



ADHERENCE TO TUBERCULOSIS PREVENTIVE THERAPY IN PEOPLE LIVING WITH HIV/AIDS.

Medical Science

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ABSTRACT

Introduction: Tuberculosis is one of the leading causes of morbidity worldwide. About 23% of the world's population has been estimated to have latent TB infection (LTBI). Treatment for LTBI with Isoniazid is an important strategy if TB is to be eradicated by 2050. **Methods:** A facility based cross-sectional study conducted in five urban health clinics in Lusaka between January and April, 2020. HIV positive adults on Isoniazid systematically selected and interviewed using structured questionnaires. Data entered in excel and imported into STATA version 14 for analysis. Descriptive statistics and Logistic regression analysis utilised. **Results:** A total of 320 respondents were included in the study. The seven day self-reported adherence rate was 81.1%. The most frequent reasons for ever missing a pill were that the patient forgot to take their medication (9.69%, N=31), were away from home and forgot to carry the drugs (9.69%, N=31) or ran out of medication (7.19%, N=23). Those that took isoniazid for 2 to 4 months were less likely to be non-adherent compared to those who had taken it for less than 2 months (aOR: 0.31, CI: 0.12, 0.74, p=0.011). Patients who experienced side effects such as vomiting and peripheral neuropathy were more likely to be non-adherent compared to those who did not have side effects (aOR: 11.40, CI: 1.95, 66.7, p=0.01) and (aOR: 3.73, CI: 1.14, 12.17, p=0.03) respectively. Having an excellent social support reduced the odds of being non-adherent compared to those who had very poor social support (aOR: 0.11, CI: 0.02, 0.72, p=0.02). **Interpretation:** Self-reported adherence to INH was high. Factors associated with poor adherence included shorter duration on INH and side effects. An excellent social support was associated with good adherence.

KEYWORDS

TUBERCULOSIS, ISONIAZID, ADHERENCE

INTRODUCTION

Tuberculosis is one of the top 10 causes of death globally. In 2017, WHO estimated 1.3 million deaths caused by TB in HIV-negative people, with an additional 300 000 deaths from TB among HIV-positive people.¹ The majority of those affected were adults 15 years and above, with 9% being PLHIV (72% being from Africa). In Zambia, out of the 62 000 people estimated to have fallen ill with TB in 2017, 18 000 died due to a cause attributable to TB.^{1,2,3,4}

About 23% of the world's population is estimated to have latent TB infection (LTBI),¹ and thus are at risk of developing active TB disease during their lifetime.⁵ HIV infected people have thirty times the risk of developing TB compared to non-HIV infected individuals.^{6,7}

The treatment of LTBI is a vital approach to eradicate TB by 2050.¹ Isoniazid preventive therapy (IPT) has been widely recommended to reduce the burden of TB in PLHIV^{8,9} through the provision of isoniazid (recommended dose for adults is 300mg/day)¹⁰ to people at high risk of developing active tuberculosis, given for a period of 6 to 12 months. The safety of IPT has been proven and minimal side effects such as hepatotoxicity and gastrointestinal symptoms reported.¹¹ In addition, IPT has been shown to effectively lower the incidence of TB in PLHIV by up to 90% if used with or without ART.^{5,12-13}

There are many reasons why patients do not adhere to treatment and this may range from health care provider failures and deeply-held cultural beliefs among patients through to economic reasons.^{15,16,17,18} Factors associated with adherence to IPT and the levels of adherence in PLHIV have not been well investigated in Zambia, therefore, the need to carry out this research.

MATERIALS AND METHODS:

This was an analytical cross-sectional study conducted in five urban Health Centers in Lusaka district which offer both Anti-retro viral Therapy (ART) and Isoniazid Preventive Therapy to PLHIV. The inclusion criteria included those 18 years of age and above, willing to participate, resident of Lusaka district and had taken INH for at least one month. The sample size was 318 and data was collected using structured questionnaires through face-to-face interviews.

The outcome variable for this study was "Adherence to Isoniazid" which was self-reported at 7 days prior to the interview and was described as "having missed a pill or not." This was supported by residual pill count. The independent variables included socio-demographic characteristics (age, sex, marital status, educational

level, religion and occupational status), adverse drug effects, socio-support, adherence counselling, duration on IPT, HIV/WHO staging at start of IPT, Cotrimoxazole intake, alcohol intake and smoking.

Data Analysis.

Data was entered into Excel after being checked for completeness and then imported into STATA version 14 for analysis. For descriptive statistics of categorical variables, numbers and percentages were reported. For the variable age, which was continuous and not normally distributed the median and inter-quartile range (IQR) were reported. The chi-squared test was used to test for association between the outcome variable and the independent categorical variables that met the assumptions of the test. For variables that did not meet the assumptions of a chi-squared test a mann-whitneys' or Fishers' exact test was used. The level of statistical significance for the tests of association was p<0.05.

Logistic regression models were fit to explore the relationship between the odds of adhering to Isoniazid and all independent variables, at both univariate and multivariable level.

Ethical Consideration: Authority to conduct research was obtained from the University of Zambia Biomedical Research Ethics Committee (UNZABREC) and the National Health Research Authority. Informed consent was obtained from each participant after explaining the purpose of the study.

RESULTS

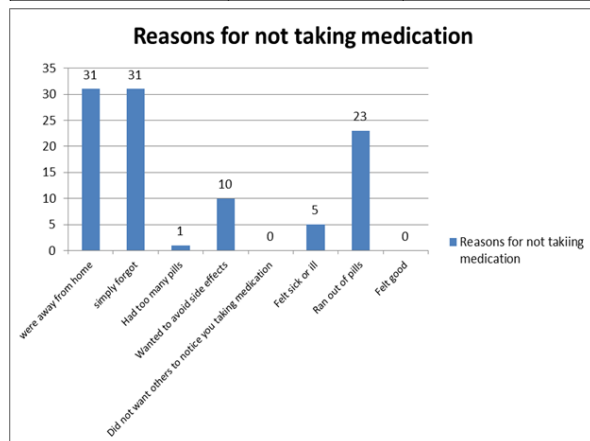
Demographics

A total of 320 respondents were interviewed during the survey which was conducted across five urban clinics within Lusaka. The proportion of females (60%) was higher than that of males (40%), with the majority of the participants being married (64%) and of Christian background (97.8%). Age distribution ranged from 18 years to 77 years, with a median of 37. The majority of the participants were self-employed (36.6%) and almost half of the participants had received secondary education. Self-reported adherence.

There was a higher proportion of participants who were adherent (81.9%) compared to those who were non-adherent (18.1%). About 31% of patients had missed a pill from the start of the course to the day of interview (Table 1). The most frequent reasons for missing a pill were that the patient simply forgot or they were away from home and forgot to carry the drugs. In addition participants claimed that they missed their pill because they ran out of medication (FIGURE 1).

Table 1: Level of adherence.

Self-reported	Adherence frequency (%)	Non-adherence frequency (%)
Within 7 days	81.9% (n=262)	18.1% (n=58)
From start of course to day of interview.	68.6% (n=220)	31.3% (n=100)

**Figure 1: Reasons for not taking medication.**

Bivariate analysis

At Bivariate analysis using Logistic regression (reporting Odds Ratio), those who took alcohol were 2.68 times more likely to be non-adherent to isoniazid compared to those who did not take alcohol (COR: 2.68, CI: 1.49, 4.79, $p=0.001$). Those who smoked were 3 times more likely to be non-adherent to isoniazid compared to those who were non-smokers (COR=3.02, CI: 1.25, 7.30, $p=0.014$). It was also observed that those who took isoniazid for more than 2 months were 66% less likely to be non-adherent compared to those who had taken it for less than 2 months, (COR: 0.34, CI: 0.16, 0.71, $p=0.004$). Participants who experienced side effects such as vomiting were 6 times more likely to be non-adherent compared to those who did not have any side effects (COR: 6, CI: 1.41, 25.43, $p=0.02$). In addition, those that reported having experience peripheral neuropathy were 3 times more likely to be non-adherent compared to those who did not have any side effects (COR: 3, CI: 1.17, 7.67, $p=0.02$). Having an excellent social support reduced the chance of being non-adherent by 80% compared to those who had very poor social support, and this was statistically significant at 95% CI (COR: 0.2, CI: 0.15, 0.78, $p=0.02$).

However, when the variables were adjusted only the variables “duration on INH” (aOR: 0.31, CI: 0.12, 0.74, $p=0.011$) “side effects” i.e. vomiting and peripheral neuropathy (aOR: 11.4, CI: 1.95, 66.7, $p=0.01$ and aOR: 3.73, CI: 1.14, 12.17, $p=0.03$ respectively) and “excellent social support” (aOR: 0.11, CI: 0.02, 0.72, $p=0.02$) remained significant.

Factors independently associated with non-adherence.

Explanatory variables that were significantly associated with non-adherence to Isoniazid at univariate analysis were all selected for analysis and fit into a logistic regression model. Factors that had least contribution to the model, i.e. those that had the highest p -value, were removed in a stepwise manner until a model with only three significant variables remained. The criterion for selecting the best fit model with factors that could explain poor adherence to Isoniazid was achieved by selecting the model with the lowest Akaike's Information Criteria (AIC) value. Therefore, the model with the variable's “alcohol”, “sideeffects” and “duration on INH” had a smaller AIC and could explain the association better compared to the full model. Table 2 shows the variables with their OR, 95% confidence and respective p -values.

Table 2: Factors independently associated with non-adherence to Isoniazid.

Factors	OR	95% CI	P-value
Alcohol			
No	ref	n/a	n/a
Yes	2.70	1.43, 5.10	0.002
Side effects			
Nil	ref	n/a	n/a
Seizures	2.93	0.28, 30.2	0.366

Dizziness	1.51	0.69, 3.33	0.297
Nausea	0.32	0.41, 2.63	0.295
Vomiting	7.32	1.61, 33.2	0.010
Abdominal pain	1.38	0.33, 5.69	0.649
Loss of appetite	1.45	0.12, 16.6	0.761
Peripheral neuropathy	2.29	0.83, 6.34	0.109
Duration on INH			
< 2 months	ref	n/a	n/a
2-4 months	0.27	0.12, 0.61	0.002
4-6 months	0.37	0.17, 0.77	0.008
> 6 months	1	-	-

DISCUSSION

This study assessed the level of adherence and associated factors among people living with HIV in selected Health Centers in Lusaka urban city through the use of self-reported adherence due to its low cost and ease of practicality. This study revealed an overall self-reported adherence rate of 81.6% within 7 days prior to the interview. Intake of alcohol and experiencing side effects such as vomiting was found to be associated with poor adherence while increased duration on Isoniazid for more than 2 months was found to be associated with a reduced chance of one being non-adherent.

The high adherence rate found in this study (81.9%) can be compared to studies done in Addis Ababa where adherence rates were reported as 86.5% and 89.5% respectively.^{20, 21} High IPT completion rates were also noted in a prospective cohort study conducted in Swaziland which attributed its high completion rates to the integration of IPT into ART services.²² This could also explain the findings in our study. In addition, self-reported studies have been shown to be affected by social desirability bias where study participants report socially desirable attributes in a way to impress the researcher.²³ According to “Tourangeau and Yan”,²⁴ they concluded that socially desirable bias is most likely to be motivated by the desire to avoid embarrassment and negative consequences. Therefore, this could have led to over reporting good behavior such as adherence to medication in this study.

However, in other studies adherence rates were much lower than what was found in this study. In one study done in Ethiopia adherence rate was found to be 68.4%,²⁵ similar to a study that was conducted in South Africa, where the adherence rate was 72%²⁶ which is also lower than this study. This may be because the level of adherence in the South African study was measured by the Arkansas method which is a more objective method where INH metabolites have to be identified in urine.

The most frequent reasons for missing a pill were that the patient simply forgot to take their medication (9.69%, N=31) or were away from home and forgot to carry the drugs (9.69%, N=31) or ran out of medication (7.19%, N=23). This is similar to other studies where the predominant reason for not adhering to IPT was forgetting to take pills.^{25, 21} In a study that was done in Dire Dawa, 21.2% of the study participants were reported to have missed doses as a result of forgetting. The same was true in a study that was conducted in Addis Ababa where 24.24% of the study participants mentioned forgetfulness as a reason for missing doses.²⁰ This implies that there is need for a program that strengthens the adherence of patients through memory aids. In this study some of the respondents had reported that they missed doses because of the side effects of the drug such as vomiting. In a study conducted in Tanzania, 14% of individuals had side effects and as a result they were forced to miss doses and were considered as non-adherent.⁸ The other reason mentioned by patients is that they were away from home. This may be attributed to their occupation because majority of the patients in our study were self-employed, therefore, the patient would have left the pills at home while out of town for work or business.

Those that took isoniazid for more than 2 months were less likely to be non-adherent compared to those who had taken it for less than 2 months (aOR: 0.31, CI: 0.12, 0.74, $p=0.011$). This is comparable to other studies done in Ethiopia where patients that took IPT >2 months were more likely to be adherent than those who took it for 1-2 months.^{21, 27} This could be explained by the fact that the repeated counseling services that the patient got from the health facilities during their long follow up period would probably make them more adherent. Patients who experienced side effects such as vomiting and peripheral neuropathy were more likely to be non-adherent compared to those who did not have any side effects (aOR: 11.40, CI: 1.95, 66.7, $p=0.01$) and (aOR: 3.73, CI: 1.14, 12.17, $p=0.03$), respectively. This could be

because symptoms such as vomiting can seriously challenge intake of food and medicine, and also affect the overall state of mood of the patient towards his/her regimen which might result into non-adherence. In addition, those that reported having an excellent social support had a reduced chance of being non-adherent compared to those who had very poor social support (aOR: 0-11, CI: 0-02, 0-72, p=0-02).

The strength of this study is that since there are few previous studies done in this area in Zambia, the results of this study could be used as a baseline for implementation of IPT programs and also further studies. The limitation of this study included the fact that the assessment of the level of adherence by self-report could be subjected to recall and social desirability biases and, as a result, level of adherence could be overestimated and at the same time association could be underestimated. In addition, the fact that this was a cross sectional study we cannot generate cause effect relationship. The use of pill count to support self-report, which was a more objective way of assessing adherence turned out to be equally subjective because clients did not carry their bottles to the clinics for refill. This study was also unable to measure all potential factors of adherence including clinic-level variables which may exert strong influence on adherence of a patient.

In conclusion, the level of adherence for this study was found to be high. Having a longer duration on Isoniazid and having an excellent social support system were significantly associated with good adherence, while experiencing side effects such as vomiting was associated with poor adherence. Among some of the reasons for missing pills were forgetfulness, leaving medication at home and running out of medication. Therefore, we recommend that counseling should be intense for patients who are in first two months of follow-up and patients should be encouraged to use reminders such as cellular phone alarms and also use memory aiding tools such as diaries.

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