Implementation of isoniazid preventive therapy in an HIV clinic in Cambodia: high rates of discontinuation when combined with antiretroviral therapy

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Abstract

Objective Data on feasibility and completion rates of isoniazid preventive therapy (IPT) in HIV-infected patient in Asia are limited. Within a hospital-based HIV programme in Phnom Penh, Cambodia, we determined the proportion completing IPT and reasons for non-completion.

Methods Retrospective cohort study using HIV/IPT programme data, including all adults starting IPT (300 mg/day self-administered for 24 weeks) from February 2011 to March 2013. All patients underwent symptom screening and further investigations as indicated. After ruling out tuberculosis (TB), IPT was started, with monthly follow-up visits. As per national guideline, IPT was only prescribed for ART-naive patients. IPT completion was defined as taking IPT for at least 22 of the planned 24 weeks. Stavudine/lamivudine/nevirapine was the preferential first-line ART regimen.

Results Among 445 ART-naive patients starting IPT (median age: 35 years (IQR: 31–43), median CD4 count 354 cells/µl (IQR 215–545) and 288 (65%) were female), 214 (48%) started ART after a median of 4 weeks (IQR 2–6) on IPT (‘concurrent ART’). Overall, 348 (78%) completed IPT. Among individuals with concurrent ART, the completion rate was 73% (157/214). Those without concurrent ART had a higher completion rate (83%; 191/231; P 0.017). The main reason for non-completion with concurrent ART was drug toxicity (mainly hepatotoxicity/rash), occurring in 22% (48/214). Without concurrent ART, the main reason for non-completion was loss to follow-up (16/231; 7%). Fourteen (3%) patients were diagnosed with TB while on IPT, of whom three had a positive TB culture at baseline. An additional 14 TB cases were diagnosed after IPT completion; four were bacteriologically confirmed.

Conclusion Although overall completion rates were acceptable, IPT discontinuation due to drug toxicity was common in patients subsequently initiating ART. Future studies should evaluate whether this relates to IPT, ARVs or both, and whether the increased toxicity would justify delaying IPT initiation until stabilisation on ART.

Keywords isoniazid, prophylactic, adverse events, completion, adverse effects, Asia

Introduction

Tuberculosis (TB) is the leading cause of death in patients infected with HIV in economically poor settings [1]. To mitigate this effect, WHO has issued the Three I’s Guidelines, comprising intensified case finding, infection control and isoniazid preventive therapy (IPT) [2–4]. The efficacy of IPT in HIV-infected individuals has been demonstrated in several clinical trials [3–5].

While a systematic review demonstrated an overall reduction of TB incidence of 32% in individuals not on antiretroviral therapy (ART), the effect was mainly confined to patients with a positive tuberculin skin test [3–5]. In a recent trial from South Africa enrolling individuals on ART, IPT reduced the risk of TB by 37% [6]. Although IPT has been recommended for people living with HIV by WHO since 1998 [7], IPT uptake at country level has traditionally been low [3, 4, 8–11]. Revised WHO guidelines providing detailed recommendations for TB screening – clearly indicating
that a tuberculin skin testing is not required for IPT [3, 4] – combined with increased efforts for integrating TB–HIV activities have led to a higher IPT uptake [12–15]. Several recent trials conducted in sub-Saharan Africa and Brazil have further added to the evidence base [16–18].

An important operational question that remains to be answered relates to the timing of IPT and ART relative to each other. Although the current WHO guideline recommends IPT irrespective of ART use, it does not precisely define how the two interventions can optimally be used together [3, 4]. In some programmes, IPT is started immediately after enrolment into HIV care, as part of the pre-ART care package [19]. In the event of subsequent ART initiation, the patient benefits from the additive preventative effect of IPT and ART [17, 18, 20, 21]. Others have argued that ART eligible patients should first be started on ART and initiate IPT several months later, when TB can be ruled out more reliably following CD4 cell recovery [22]. Concurrent use of IPT and ART carries the risk of overlapping toxicity and difficulties in identifying the culprit drug, especially if both are initiated within a short time span. In individuals recently started on ART in a recent trial in South Africa, subsequent initiation of INH was associated with a 2.7-fold increased risk of severe liver function test abnormalities, but the difference did not reach statistical significance. However, the 95% CI was very wide, with the upper border reaching up to a 13-fold increased risk [6].

Asia hosts around 13% of all HIV-infected individuals but carries around 60% of the global TB burden [14, 23]. South-East Asia has a relatively large burden of TB–HIV coinfection. However, the evidence base on IPT in Asia remains weak with only one clinical trial on IPT in HIV-infected individuals conducted in the region. This trial, conducted in India, did not include the most commonly used WHO recommended regimen of 6 months of isoniazid (INH) [24]. Moreover, there is a dearth of studies on the feasibility of implementing and tolerability of IPT in routine practice within the Asian setting. The few reports from Thailand [25, 26] employed IPT targeted by tuberculin skin testing, which is not feasible in many low-income high TB burden countries. Moreover, there are indications from various settings that completion of IPT could be low [7, 27, 28], jeopardising its overall impact.

In this study, we aimed to determine the proportion of patients who completed self-administered IPT in a hospital-based HIV programme in Cambodia, and the reasons for non-completion. We also report on the incidence of tuberculosis during or after IPT.

Methods

Study setting

Cambodia is a low-income country in South-East Asia, with an estimated population of close to 15 million. Cambodia ranks second globally in terms of TB prevalence and first in terms of TB-related mortality [14]. In 2012, the estimated incidence and prevalence of all forms of TB was 411/100 000 inhabitants and 764/100 000 inhabitants, respectively [14]. A prevalence of TB in newly diagnosed patients with HIV of around 15–20% has been documented [29]. Conversely, around 4% of TB cases were found co-infected with HIV [14]. The national HIV and TB programme started four IPT pilot sites in 2003 and scaled-up to 24 sites nationwide in 2010 [30, 31].

Since March 2003, the Sihanouk Hospital Center of HOPE (SHCH), a non-governmental hospital, has been providing free HIV care (including ART and management of opportunistic infections) for adults, as part of the national programme, with currently more than 3000 adults on ART in regular follow-up. In February 2011, SHCH initiated IPT according to the Cambodian national TB/HIV guideline.

Study design and population

We conducted a retrospective cohort study, including all adult (>18 years) patients starting IPT within the SHCH HIV care programme between 15 February 2011 and 15 March 2013. Data were censored on 15 March 2014 to ensure a minimal follow-up period of 6 months after the planned 6 months of IPT.

TB screening and diagnostic procedures

According to the guideline, all patients with HIV were systematically screened for TB in the HIV clinic at each clinical encounter using the three symptoms’ screening (any cough or fever at any time or drenching night sweats for more than 2 weeks in the past 4 weeks) [29]. Those who screened positive underwent further diagnostic work-up for TB [32–34]. Diagnostic investigations comprised sputum smear microscopy and culture (Löwenstein-Jensen medium; single culture/patient), chest radiography, abdominal ultrasound and lymph node aspiration. GeneXpert was not part of the routine diagnostic work-up. We followed WHO criteria for smear-positive pulmonary TB (PTB), smear-negative pulmonary TB or extrapulmonary TB (EPTB) diagnosis [32–34].
Initiation and monitoring of IPT

According to the national guideline, IPT had to be initiated when TB had been ruled out; the patient was not on ART; there was no alcoholism (daily alcohol consumption); no known liver dysfunction; and no history of allergy to INH. Two groups of patients were eligible for IPT: asymptomatic individuals (negative symptom screening) and individuals scoring positive on any of the three symptoms but with TB ruled out after subsequent investigation. The decision by the national programme to provide IPT only to ARV-naïve individuals was based on the assumption that these individuals were most likely to benefit and hence – in the first stage of the IPT roll-out – should be prioritised.

For eligible patients, the physician in charge provided counselling on the benefit of IPT and the potential side-effects. If the patient agreed, INH 5 mg/kg per day (standard adult dose of 300 mg once daily; 200 mg/day if weighing <40 kg) was prescribed for a total duration of 24 weeks, in combination with pyridoxine 50 mg per day. At each monthly follow-up visit, patients were evaluated for TB (symptom screening), adherence to and safety of IPT, and IPT was dispensed for 1 month. Those with a positive TB screen underwent a diagnostic work-up to rule out active TB. Liver enzymes were checked only when clinically indicated (symptoms/signs compatible with hepatotoxicity such as jaundice, nausea and vomiting). Indications to discontinue IPT included poor adherence, severe peripheral neuropathy (WHO grade 3–4), severe rash and liver function tests more than three times the upper limit of normal in a symptomatic patient. For individuals in whom IPT initiation was followed by discontinuation of ART with possibly overlapping toxicity (e.g. hepatotoxicity while taking nevirapine), the SHCH practice was to first discontinue INH. If no improvement occurred, this was followed by ART discontinuation. In case of severe toxicity, both drugs were stopped at once.

Management of ART and opportunistic infections

All patients with WHO stages II/III/IV disease or a CD4 count less than 200 cells/μl were given cotrimoxazole prophylaxis. Fluconazole primary prophylaxis was prescribed for patients with WHO stage III and IV disease or CD4 count below 100 cells/μl, after ruling out cryptococcal infection using a cryptococcal antigen detection test on blood. ART was initiated according to WHO recommendations: all patients with WHO stage III or IV disease or a CD4 cell count less than 350 cells/μl [33, 34]. First-line treatment consisted of a generic fixed-dose combination of stavudine, lamivudine and nevirapine. For patients with TB, nevirapine was replaced by efavirenz. The national guideline did not specify at what point in time ART had to be initiated after starting IPT.

Follow-up was carried out monthly during the first 6 months of ART and subsequently every 2–3 months for clinically stable patients. Baseline laboratory testing prior to ART initiation included haematology, liver and renal function tests, hepatitis B and C serology, and CD4 cell count. A full blood count and CD4 cell count were carried out every 6 months after ART initiation, with liver function tests performed more regularly. Details of the TB and ART programme have been previously reported [35–38].

Data collection and statistical analysis

For routine care, TB-related information was prospectively collected using standardised data collection forms from the HIV–TB programme of the hospital with regular quality checks. Additionally, TB data were collected separately as part of routine monitoring of the TB programme. For this analysis, data from the HIV database were compared with the hospital’s TB programme data, and inconsistencies resolved by file review.

IPT programme outcomes were stratified as completion (having taken at least 22 weeks of the planned 24 weeks of IPT) and non-completion (failure to complete 22 weeks for any reason). The 22-week cut-off was used to allow for minor deviations of the protocol, which could sometimes be performed for practical reasons and which were unlikely to undermine the efficacy of IPT. Reasons for non-completion were classified as all-cause death, loss to follow-up, patient decision (refusal), doctor decision, TB diagnosis while on IPT, drug toxicity and other. Baseline patient characteristics were described using medians and interquartile ranges (IQR) for continuous data and frequencies and percentages for categorical and binary data. Groups were compared using the chi-square or Fisher’s exact test.

Ethics

Since the launching of the HIV programme, clinical data have been routinely collected for purposes of programme monitoring and evaluation, and research. Patients were requested to give informed consent to store and use their data. Data collection and informed consent procedures were approved by the Institutional Review Board of the SHCH and the Institute of Tropical Medicine, Antwerp, Belgium. No patient identifiers were included in the data set used for this analysis.
Results

Between 15 February 2011 and 15 March 2013, 875 ART-naïve individuals were seen at the HIV clinic. Among those, 244 had already or were subsequently started on TB treatment, 445 initiated IPT, and 186 never initiated IPT or TB treatment (Figure 1).

Of the 445 initiating IPT, 157 (35%) were male; the median age was 35 years (IQR 31–43), see Table 1. There were 11 (2.5%) individuals with prior TB treatment before IPT initiation. The median CD4 count before IPT was 354 cells/µl (IQR 215–545). IPT was started a median of 20 days (IQR 0–827) after enrolment in HIV care. A total of 214 (48%) individuals started ART within a median of 31 days (IQR 15–49) after starting IPT, and 92 (21%) individuals began ART after IPT completion.

Of the 445 individuals who started IPT, 348 (78%) completed at least 22 of the 24 planned weeks (Figure 1).

The median time to IPT discontinuation was 8 weeks (IQR 5–13) after IPT initiation.

Loss to follow-up was the main reason for INH discontinuation in the group not on ART during IPT (Table 2). Conversely, toxicity was the most common reason for IPT discontinuation in individuals on concurrent ART, occurring in 46 (22%) of the 205 individuals initiating nevirapine-based ART and in two (25%) of the eight individuals on efavirenz-based ART. Toxicity occurred a median of 5 weeks (IQR 4–12) after IPT initiation in patients not on ART. When concurrent IPT/ART was given, toxicity occurred after a median of 9 weeks (IQR 6–14) on IPT and a median of 4 weeks (IQR 2–6) on ART. In the group of individuals starting ART while on IPT, hepatotoxicity was documented in 32 (16%) of the 205 individuals initiating nevirapine-based ART and in two (25%) of the eight individuals on efavirenz-based ART.

Figure 1 Flowchart describing inclusion in the study, subsequent initiation of antiretroviral treatment (ART), (non)-completion of isoniazid preventive therapy (IPT) and diagnosis of tuberculosis, Phnom Penh, Cambodia (2011–2013).
Table 1 Baseline characteristics of adults started on isoniazid preventive therapy (IPT), Phnom Penh, Cambodia (2011–2013; N = 445)

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%), median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>157 (35.3)</td>
</tr>
<tr>
<td>Female</td>
<td>288 (65.7)</td>
</tr>
<tr>
<td>Age, years</td>
<td>35 (31–43)</td>
</tr>
<tr>
<td>Baseline CD4 count, cells/µl (n = 400)</td>
<td>354 (215–545)</td>
</tr>
<tr>
<td>Time from enrolment to IPT in days</td>
<td>20 (0–827)</td>
</tr>
<tr>
<td>ART initiation</td>
<td></td>
</tr>
<tr>
<td>Not started</td>
<td>139 (31.2)</td>
</tr>
<tr>
<td>During IPT</td>
<td>214 (48.1)</td>
</tr>
<tr>
<td>After IPT</td>
<td>92 (20.7)</td>
</tr>
<tr>
<td>ART regimen (n = 306)</td>
<td></td>
</tr>
<tr>
<td>Nevirapine containing</td>
<td>280 (91.5)</td>
</tr>
<tr>
<td>Efavirenz containing</td>
<td>25 (8.2)</td>
</tr>
<tr>
<td>Lopinavir containing</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Hepatitis B surface antigen (+); (n = 317)*</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>29 (9.2)</td>
</tr>
<tr>
<td>Negative</td>
<td>285 (90.8)</td>
</tr>
<tr>
<td>Hepatitis C antibody (+); (n = 319)*</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>16 (5.1)</td>
</tr>
<tr>
<td>Negative</td>
<td>301 (94.9)</td>
</tr>
</tbody>
</table>

ART, antiretroviral treatment; IQR, interquartile range.
*B: Testing for hepatitis B and C was routinely performed as part of the pre-ART.

Among individuals tested for hepatitis B or C coinfection, the risk of IPT discontinuation due to hepatotoxicity was statistically significantly higher for hepatitis B coinfection (7/29 (24%) vs. 28/288 (10%); P = 0.018) but not significantly higher for hepatitis C coinfection (3/16 (19%) vs. 32/303 (11%); P = 0.307). There were no deaths attributed to INH toxicity. Four patients discontinued IPT at their own request at a median of 7 weeks after starting IPT.

A total of 14 (3.1%) cases of tuberculosis were diagnosed during IPT, at a median of 7 seven weeks (IQR 2–9) after IPT initiation (Table 3). Six of the 14 cases had initiated ART after IPT; the median CD4 count at IPT start was 97 cells/µl (IQR 46–431). Three of the 14 cases were culture confirmed. All three were smear negative but culture positive at baseline. For the remaining 11 TB cases, culture results at the time of TB diagnosis were available for 10. None grew Mycobacterium tuberculosis. For one smear-positive TB, culture grew non-tuberculous mycobacteria.

Another 14 TB cases were diagnosed after IPT, at a median of 13 weeks (IQR 4–43) after IPT discontinuation. Thirteen of the 14 cases had initiated ART after IPT; the median CD4 count at IPT start was 204 cells/µl (IQR 42–348). TB culture results were available for 12, with three positive culture results. This included one patient who discontinued IPT after 12 weeks of use due to toxicity and had a positive TB culture 5 months after IPT discontinuation, with resistance to isoniazid, rifampicin and streptomycin. A second patient completed IPT and had a positive culture several months later, with resistance to isoniazid, rifampicin, streptomycin and ethambutol. Both were TB, possibly MDR-TB, contacts. The third patient had discontinued IPT due to toxicity after 5 weeks and developed (pan-susceptible) TB 2 years later.

Discussion

This is one of the few studies reporting on the implementation of IPT in HIV-infected patients in Asia. Whereas completion rates were acceptable and comparable with other reports, loss to follow-up was common for patients not yet eligible for ART when starting IPT. Conversely, discontinuation of IPT due to toxicity was common in those initiating ART while on IPT.
The clinical practice in our programme of first evaluation for ART eligibility and preparation for ART initiation is likely to encourage early ART initiation following IPT discontinuation due to presumed drug toxicity was even more common in individuals with concurrent ART, occurring in around one in five individuals. This could be due to a particular feature of our study, namely that IPT was only prescribed to individuals not (yet) on ART, in line with the national guidelines. Consequently, IPT might, similarly to cotrimoxazole, be initiated immediately after enrolment in the HIV care programme, but – after evaluation for ART eligibility and preparedness – ART would be started a few days to a few weeks later. The concurrent use of ART and IPT, with overlapping toxicity (e.g. liver, rash and neurotoxicity), might have increased the overall toxicity events in this study, especially if both were initiated within a short time span. Given the lack of a control group (e.g. patients on ART only), we can, however, not conclude on the extent of additional toxicity that this would entail. Moreover, the observed toxicity might have been due to INH, ARVs or both. Nevertheless, the 21% (43 of 205) of individuals developing skin or liver toxicity requiring discontinuation of nevirapine was clearly higher than the 8–14% we previously reported in our programme when nevirapine was prescribed without concurrent IPT [47].

The clinical practice in our programme of first discontinuing IPT when skin or liver toxicity occurs after

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### Table 3 Tuberculosis (TB) culture results of individuals diagnosed with TB during or after isoniazid preventive therapy (IPT), Phnom Penh, Cambodia (2011-2013)

<table>
<thead>
<tr>
<th>Culture results at time of TB diagnosis</th>
<th>Smear (+)</th>
<th>Smear (-)</th>
<th>EPTB; n = 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>during IPT</td>
<td>Smear (+)</td>
<td>Smear (-)</td>
<td>EPTB; n = 8</td>
</tr>
<tr>
<td>Not done</td>
<td>–</td>
<td>(3)†</td>
<td>–</td>
</tr>
<tr>
<td>Sterile</td>
<td>–</td>
<td>(S)</td>
<td>–</td>
</tr>
<tr>
<td>Growth of NTM</td>
<td>1 (S)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Growth of MTB</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Culture results at time of TB diagnosis</th>
<th>Smear (+)</th>
<th>Smear (-)</th>
<th>EPTB; n = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>after IPT</td>
<td>Smear (+)</td>
<td>Smear (-)</td>
<td>EPTB; n = 6</td>
</tr>
<tr>
<td>Not done</td>
<td>1 (ND)</td>
<td>1 (ND)</td>
<td>–</td>
</tr>
<tr>
<td>Sterile</td>
<td>2 (S); 1 (ND)</td>
<td>2 (S); 3 (ND)</td>
<td>–</td>
</tr>
<tr>
<td>Positive</td>
<td>MTB</td>
<td>1 (ND); 1 (ND)</td>
<td>1 (S)</td>
</tr>
<tr>
<td>NTM</td>
<td>1 (S)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**EPTB,** extra-pulmonary tuberculosis; **NTM,** non-tuberculous mycobacteria; **MTB,** mycobacterium tuberculosis; **PTB,** pulmonary tuberculosis.

*Baseline culture results is given in parenthesis, S, sterile; ND, not done; no cultures were contaminated.
†Started on IPT but later diagnosed with TB when baseline culture results became available: smear-negative, culture positive PTB.
recent ART initiation could be criticised because in this scenario, ART was more likely to be the culprit. However, the risk of IPT-related toxicity (particularly liver toxicity) extends beyond the first few weeks [46]. Moreover, it was felt among treating clinicians that avoiding unnecessary discontinuation of ART – with the associated risk of HIV resistance – should prevail over IPT discontinuation.

From an operational perspective, the key concern is not whether the drug toxicity leading to IPT discontinuation was due to INH or the ARVs. The key concern is that a high rate of patients discontinued IPT due to drug toxicity when ARVs and IPT are initiated within a short time span, and this is likely to significantly decrease the overall effectiveness of IPT. Some have argued that it might be better to clearly separate the initiation of IPT and ART. In this scenario, ART eligibility would be assessed prior to INH prescription and ART eligible patients would first be started on ART, followed by IPT several weeks to months later [22]. However, there is currently insufficient evidence to recommend this approach. Prospective studies should first quantify the extent of increased toxicity by coprescription. If confirmed, it remains to be assessed whether this would be sufficiently pronounced to justify delaying IPT initiation, because delayed IPT prescription would obviously decrease its impact on TB prevention.

As expected, a few prevalent TB cases were missed and only revealed by culture, but all responded well to first-line therapy. A relatively high number of TB incidence was diagnosed during or early after discontinuing IPT. As there was no control group, IPT effectiveness could not be determined. Moreover, most TB diagnoses were not bacteriologically confirmed, casting doubt whether these were true TB cases. Fear of missing active TB in a patient bacteriologically confirmed, casting doubt whether these were true TB cases. Fear of missing active TB in a patient on IPT could have led to overdiagnosis. On the other hand, most cases comprised EPTB in patients with advanced HIV disease. Diagnosis often relied on abdominal ultrasound findings, which have been found to be highly specific in our setting [48]. The evidence base for effectiveness of IPT for HIV patients in Asia remains limited. Programme data from Thailand suggest it to be effective in tuberculin skin test-positive individuals [25, 26]. Pending clinical trial evidence, careful evaluation of programme data in countries implementing IPT is warranted.

Conclusions

IPT implementation was feasible in this HIV programme in South-East Asia, with acceptable completion rates. However, IPT was relatively frequently discontinued in patients subsequently initiating ART, mainly due to drug toxicity. Further comparative studies are required to determine to what extent initiation of IPT and ART within a short time span indeed results in additional toxicity, and if so, whether this additional toxicity is sufficient to recommend a delay in IPT initiation.

Acknowledgement

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