Loss to follow up fromisoniazid preventive therapy among adults attending HIV voluntary counseling and testing sites in Uganda

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\textbf{A R T I C L E   I N F O}

Article history:
Received 24 November 2010  
Received in revised form 19 October 2011  
Accepted 19 October 2011  
Available online 10 December 2011

Keywords:
IPT  
Loss to follow-up  
NGO  
VCT  
Uganda

\textbf{A B S T R A C T}

Among HIV-infected adults attending non-governmental organization voluntary counseling and testing and HIV voluntary counseling and testing (VCT) sites in Uganda that provide a nine-month course ofisoniazid preventive treatment (IPT), we report on loss to follow-up (LTFU) and its associated risk factors. The design was a retrospective cohort study of program data spanning a three year period (2006–2008). A total of 586 IPT patients were enrolled of whom 335 (57.1\%) were females with a mean age of 34 years. Of those starting IPT, 341 (58.1\%) were lost to follow-up, 197 (33.6\%) completed IPT, 29 (4.9\%) were discontinued and 19 (3.2\%) died. The return rates at one, three, five and seven months were 78.0\% (457), 62.1\% (364), 52.9\% (310) and 33.6\% (197) respectively. Being less than 30 years of age, widowed, separated, or divorced were found to be associated with a higher risk of loss to follow-up. Sudden improvement in retention on IPT was observed between the years 2006 and 2007, although causes of the improvement are poorly understood hence the need for more research.

At non-governmental VCT sites in Uganda, six out of ten individuals enrolled on IPT are lost to follow-up and efforts to reduce this attrition including systems strengthening might play a critical role in the success of IPT programs.

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1. Introduction

Sub-Saharan Africa is currently faced with a high dual burden of tuberculosis (TB) and HIV/AIDS.\textsuperscript{1} HIV adversely affects TB control in a number of ways: an HIV infected person has a much higher risk of developing active TB compared to an HIV negative person,\textsuperscript{2} TB case rates have increased several-fold, overwhelming health services\textsuperscript{3} and TB is the leading cause of death among HIV infected persons.\textsuperscript{4}

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Isoniazid preventive therapy (IPT) – isoniazid given for 6–9 months to HIV positive individuals – has been shown to reduce the risk of individuals developing active TB by 33\%\textsuperscript{5–7} and 56\% if given for 36 months.\textsuperscript{7} The World Health Organization (WHO) thus recommends IPT as part of the minimum package of care for HIV-infected individuals.\textsuperscript{8,9} Despite this recommendation that was made in 1998, only one country in sub-Saharan Africa, i.e., Botswana, currently implements IPT on a national scale. Loss to follow-up (LTFU) rates in Botswana have been reported to be as high as 63\%.\textsuperscript{10}

In Uganda, although IPT has been recommended in the Uganda national policy guidelines since 2006,\textsuperscript{11} IPT implementation has been largely confined to research settings.
where the primary focus has been on efficacy. 12–14 In particular, there is no information on LTFU and feasibility at program level.

The AIDS Information Centre (AIC), a non-governmental organization, has been a pioneer in the implementation of IPT within HIV voluntary counseling and testing (VCT) sites in Uganda. The AIC follows a VCT protocol that is generic for the entire country, in which clients are screened for HIV and TB at the initial visit. Those found with active TB are started on TB treatment whereas those found HIV positive are referred for care. The HIV positive individuals with latent TB are initiated on IPT. There is generally no information on rates of LTFU by VCT programs; furthermore risk factors associated with LTFU in the VCT setting have not been well characterized: this information could inform policy. Among adult people living with HIV (PLHIV) enrolled in the AIC IPT program we report on LTFU rates and associated risk factors.

2. Methods

This was a retrospective cohort study using routine program data generated from 1 January 2006 to 31 December 2008 at two AIC VCT sites, located in the central (Kampala) and east central (Jinja) parts of Uganda. Both Kampala and Jinja are urban and industrialized areas majorly inhabited by people who are gainfully employed. Loss to follow-up data, including all records of patients in the study period was retrieved from the IPT register.

2.1. Study population

As recommended by the AIC IPT guidelines, patients eligible for IPT included: tuberculin skin test (TST) positive patients in WHO stage 1 and 2, in whom active and previous TB was excluded; patients living within a radius of 20 km from the VCT site, willing to stop alcohol, without a history of hepatitis or a seizure disorder; and not pregnant or breastfeeding. Patients who consented to enroll onto the IPT program were informed that there were no incentives given on enrolling into the program. All consecutive patients on the IPT register for 2006–2008 were included in the analysis.

2.2. Diagnosis of HIV and exclusion of active TB

HIV testing was done using a serial testing algorithm and in line with national guidelines. 15 Determine (Abbott Laboratories, Abbot Japan Ltd., Tokyo, Japan) was used as a first line test and specimens that were found positive were confirmed with stat-pack (Chembio Diagnostics System Inc, NY, USA). In case of discordance, Unigold (Trinity Biotech plc, Bray, Ireland) was used as the tie breaker.

A symptom screen checklist which includes enquiry about cough lasting more than two weeks, fever, hemoptysis, weight loss and night sweats as well as a physical examination was used to exclude active TB. Patients who had a cough underwent sputum microscopy for acid fast bacilli on-site. Those with negative sputum smears but who were suspected of having TB were given a course of oral antibiotics. Those who did not improve based on clinical assessment underwent chest radiography and were diagnosed with smear negative TB if the chest X ray was suggestive of TB.

2.3. Isoniazid preventive therapy

Clients whose HIV results were positive were referred to the clinician for IPT eligibility screening and counseling. Isoniazid preventive therapy was offered for a period of nine months. The isoniazid was self-administered and offered at a daily oral dose of 300 mg. Pyridoxine at a dose of 25 mg daily was given to all patients to prevent peripheral neuropathy.

All patients were initially required to return for a one month follow-up visit after which they returned at two monthly intervals until seven months. Drug compliance was assessed on the basis of self-report. At each visit, patients underwent screening for side effects and active TB. Suspected TB cases were investigated for active TB. Confirmed cases were switched to standardized anti-TB treatment.

For the purposes of this study, a patient who presented at the seven month visit was considered to have completed IPT since WHO recommends six months of IPT as being sufficient. Any patient who did not turn up for a scheduled drug collection between one and seven months was considered lost to follow-up. Other IPT outcomes were defined as follows: discontinued: a patient who was stopped from continuing IPT because of side effects, pregnancy or not returning within a two week delay period from the scheduled visit date; died: a patient known to have died while on IPT.

2.4. Statistical analysis

Data was entered on Epi Info 2000 (CDC, Atlanta, USA) and analyzed using the Statistical Package for Social Scientists (SPSS) version 12 (SPSS Inc., Chicago USA). The LTFU rate at one, three, five and seven months was determined. Measures of risk were determined using adjusted odds ratios. Odds ratios were adjusted using multi-variate logistic regression. The dependent variable was IPT non-completion. Confidence intervals of 95% were used throughout and a p-value of ≤ 0.05 was set as being statistically significant.

3. Results

3.1. Characteristics of the study population

A total of 10,686 individuals tested HIV positive at the two AIC sites. Figure 1 shows the exclusions and drop outs before enrolment on IPT. A total of 1039 TST positive individuals were considered eligible for IPT, of whom 586 (56.4%) were started on IPT which included 335 (57.1%) females. The mean age of all patients was 34 years. Of the 8164 HIV positive individuals screened for TB, 226 (2.8%) were detected with active TB and were offered standardized anti-TB treatment.
Program TST: Return Figure 52.9% in Table 3.2.

<table>
<thead>
<tr>
<th>Completed</th>
<th>Died</th>
<th>Discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td>67 (26.5)</td>
<td>7 (2.8)</td>
<td>15 (5.9)</td>
</tr>
</tbody>
</table>

86 P.M. rate follow-up LTFU schedule.

Figure 1. Isoniazid preventive therapy (IPT) among HIV-positive individuals at two AIDS Information Center sites, Uganda. TST: Tuberculin skin test; VCT: Voluntary counseling and testing.

3.2. Isoniazid preventive therapy outcomes and loss to follow-up

Table 1 shows IPT outcomes and the return rate by visit schedule. The IPT completion rate was 33.6% while return rate at one, three, five and seven months was 78.0%, 62.1%, 52.9% and 33.6% respectively. The study revealed a decrease in LTFU from 2006 (64.5%) to 2008 (52.5%) and an overall LTFU of 58.2% (Table 1).

3.3. Risk factors associated with loss to follow-up

There was no significant gender difference observed however significant risk factors for LTFU included age under 30 years, having no education or only primary education and being divorced, widowed or separated. The risk for LTFU was also found to significantly reduce during 2007 and 2008 compared to 2006 (Table 2).

Table 1

| Return rate expressed as number (cumulative percentage) and outcomes of patients enrolled on the AIDS Information Center’s isoniazid preventive therapy program in Uganda |
|---|---|---|---|---|
| | 2006 | 2007 | 2008 | Total |
| Enrolled | 253 | 156 | 177 | 586 |
| Returned for 1 month visit | 183 (72.3) | 126 (80.8) | 148 (83.6) | 457 (78.0) |
| Returned for 3 month visit | 144 (56.9) | 96 (61.5) | 124 (70.1) | 364 (62.1) |
| Returned for 5 month visit | 120 (47.4) | 83 (53.2) | 107 (60.5) | 310 (52.9) |
| Returned for 7 month visit | 67 (26.5) | 60 (38.5) | 70 (39.5) | 197 (33.6) |
| Lost to follow-up | 164 (64.5) | 84 (53.8) | 93 (52.5) | 341 (58.2) |
| Discontinued | 15 (5.9) | 5 (3.2) | 9 (5.1) | 29 (4.9) |
| Died | 7 (2.8) | 7 (4.5) | 5 (2.8) | 19 (3.2) |
| Completed | 67 (26.5) | 60 (38.5) | 70 (39.5) | 197 (33.6) |
Table 2
Risk factors for loss to follow-up in the AIDS Information Center’s isoniazid preventive therapy program from 2006–2008, using client records with complete data based on key analysis variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>n/N (%)</th>
<th>Adjusted odds ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>102/251 (40.6)</td>
<td>1</td>
<td>0.958</td>
</tr>
<tr>
<td>Female</td>
<td>155/335 (46.3)</td>
<td>1.0 (0.7–1.5)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥40+</td>
<td>45/123 (36.6)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>112/267 (41.9)</td>
<td>1.4 (0.9–2.0)</td>
<td>0.181</td>
</tr>
<tr>
<td>&lt;30</td>
<td>100/196 (51.0)</td>
<td>2.5 (1.5–4.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>153/369 (41.5)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Primary or less</td>
<td>73/137 (53.3)</td>
<td>1.7 (1.1–2.5)</td>
<td>0.014</td>
</tr>
<tr>
<td>Tertiary</td>
<td>31/80 (38.8)</td>
<td>0.9 (0.5–1.6)</td>
<td>0.851</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>53/129 (41.1)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Currently married</td>
<td>114/272 (41.9)</td>
<td>1.5 (0.9–2.3)</td>
<td>0.111</td>
</tr>
<tr>
<td>Divorced/separated/widowed</td>
<td>90/185 (48.6)</td>
<td>1.8 (1.1–3.0)</td>
<td>0.024</td>
</tr>
<tr>
<td>Main reason for VCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived risk</td>
<td>118/289 (41.5)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ill health</td>
<td>62/141 (44.0)</td>
<td>0.9 (0.6–1.4)</td>
<td>0.709</td>
</tr>
<tr>
<td>Preventive measure</td>
<td>44/98 (44.9)</td>
<td>1.2 (0.7–2.1)</td>
<td>0.494</td>
</tr>
<tr>
<td>Unspecified reasons</td>
<td>33/58 (56.9)</td>
<td>1.8 (1.0–3.5)</td>
<td>0.066</td>
</tr>
<tr>
<td>Cohort year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>166/253 (65.5)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>84/156 (53.8)</td>
<td>0.4 (0.3–0.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>2008</td>
<td>93/177 (52.5)</td>
<td>0.6 (0.4–0.8)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

4. Discussion

This is one of the first studies looking at retention on IPT within a routine program setting in Uganda. The study shows that six out of every ten individuals enrolled on IPT are lost to follow-up which is similar to the findings of a Botswana study. Risk factors associated with this attrition include age under 30 years, having primary level or no education and being divorced, widowed or separated and enrollment on the IPT at AIC in the year 2006. These findings indicate the need for a modified IPT implementation strategy in low and middle income settings that promotes retention. The current WHO drive for increasing the duration of IPT to 36 months without new strategies for enhancing retention will need re-examination in a program context.

In this study we observe an improvement in patient retention from 26.5% in 2006 to 39.5% in 2008. Although it was not in the scope of this study to explore the possible causes of patient retention, it may probably be due to improvement in the service delivery. Importantly, there was a high attrition rate between the HIV positive test and enrolment for IPT. We attribute this to the process of IPT recruitment which is prolonged by investigations to exclude active TB, the 48 to 72 hour turnaround time for TST as well as poor supply of logistics for IPT medicines resulting in isoniazid stock-outs. Giving HIV positive results at the same sitting with providing IPT specific screening and counseling could have in part minimized this high attrition rate. Procurement and supply of IPT has now become the responsibility of the National TB Program, and this has resulted in considerable improvements of isoniazid stocks. Considerations for proper placement of the IPT programs within the framework of existing national structures are thus important.

The WHO recommendations of ‘IPT for all HIV-infected living in populations with a high prevalence of tuberculous infection’ that have recently been adopted by Ministry of Health Uganda for both public and private provider service providers in the country may reduce attrition rates between the HIV positive test and IPT initiation. This however may not impact on the LTFU rates after IPT initiation thus rendering the findings in this study still valid. Conversely, given that only 1039 patients were eligible for IPT out of 3165 who accepted TST as well as the limited protection that IPT provides to those who are TST-negative, deeper thought on, and cost effectiveness analysis of the IPT scale-up according to WHO are needed.

Although there was a progressive LTFU through the entire IPT period more than 30% of all losses occurred within the first month of treatment. This finding suggests the need to improve the initial adherence counseling and education on the importance of remaining compliant.

Some of the possible reasons for LTFU may include: adverse drug reactions due to isoniazid although these were minimized by the program’s routine provision of pyridoxine to all enrolled clients; inconsistent IPT supplies; people enrolled on IPT are a relatively healthy cohort (WHO stage 1 and 2) who do not see the relevance of IPT over the nine month period and are also inadequately counseled for the same; health workers may not understand the benefits of IPT and therefore may not adequately encourage patients to be compliant; patients who visit other health care facilities or those that are transferred out might drop IPT; and finally IPT structures are still too centralized meaning that patients have to travel relatively long distances to reach the AIC sites which are currently providing IPT in Uganda.

The associated difficulties and transport costs may be a deterrent to IPT compliance. A possible way forward in improving IPT access is to decentralize continued
counseling and access to IPT ‘drug refills’ to the community level. This will require liaison with existing associations of people having AIDS and related networks as well as village health teams where applicable, training and a system for drug monitoring and supervision. Considering that continued screening for TB among those who start IPT involves a simple symptom screening, it would seem reasonable to think that this activity could be easily task-shifted to trained community workers. They should be trained to advise patients to stop IPT and refer to a community nurse or the closest health facility in case TB is suspected.

In most HIV programs, direct costs, stigma, life style, travel, and side effects have been identified as major drivers for non-compliance.16 The fact that people under 30 years had a higher risk of LTFU might be a reflection of low risk perception. Alternatively, since the majority of Ugandan youth are unemployed,17 their less stable economic situation might result in their being unable to meet travel and other costs associated with IPT.18–21

Having no education or attaining only primary education was associated with a higher risk of LTFU. An earlier study by Wandwalo and Mørkve demonstrated significant differences in knowledge on TB disease and treatment according to the number of years of school education in Mwanza, Tanzania and its association with poor adherence and LTFU.20 Wandwalo et al.’s findings might therefore explain the association between education level and LTFU reported by this study.

Being divorced, widowed or separated was also a significant risk factor for LTFU. Differences in health care utilization by marital status have been reported previously,21 and high IPT default rates among the widowed, divorced or separated reported in this study might suggest that people in broken relationships might be less compliant due to a gap in support of close relatives which is fundamental in coping with HIV/AIDS and sustaining compliance.23–26 Higher risk in the widowed, separated and divorced group might also be linked to increased household responsibilities which require shouldering workload that could have been shared between two household heads.

In addition to groups at risk, this study highlights a number of important operational observations at the health facility level. First, the national policy recommends TST as part of the eligibility criteria, however, the WHO suggests that this is not necessary in resource limited settings. It seems justified to drop the step of performing TST and offer IPT to all HIV positive patients (irrespective of TST) since 760 (22%) of those offered TST dropped out due to this step. Second, the issue of isoniazid stock-outs which actually prevented 44% of all IPT eligible individuals from enrolling is unacceptable and challenges the credibility of the IPT program in the eyes of patients, health workers and the community at large. These stock-outs reflect lack of clarity in procurement and management responsibilities linked to isoniazid in 2006 and 2007. This issue has now been clarified in collaboration with the National Tuberculosis and Leprosy Program (NTLP) which has taken up responsibility and should avoid further stock outs. Whether streamlining IPT product logistics in 2007 explains the sudden increase in retention to IPT observed by this study needs to be further explored. Finally, an important positive spin-off of this study is that systematic TB screening of HIV positive individuals at VCT centres detected 226 TB cases constituting 3% of the cohort. These individuals might have been missed without this active TB screening strategy. This highlights the relevance of ensuring that active TB screening and referral is included at all VCT sites and is a worthwhile endeavor in itself.

The strengths of this study were: it was conducted in a routine program setting and the findings are thus likely to reflect the operational reality on the ground; the study adhered to a well defined protocol; and adherence to the STROBE guidelines on reporting was observed.27

The limitations of this study were: like other studies using secondary data, this study could not exhaustively assess all factors, such as distance, cost and time to health facility that might influence LTFU; for the same reason, IPT completion was measured using a proxy of 7-month drug pick-up which might have overestimated the IPT completion rate; and IPT is given to a very selected cohort due to the exclusions and envisaged dropouts therefore the findings might not necessarily be generalizable to a wider cohort. In addition, the study did not collect information relating to TB infection and disease including Baccille, Calmette, and Guerin (BCG) vaccination history, and contact with an active TB case.

At non-government organization VCT sites in Uganda, six out of ten individuals are lost to follow up. The patient-related risk factors for LTFU from IPT include age less than 30 years, little formal education and a broken family whereas poor logistics management of IPT products constitute one of the major health system risk factors. These findings should alert those intending to implement IPT programs about the importance of strategically addressing attrition between HIV positive results and IPT initiation and patient retention in IPT programs. The sudden improved retention on IPT observed between 2006 and 2007 suggests systems strengthening might play a critical role in the success of IPT programs. More studies could be done to further examine this.

Authors’ contributions: PMN, RB and KB conceived the study; PMN, JKM, RW and KB designed the study; PMN, NK and RZ analysed and interpreted the data; PMN, JKM and RZ drafted the manuscript; JKM, NK, RW, KB and RZ critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. PMN is guarantor of the paper.

Acknowledgements: Fredrick Baruga for his input in the data assembly.

Funding: This research was supported through an operational research course, which was jointly developed and run by the Centre for Operational Research, International Union Against Tuberculosis and Lung Disease, and the Operational Research Unit, Medecins sans Frontieres, Brussels.

Competing interests: None declared.
Ethical approval: Ethical approval was obtained from Makerere University School of Public Health research ethics committee, Uganda National Council for Science and Technology and from the Ethics Advisory Group of the International Union against TB and Lung disease.

References