

RESEARCH ARTICLE

Correlates of adherence and utilization of Isoniazid preventive therapy in HIV patients

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ABSTRACT

Objective: Isoniazid (INH) is given to individuals with latent infection of tuberculosis in order to prevent progression to active disease. It is important to understand factors associated with non-adherence to prophylactic Isoniazid. This study aimed to identify correlates of adherence and utilization of Isoniazid in HIV positive patients and to explore the opinions of patients and health care providers.

Methods: Participants eligible for the study were 403 randomly selected HIV positive individuals taking INH on follow up in Yekatit 12 hospital. Adherence was measured by self-report of INH tablets taken for past 3, 7 and 30 days. In depth interview was also conducted on recruited patients and health professionals.

Results: Adherence to INH was 94% for last 7 days. INH related common side effects were reported by 142 participants (35.2%) and only 53 (13.2%) discontinued. The odds of adherence was 104, 7.7 and 34.8 [95% Confidence Interval (18.7, 582.6), (2.6, 22.9) and (4.4, 272.6)] times higher among those patients who did not have jaundice, skin rash and seizure compared to those who developed, respectively.

Conclusion: The prevalence of adherence to INH in Yekatit 12 hospital was better than other local and African studies and the reasons for poor adherence was strongly associated with occurrence of jaundice, skin rash and seizure. Comprehensive care and support, sustainable drug supply and evaluation of side effects are recommended. *J Microbiol Infect Dis* 2015;5(2): 45-50

Key words: Tuberculosis; HIV; adherence, Isoniazid, preventive therapy, side effects

HIV pozitif hastalarda koruyucu İzoniyazid tedavisinin kullanımı ve uyumla ilişkisi

ÖZET

Amaç: Latent tüberküloz enfeksiyonu olan bireylere aktif hastalığın ilerlemesini önlemek için İzoniyazid (INH) profilaksisi verilir. Uyumsuzluk ile ilişkili faktörleri anlamak profilaksi başarısı için önemlidir. Bu çalışmada HIV pozitif hastalarda uyuma ilişkin faktörleri tespit etmek, hastaların ve sağlık hizmeti sunucularının görüşlerini keşfetmek hedeflendi.

Yöntemler: Çalışmaya Yekatit 12 hastanesinde takip edilen uygun 403 rastgele seçilmiş HIV pozitif ve INH profilaksisi alan hasta dahil edildi. Uyum, hastaların son 3, 7 ve 30 günde aldıkları INH tabletlerini öz-bildirim metodu ile bildirmeleri ile ölçüldü. Hastalar ve sağlık profesyonelleriyle derinlemesine görüşmeler yapıldı.

Bulgular: INH uyumu son yedi gün için % 94 idi. INH ilgili ortak yan etkiler 142 katılımcı (% 35,2) tarafından bildirildi ve sadece 53 (% 13,2) olguda tedavi kesildi. Sarılık, deri döküntüsü ve nöbet gelişmeyen hastalarda sırasıyla 104, 7,7 ve 34,8 [% 95 Güven Aralığı (18,7-582,6), (2,6-22,9) ve (4,4-272,6)] kat fazla uyum olduğu saptandı.

Sonuç: Yekatit 12 hastanesinde INH uyum sıklığı diğer yerel ve Afrika çalışmalarına göre daha iyidir ve kötü uyum nedenleri içinde ciddi sarılık görülmesi, deri döküntüsü ve havale gelişimi bulunmaktadır. Kapsamlı bakım ve destek, sürdürülebilir ilaç temini ve yan etkilerin değerlendirilmesi önerilir.

Anahtar kelimeler: Tüberküloz, HIV, uyum, Isoniazid, koruyucu tedavi, yan etkiler

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INTRODUCTION

Tuberculosis (TB) remains a major global health problem.¹ There were almost nine million new cases in 2011 and 1.4 million TB deaths 430,000 Human Immunodeficiency Virus (HIV) associated TB deaths in the same year.¹ Short-course regimens of first-line drugs that can cure around 90% of cases have been available since the 1980s.²

The risk of developing TB is between 20 and 37 times greater in people living with HIV than among those who do not have HIV infection.³ Latent TB infection results when individuals infected with *M. tuberculosis* carry the organism in a latent state, which is characterized by slowed or intermittent metabolism and replication below the level necessary to produce clinical illness. The risk of reactivation of latent infection is greatly increased in individuals with immune suppression, most notably that due to HIV infection.⁴

Isoniazid is given to individuals with latent infection with *Mycobacterium tuberculosis* in order to prevent progression to active disease.⁵ Exclusion of active TB is critically important before isoniazid preventive therapy (IPT) is started. The absence of all of current cough, night sweats, fever, or weight loss can identify a subset of adolescents and adults living with HIV who have a very low probability of having TB disease that can reliably be initiated on IPT. This screening rule has a negative predictive value of 97.7% (95% CI 97.4-98.0) at 5% TB prevalence among people living with HIV.^{5,6}

The main cause of anti-tuberculosis drug resistance is inadequate treatment of active TB. Therefore, any risk for a small increase in the incidence of Isoniazid resistance attributable to wider use of IPT needs to be weighed against its benefit in reducing TB incidence.⁷

One of the collaborative TB/HIV activities by WHO is to have 100% coverage of IPT for people living with HIV attending HIV care services among those eligible by 2015.^{1,2}

Promoting research is a key component of the "Stop TB Strategy", as exemplified through the insertion of a concise Operational Research section in the new Global Plan to Stop TB 2011-2015, and was recently identified as a major area in which global action is urgently needed.⁸

There were 5442 (8%) of HIV patients diagnosed with TB in Ethiopia in 2011 and only 30,816 people living with HIV were provided with IPT during the same year.⁹ Point estimates for HIV incident TB

cases in 2011 were in the range of 27 to 41 cases per 1000 population.^{9,10}

Ethiopia has had mechanisms for TB/HIV collaborative activities since 2002. However, no published account has defined the role of these collaborative efforts in strengthening linkages between HIV and TB management units at the point of care level, this supports the rates of HIV testing and linkage to CPT being higher than screening HIV positives for TB, initiation of IPT, referral, linkages, and TB diagnostic capacity.^{9,10}

Adherence rates for IPT varied widely from 34% to 98% from observational studies and did not directly address whether poor adherence adversely affects individual or program outcomes and a number of factors were identified to improve adherence.³ Since the implementation has gaps in scaling up the recommendation on IPT for people living with HIV evidenced by limited local and global data.^{6,7-9} Hence, the purpose of the study is to determine factors associated with adherence of IPT and its use to influence standard of practice and implementation of existing national and global policy and guidelines on use of IPT for eligible people living with HIV. The aim of this study is therefore to measure the magnitude of adherence among HIV patients who are taking INH, identify correlates of adherence to use of INH and explore the opinions of patients and health care providers about factors affecting adherence and utilization of INH.

METHODS

Facility based cross sectional study on people living with HIV complemented by a qualitative study using in depth interview. HIV positive individuals of age above 15 who were ever enrolled to HIV care and treatment on IPT and on follow up in Yekatit 12 hospital. The study population was sample adults who were receiving IPT for at least one month before the initiation of the study, during August 07 to October, 03, 2013.

The sample size of 403 participants is determined by assuming stabilized adherence prevalence rate 50%, giving any particular outcome to be with 5% marginal error and 95% confidence interval of certainty ($\alpha=0.05$), and 5% allowance for abstains and refusal was considered. The actual sample size was computed using single population proportion formula.

For in depth interview 12 respondents, three of whom were males and six females and eligible for the quantitative study, one peer counselor for the adult ART clinic and two nurses working at ART clinic

ic were used. All HIV positive individuals attending HIV Clinic of the study hospital and who fulfilled the entry criteria were identified and randomly selected.

Questionnaire developed based on the format from demographic health survey (DHS).¹¹ Originally developed in English then translated to Amharic and back translated to English by a different translator who was blinded to the original questionnaire to check for its consistency. Three data collectors were selected from a different facility qualified in bachelor of health science and one field supervisor qualified in doctor of medicine was selected from the same facility.

Training using lecture and demonstration on data collection procedure and supervision was given for two days. Questionnaire was pretested at different facility involving enumerators and supervisor and important findings were used to modify questionnaire.

Data was collected at the study hospital. Face to face interview technique was used. For non-respondents random sampling for next participant was applied. Data collection for in depth interview was done by the principal investigator using open ended questionnaire and tape recorder.

The dependent variable was self-reported adherence to IPT in the last 3, 7, and 30 days. Independent variables were socio-demography status, travel time to clinic, ART and other medications use, knowledge about IPT, belief on effectiveness of INH, report of side effects; nausea, vomiting, jaundice, skin rash, numbness and seizure, previous treatment of tuberculosis, use of khat (*Catha Eduilis*), alcohol and cigarette and compliance on clinical appointments.

Screening tool for measuring level of adherence was using percent of pill taken which is calculated as ratio of pill taken to pill prescribed over the past 3, 7, and 30 days. Adherence level 80% and above considered adherent and less than 80% as non-adherent.¹² After data collection, the data was coded on pre-arranged coding sheet by the investigator and the corresponding code number was written at each questionnaire margin and data entry was done using Epi Info version 3.5.3, SPSS version 16 for data analysis was used and EndNote X2 for reference citation.

Multivariate binary logistic regression analysis was used to assess the strength and significance of association between the covariates and the outcome variables of interest. Significance level was decided when a *p*-value <0.05 was obtained at each

level of analysis. All variables found statistically significant at the bivariate level entered in the multivariate models for each dichotomy outcome of INH taken last 3, 7 and 30 days.

The qualitative data was first transcribed word for word and then translated to English language. The English version was exported into Open Code software version 3.6.2.0. The software was used for coding and categorization. Thematic content analysis was used. Moreover, some verbatim were used in the report to better reveal the opinions and perceptions of key informant interviewees.

Ethical clearance was obtained from both research ethics committees of school of public health Addis Ababa University and Addis Ababa city administration health bureau. Each participant gave Informed consent for participation in the study.

RESULTS

From the sampled population of 403 eligible clients 149 (37%) and 245 (63.03%) were males and females respectively. The mean age was 38.8 years (Table 1). ART was initiated for 93.1%, among those 363 (90.1%) were on first line regimen and 12 (3%) on second line regimen. Medications prescribed for other chronic medical illnesses and/or preventive therapy additional to INH and ART were for 105 (26.1%) of cases. Those who discontinued ART for more than one month were 10 (2.7%), reported reasons being holy water use (*n*=6), sickness (*n*=2) and felt healthy and lack of support (*n*=2).

INH related common side effects were reported by 142 (35.2%) cases and vomiting was the most common 93 (65.5%) cases, skin rash 33 (23.2%), jaundice 8 (5.6%), seizure and numbness each accounting 4 (2.8%). Among respondents who reported one or more of the above symptoms only 53 (13.2%) discontinued INH which showed that most that had vomiting continued taking INH. The dosing of INH for once daily and six months were satisfactory 358 (88.8%) and 331 (82%) respectively. Appointment for next refill per patient demand was 101 (25.1%) and only 5 (1.2%) were cigarette smokers.

The odds of adherence to INH for the last 7 days was 104 times [95% CI (18.7, 582.6), *p*<0.012] higher among patients who did not report jaundice, similarly adherence was 7.7 times [95% CI (2.6, 22.9), *p*<0.032] and 34.8 times [95% CI (4.4, 272.6), *p*<0.000] higher among patients who did not report skin rash and seizure respectively (Table 2). Adherence to INH was also significantly observed for jaundice, skin rash and seizure for last 3 and 30 days (Table 3).

Table 1. Socio demographic characteristic of respondents at Yekatit 12 hospital

Variables	n=403 (%)
Sex (Male)	149 (36.97)
Level of education:	
Never been to school	41(10.2)
1-8	96(26.5)
9-12	153 (42.3)
College	113 (31.3)
Occupation	
Civil servant	8 (19.3)
Private employee	95(23.6)
Trader	24(6)
Daily laborer	45(11.2)
Unemployed	136(33.7)
Others	25(6)
Monthly income	
Unknown	58 (14.4)
<50 \$	70 (17.4)
50-150 \$	192 (47.6)
≥150 \$	83 (20.6)
How long takes to the clinic	
<60 minutes	128 (31.8)
60-120 minutes	204 (50.6)
≥ 120 minutes	71 (17.6)
Mean ± SD	69.6 ± 34.6

The respondent from the in-depth interview said "TB is a major disease and transmitted from person to person through cough, sputum, sharing cups and cold exposure" and they believed INH is important for prevention of TB.

The opinion of a female peer counselor was reiterated as "I do not counsel clients on INH together with counseling for ART adherence since I do not have adequate information".

The opinion from the two nurses at ART clinic: They rarely saw side effects of INH. Based on their experience most do not discontinue INH. Both nurses said the ART clinic is busy and they are less motivated to initiate INH. The reported reason to stop INH was gastric pain, forgot to take and went to holy water.

When patients had physician visit they missed the next refill since physicians miss INH on the chart. Generally physicians neither initiate IPT nor encourage nurses. Because of interrupted supply of either INH alone or both INH and pyridoxine the nurses usually were reluctant to initiate IPT.

Table 2. The association of side effects with INH adherence for last 7 days

Variables	INH adherence last 7 days, Yes (%)	INH adherence last 7 days, No (%)	Crude unadjusted OR, (95% CI)	Adjusted OR (95% CI)	p-value
Jaundice, No	377 (93.5)	18 (4.5)	62.8 (11.8, 333.3)	104 (18.7, 582.6)	0.012
Skin rash, No	352 (87.3))	18 (4.5)	4.4 (1.6, 11.9)	7.7 (2.6, 22.9)	0.032
Seizure, No	377 (93.5)	22 (5.5)	17.1 (2.3, 127.5)	34.8 (4.4, 272.6)	<0.001

Table 3. The association of side effects, previous TB treatment and appointment per demand with INH adherence for last 3 and 30 days in Yekatit 12 hospital

Variable	INH adherence last 3 days No (%)	Yes (%)	Crude unadjusted OR (95% CI)	Adjusted OR (95% CI)	p-value
Jaundice, No	12 (3)	383 (95)	95.8(17.5, 524.2)	169.8(23, 1250)	0.006
Skin rash No	12 (3)	358 (88.8)	6.6 (2.3, 19.0)	23 (6, 95.4)	0.005
Seizure No	17 (4.2)	382 (94.8)	7.5 (0.7, 75.8)	66.4 (4.9, 908)	<0.001
Previous TB treatment No	276 (68.5)	109 (27%)10(2.5)	3.2 (1.2, 8.2)	2.44 (0.7, 8.8)	0.115
Appointment, Per demand, No	294 (73)	91(22.5)10(2.5)	4(1.6, 10.5)	4.5 (1.2, 17.1)	0.017
INH adherence last 30 days					
Jaundice, No	16 (4)	379 (94%)	71 (13.3, 380)	131 (22.9, 753)	0.004
Skin rash, No	15 (3.71)	355 (88.1)	6.4 (2.4, 17)	11.8 (3.9, 35)	0.002
Seizure, No	21 (5.2)	378 (93.8)	6 (0.6, 60.2)	14.6 (1.4, 156)	<0.001

DISCUSSION

In this study we tried to see the correlates of adherence and utilization of INH among people living with HIV in Yekatit 12 hospital based on self-reported adherence and its determinants. The study showed prevalence of adherence to INH taken for past 7 days prior to the date of response was 379 (94%), 3 days prior 385 (95.5%) and 30 days prior 381 (94.5%) which was comparative across the three different days. Similar cross sectional study in Ethiopia showed adherence rate of 86.5% over past 7 days¹² and the Botswana three year case control study in eight public health clinics also showed 78% of adherence despite a prolonged 36 month period of prophylaxis.¹³ In another cross sectional study from rural south Africa adherence rate at 6 months of completion of IPT was 47%.¹⁴

Observational studies compiled by WHO showed over all adherence rates of 34% to 98%.³ The current studies' prevalence of adherence close to the upper limit of WHO's report and higher than other studies could be due to the mean number of INH tablets prescribed was 55.5 compared to the other studies who completed 6 months to 3 years of prescribed INH.^{12,13-18}

The report of side effects attributed to use of INH from other studies was considered in general^{12,13-18} than the current studies' approach which tried to see each possible reported side effect and its association with adherence such as vomiting was reported most commonly than other side effects but had no statistical significance on adherence to INH for last 3, 7 or 30 days also those studies were done few years after IPT program implementation and scale up¹⁵⁻¹⁷ where by clients' adherence could be low for a relatively new program compared to the current study.

The wide range of 95% confidence interval in jaundice, skin rash and seizure could be explained by small sample size and few number of occurrences significantly affecting adherence this findings could be confounded by the potential toxicity to occur due to either the ART regimen or cotrimoxazole since 96% of respondents were taking the later and/or since it is self-reported patients might be preoccupied by potential side effects and attributes for non-genuine complains or one might have been dealing with a different disease or it could be searching for a medical reason to discontinue INH and minimize blame by the health care providers for non-adherence.

Physicians were reluctant to initiate or motivate staff nurses on utilization of IPT which is supported by qualitative study from Brazil there was a poor adherence for detection and treatment of latent tuberculosis infection among HIV-infected patients by physicians in Rio de Janeiro.¹⁹ Clients' believe for imaginary idea of prevention with a potentially toxic drug, pill burden, prescription only for one month and lack of trust when the supply is inconsistent after initiation for few months is partly consistent with a systematic review of qualitative studies Patient choice in taking treatment is framed by the physiological and psychological impacts of the disease and also by the social and cultural structures in which the person is immersed.²⁰⁻²¹

The strengths of this study; it involved a relatively larger sample size than the other local studies, had included qualitative study method and it tried to look for additional factors affecting adherence to IPT regarding occurrence of side effects and availability of other comprehensive care and support.

The limitations are since there is no a "gold standard" for assessment of adherence, we used self-reported adherence which might introduce recall bias. The fact that it is a cross sectional study we cannot generate cause effect relationship. The study is done in a single center where by diversity of population could have been missed for comparison and it has a limited generalizability for other public health facilities.

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