shows the proportion of the children by gender that attended monthly follow up visits for their IPT refill. There was a steady decline in the number of children who came for follow up and drug refill from the 1st to the 6th month. Of the fifty five children that commenced INH in the first Month, only twenty four of them attended clinic monthly for review, drug refill and completed the 6 month course of INH, giving an IPT adherence rate of 49.6%. Identified reason for not returning for follow up include 'My child is not sick', No transport Money to bring the child, ' My child is writing exams", "My child is tired of the drugs". "The Health workers are not friendly especially when we come late and long waiting time before collecting medications".

4. DISCUSSION

It was found that over half (58.7%) of the recruited TB contacts were males while 50.8% were children of the TB cases. Though these children were recruited by contact tracing, it is not surprising to find that many studies have shown more males than females as having tuberculosis [18-21]. That more of the recruited child contacts are children of TB cases emphasizes the need for active contact tracing once an adult case of TB is diagnosed as childhood TB is a reflection of adult TB pool.

This study showed that all the social class was represented but more (46.1%) of them belonged to the lower social class. This is typical of findings in other studies as tuberculosis has been described as a disease of poverty [18,22]. These individuals are more likely to live in overcrowded homes and in areas with high population density.

Evaluation of the clinical and laboratory data showed that six of the study participants had active TB disease giving a TB prevalence among the child TB contacts of 12.7%. This finding is higher than 5.7% reported by Munir et al. [23] in Hyderabad, Pakistan and 1.1% reported by Rajeshwar et al. [24] in India. These studies had higher sample sizes and this may have contributed to their lower prevalence. These further highlights the importance of early contact tracing in TB control as it enhances early detection of active TB disease and hence reduce the incidence of complications and treatment failure. Efforts at intensifying contact tracing must be encouraged and supported at all levels.

An interesting finding among the study participants was that about a fifth (20.6%) of them were seropositive to HIV. This HIV status invariably reflects that of their parents, as the study population may not have been sexually active and shows the strong relationship between TB and HIV. These children were eventually commenced on HAART and are still on follow up.

Isoniazid preventive therapy (IPT) has been identified as an effective TB control strategy both in industrialised and developing countries [8-13]. A challenge in its use is the fact that tuberculosis has to be excluded before its initiation and this is cost intensive considering the endemicity of TB in our environment. Another challenge posed by IPT which is one of the objectives of this study is that of adherence to its use [14]. Despite initial and reinforced adherence counselling given to the care givers of these participants before initiating and while on medications and repeated phone call reminders for follow up visits, an adherence rate of 49.6% was achieved in our study. This finding is similar to an adherence rate of 47.1% reported by Rowe et al. [25] in Rural South Africa. It is however, less than adherence rates recorded in other developing countries, like Brazil (61%), [26] Uganda (62% and 70%) [27, 28] and Thailand (69%) [29]. Notably, in both the Thailand and Ugandan studies, defaulters were traced back to the community by mail or through home visits by a social worker, a strategy that was not employed in our study. Another

interesting observation in this study was the fact that twelve (92.3%) of the thirteen children who were found to be HIV seropositive did not have active TB disease and were adherent to the six Month of IPT.

Prominent among the identified reasons for lack of adherence include: my child is not sick, no transport money to bring the child, my child is writing exams, unfriendly attitude of the health workers especially when we come late and long waiting time before collecting medications. These reasons reflect an interplay between the quality of health service delivery, social and economic factors. Studies have shown that people are reluctant and less likely to take medications when they are well than when they are sick and that they are also prone to stop the medications when they feel well [30-35]. Since these children on IPT were apparently well, the play out of this factor on the adherence rate is quite obvious. This may also be probably why those who were HIV seropositive were more adherent as the danger of falling ill was considered more likely among them. Poverty is an underlying factor in several health challenges in developing countries [36] so its not a surprise to find that it is used as a reason for failure to come to the hospital among interviewed defaulters. Giving of money for transport may be an incentive to boost adherence but its sustainability is doubtful and hence not a reliable measure and practical experience has shown that when such stipends are made available, they are often diverted to other personal needs that the individual considers more important.

Factors such as high patient load, long working hours and poor remuneration of health workers have been shown to adversely affect health workers attitude and outcome of patient care in resource limited settings [36]. Improving on these factors, training and retraining of health workers on stress management measures and attitudinal change may portend a positive outlook on improving adherence. The use of phone calls to remind patients of follow up and drug refill days contributed positively to adherence initially but soon the care givers were no longer motivated by it.

The foregoing suggests that adherence to IPT in this study is low. It is also obvious that the barriers to adherence are real life issues that must be addressed for any significant progress in the use of IPT in TB control especially among apparently well close contacts who are HIV seronegative. Poor adherence to IPT will lead to increased incidence of Drug resistant TB (DRTB) as INH is one of the important drugs in the management of drug sensitive TB. This is worsened by the fact that drug sensitive testing (DST) is still a luxury in many TB centres in resource limited countries and so are not routinely done prior to commencement of anti TB drugs.

The question that arises is how can these lessons on adherence be translated into better clinical practice and TB control? Having said that money incentives are not sustainable, the economic barriers faced by these participants was identified as a barrier to adherence and must be addressed. Strategy like community tracing of defaulters using trained social workers and community nurses can improve adherence as was shown in the Ugandian and Thailand studies [25-27]. Also, use of well-supervised and convenient ambulatory treatment centres that are manned by trained lower cadre health staff as well as better organised health services in which health posts are in close proximity to patients' homes is advocated. Considering the morbidity and mortality associated with TB and where possible, a national program of child support grants for care givers of children on IPT is a welcomed development, so meeting basic needs competes less often with health care for limited household resources.

5. CONCLUSION

This study concludes that the TB prevalence of 12.7% among child contacts of adults with newly diagnosed PTB is high. Early contact tracing is needed to evaluate all child contacts for PTB so as to commence treatment for those with active TB and IPT to at risk children who are less than 5 years of age. Adherence counselling and tracing of defaulters is important for all parents / care givers whose children are enrolled in IPT.

CONSENT AND ETHICAL APPROVAL

Ethical approval for the study was obtained from the Rivers State Ministry of Health while verbal consent was obtained from the parents/ caregivers of the children.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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