Adverse events with isoniazid preventive therapy: experience from a large trial in South Africa

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Abstract

Objectives: We describe isoniazid-related adverse events in Thibela TB, a cluster-randomised study of community-wide isoniazid preventive therapy (IPT) among gold miners in South Africa, where HIV prevalence is estimated at 30%.

Methods: Consenting employees were screened prior to IPT for active tuberculosis and increased risk of isoniazid toxicity using a questionnaire and chest radiograph. Study-defined IPT-related adverse events were sought at each study visit: liver function tests were only performed if clinically indicated. In a sub-study, we questioned consecutive participants at baseline and months 1, 3 and 6 concerning minor IPT-related adverse events.

Results: Among 24,221 participants (95.2% male, median age 40 years), 130 individuals had 132 study-defined adverse events (0.54%); 61 (0.25%) possible hypersensitivity rash, 50 (0.21%) peripheral neuropathy, 17 (0.07%) clinical hepatotoxicity and 4 (0.02%) convulsions. Four events (two hepatotoxicity, one fatal, and two convulsions) fulfilled criteria for seriousness. Clinical hepatotoxicity was associated with consumption of alcohol (0.11% vs. 0.03% if no alcohol consumed, odds ratio 3.9 [95% confidence interval 1.2-12.1]), but not with sex, age, weight or concurrent antiretroviral therapy. In the sub-study, 324/498 (65.1%) participants reported better health since starting IPT; 180/324 (55.6%) reported that this was because of increased appetite. The frequency of specific minor symptoms was low among those taking IPT, and all symptoms were reported less often than at baseline.

Conclusions: The risk of adverse events, particularly hepatotoxicity, was very low in this population. Our data suggest that clinical criteria can safely be used for screening prior to and monitoring during IPT.

Keywords: Isoniazid preventive therapy, tuberculosis, HIV, adverse effects

Introduction

Isoniazid preventive therapy (IPT) is, along with intensified case finding and infection control, a key component of the World Health Organization's "3 Is" strategy to reduce the burden of tuberculosis among people with HIV infection. Although IPT is effective in reducing tuberculosis incidence among people with HIV [1], implementation has been disappointingly slow [2]. One obstacle to implementation is concern about adverse events attributable to isoniazid, in particular hepatotoxicity, which is rare but potentially life-threatening [3], particularly if isoniazid is continued in the context of symptomatic hepatitis.

In South African gold mines, tuberculosis has been a major occupational health problem for decades, attributed to a high prevalence of silica dust disease and congregate living conditions. The advent of HIV infection in the 1990s exacerbated this problem, with tuberculosis incidence rising to exceed 4000 per 100,000 [4], despite comprehensive tuberculosis control programmes managed by the mine health services. We are conducting a cluster-randomised trial ("Thibela TB") to determine the effect of community-wide screening for active tuberculosis followed by IPT offered to all members of the cluster (all employees of a gold mine shaft) unless isoniazid is specifically contraindicated (trial registration ISRCTN63327174). We report, firstly, IPT-related adverse events in this trial, and, secondly, a substudy among trial participants to describe minor IPT-related symptoms.

Methods

Thibela TB study

The Thibela TB study, described in detail elsewhere [5], is a cluster randomised trial of community-wide IPT in South African gold mines, with a total study population of around 80,000. In intervention clusters, all employees were offered screening for active tuberculosis using a symptom screen and digital chest radiograph: those identified as tuberculosis suspects were referred to mine health services for further investigation and treatment. All individuals with no evidence of active

tuberculosis and no other specific contraindication were offered IPT (300mg with 25mg pyridoxine, self administered, daily for nine months). Trained research nurses were responsible for enrolment, monthly review of participants and IPT dispensing, reflecting how this intervention would be implemented in an operational setting.

Criteria for non-eligibility for isoniazid preventive therapy

Criteria for non-eligibility for IPT (in addition to suspected active tuberculosis) were defined to identify individuals at higher risk of toxicity from isoniazid, determined by self-report. These were: known or suspected hypersensitivity to isoniazid; history of chronic liver disease; symptoms suggesting active hepatitis; alcohol use exceeding 28 units per week (for men, or 21 units for women); history of convulsions; history of psychosis; peripheral neuropathy grade 2 (moderate) or greater, as defined by the AIDS clinical trials group [6]; pregnancy, up to three months post partum, or women of child-bearing potential who declined to use contraception; concomitant medication with phenytoin, carbamazepine, warfarin, theophylline, disulfiram, selective serotonin reuptake inhibitor antidepressants, ketoconazole or itraconazole; and weight less than 40kg.

Definition of adverse events

Adverse event reporting, designed to ensure participants' safety, not to identify unexpected new adverse events potentially associated with isoniazid, was limited to study-defined events in the pre-specified categories of hepatitis, hypersensitivity, peripheral neuropathy, convulsions and psychosis, between the first IPT dispensing date and two months after the last IPT dispensing date (i.e. one month after the last scheduled dose of IPT). Among participants who had been dispensed IPT, we recorded all pregnancies in this timeframe, to detect any adverse pregnancy outcomes; and reported to the Ethics Committee all deaths (regardless of cause).

Adverse events were defined as serious if they resulted in death, were life-threatening, required hospitalisation or prolonged existing hospitalisation, or resulted in a congenital abnormality or birth defect [6]. Liver enzyme abnormalities were graded mild, moderate, severe or potentially life-threatening if they were 1.25-2.5, 2.6-5.0, 5.1-10.0, and >10.0 times the upper limit of the laboratory normal range, respectively. Adverse events were classified as *definitely associated* with the study medication if the adverse event and administration of study agent were related in time, and a direct association could be demonstrated; as *probably associated* if the adverse event and administration of study agent were reasonably related in time, and the adverse event was more likely explained by study agent than other causes; as *possibly associated* if the adverse event and administration of study agent were reasonably related in time, and the adverse event could be explained equally well by causes other than study agent; and as *not associated* if the adverse event was clearly explained by another cause not related to the study agent.

Ascertainment of possible adverse events

We undertook an educational programme in intervention clusters to ensure that participants understood IPT, were aware of potential adverse effects, and what action to take should they experience such effects. Participants were encouraged to report all intercurrent illness to study staff, and to show their study medication card whenever they attended for any health care. Symptoms suggesting adverse events were sought at each follow-up visit, and adverse event education reinforced. Treatment supporters followed up defaulters to encourage retention, and to check whether non-attendance was due to an adverse event. Mine health service staff were briefed to report potential adverse events. Deaths were ascertained by follow-up of defaulters, and using company human resources data.

Study adverse event algorithms prioritised participants' safety; if staff were uncertain whether a symptom represented an adverse event, they discontinued the study medication, reported a

possible adverse event, and referred the participant to the mine health services for further management. Two of the study-defined adverse events, rash and peripheral neuropathy, were usually diagnosed clinically by study staff. A study physician followed up possible adverse events using health service records; one or both clinically-qualified senior investigators assessed the likely relationship between serious adverse events and isoniazid.

The clinical management of individuals with suspected or proven tuberculosis, of HIV disease and of suspected adverse events was undertaken by the mine health services. To maximise acceptability, HIV testing was not part of this study, and individuals were not asked to report their own HIV status, but a history of antiretroviral therapy or previous IPT was considered to indicate enrolment in HIV care services. We did not collect information on cotrimoxazole use. HIV prevalence among gold miners in one of the companies participating in the study was 29% in 2001 [7].

Isoniazid tolerability substudy

In a cross-sectional substudy involving four of the eight intervention clusters, consecutive consenting individuals were recruited at the point of IPT dispensing on the day of enrolment to Thibela TB, and at follow-up visits at one, three or six months after starting IPT (separate samples at each time point). They were interviewed using a structured questionnaire starting with open questions about general health and symptoms experienced before or since starting IPT, followed by closed questions about specific minor symptoms. For participants taking IPT we asked about symptoms since the start of IPT (period prevalence), and currently (point prevalence); for those interviewed prior to IPT, we asked about symptoms over the previous two weeks.

Statistical analysis

We investigated associations between hepatotoxicity and its potential risk factors, calculating odds ratios and 95% confidence intervals using logistic regression.

Ethical approval

Both the Thibela TB study and the sub-study investigating minor side effects were approved by the Research Ethics Committees of the University of KwaZulu-Natal and the London School of Hygiene & Tropical Medicine. All participants gave written or witnessed verbal consent.

Results

Thibela TB adverse events

Between July 2006 and July 2009, 24221 participants (95% male, median age 40 years, 98% black ethnicity, 55% living in hostel accommodation) started IPT. Among these, 132 possible adverse events (0.54%) were reported among 130 individuals. Two individuals reported more than one adverse event: one possible hypersensitivity rash and possible peripheral neuropathy at the same visit; another presented with convulsions and two weeks later developed hepatitis (described below). One adverse event resulted in death, giving an overall risk of IPT-related death of 1 in 24,221 (4 per 100,000, 0.004%).

The most common adverse events reported in the main study are summarised in table 1 and described by category below.

Hypersensitivity

61 participants (0.25%) were reported to have a rash consistent with hypersensitivity, all graded mild or moderate, a median 20 days after IPT start. None were definitely and six probably related to IPT. Among 44 participants attending for review, the outcome was resolved for 42 and continuing for two. 16 individuals subsequently restarted IPT without further reported adverse events.

Peripheral neuropathy

50 participants (0.21%) reported symptoms consistent with peripheral neuropathy, all graded mild or moderate, starting a median 34 days after IPT start. Three had reported symptoms consistent with mild peripheral neuropathy (not a contraindication to IPT) at enrolment. None were graded definitely and four probably related to IPT. Among 40 participants who attended for review, for 37 symptoms had resolved; three were continuing, one with increased severity (and these three therefore permanently discontinued IPT). Most (29/34) patients who were asymptomatic at enrolment but reported symptoms graded mild during IPT were once again asymptomatic at review, and were therefore eligible to restart IPT; 23/29 restarted IPT (including two who had symptoms suggesting mild neuropathy at enrolment), with no subsequent adverse event.

Hepatotoxicity

17 participants (0.07%) reported symptoms consistent with hepatotoxicity, a median 117 (range 2-263) days after starting IPT. Clinically, the severity was graded as mild in 11, moderate in two and severe in four; among 13 participants with liver function test results, three had grade 1 and ten grade 4 abnormalities. Two events fulfilled criteria for seriousness (one hospitalisation, the patient subsequently making a full recovery, and one death; both considered definitely related to IPT). Two events were classified as definitely, one as probably and 12 as possibly related to IPT; two were more likely due to a cause other than IPT (one due to documented acute hepatitis B infection; one, with onset two weeks after discontinuation of IPT, more likely due to albendazole treatment for cysticercosis). IPT was restarted in two individuals who had grade 1 elevation of transaminases, without recurrence of symptoms. IPT was permanently discontinued among all others.

The man who died was aged 48 and, at enrolment, reported drinking 12 units of alcohol per week. He developed abdominal pain 140 days after starting IPT and presented initially to the mine health services. There was no documentation of enquiry about drug history, and IPT was not stopped. He presented to the health service nine days later with jaundice: IPT was stopped; his ALT was 1748 IU/l

(upper limit of normal 40), and markers for hepatitis A and B were negative. He was seen by study staff at a routine review three days later and admitted to hospital the next day but developed hepatic encephalopathy and died.

Associations between demographic factors, concurrent drug and alcohol use for the 15 cases at least possibly attributable to IPT are shown in table 2. There was no evidence of association between hepatotoxicity and sex, age group, ethnic group or baseline weight; although power of the analysis to detect associations with sex and ethnic group was low. Individuals reporting alcohol consumption were more likely to experience hepatotoxicity (odds ratio 3.9 [95% confidence interval 1.2-12.1] for any vs. no alcohol consumption), though the overall risk was very low (0.03% vs. 0.13% vs. 0.04% among those reporting zero, 1-14 and 15+ units of alcohol per week respectively). No cases of hepatotoxicity occurred in participants with a medication history consistent with HIV clinic attendance.

Convulsions

Four participants reported a convulsion after the start of IPT. Two events fulfilled criteria for seriousness (both because of hospital admission). Two events were classified as probably related to isoniazid and two as unrelated (one due to cysticercosis diagnosed on cerebral imaging; the other due to epilepsy which had been diagnosed prior to enrolment in Thibela TB but was not disclosed to the study team; the participant had spontaneously discontinued anticonvulsants prior to enrolment). Of the two cases considered related to isoniazid, one was a participant who took an overdose of isoniazid and paracetamol and had a witnessed seizure in hospital. The other was a first fit in an individual with no prior history of epilepsy. IPT was stopped permanently and all made a full recovery.

Other events

No episodes of psychosis were recorded. Despite efforts to ensure that women of child-bearing potential only received IPT if they were using reliable contraception, 14 women became pregnant after starting IPT. Of these, 11 reported delivery of a healthy child; two reported spontaneous abortions (one after a motor vehicle accident); and one reported termination of pregnancy.

Substudy of minor adverse events

337 Thibela TB participants were interviewed before starting IPT, 162 at visit one (end of first month of IPT); 167 at visit three and 169 at visit six. Refusals to take part in this substudy were not formally documented, but reported by staff to be very rare. Demographic data were available for 833/835 substudy participants: 815 (97.8%) were male, the median age was 42 (IQR 32-49) years and 827/833 (99.3%) were of black ethnicity, and 498/833 (59.8%) lived in hostel accommodation. Substudy participants were demographically similar to the 24221 main study enrolees (97.8 vs. 95.2% male; median age 42 vs. 40 years, 99.3 vs. 98.2% black ethnicity) and were more likely to live in a hostel (59.8% vs. 49.0%), likely reflecting small differences between all enrolees and individuals retained in follow-up.

<u>General and open questions concerning effects of IPT</u>

Among 498 individuals interviewed after 1, 3 or 6 months of IPT, in response to the question “How do the tablets [IPT] make you feel?”, 312 (62.6%) reported feeling much better, 12 (2.4%) slightly better, 157 (31.5%) no change, 15 (3.0%) slightly worse and 2 (0.4%) much worse. Of the 324 reporting feeling better on IPT, responses to the open question “What makes you say that?” are shown in table 3. Overall, 180/324 (55.6%) participants reported feeling better on IPT due to increased appetite; 126/324 (38.9%) due to increased energy levels or improved general health, 26/324 (8.0%) due to improved sleep or reduced tiredness and 13/324 (4.0%) due to increased sexual drive. Among the 17 feeling worse on IPT, three reported that increased appetite was disadvantageous and three reported increased tiredness or worsening sleep.

Prevalence of specific symptoms before and while taking IPT

Table 4 shows the period prevalence of specific symptoms experienced during and prior to IPT, ascertained by closed questioning. Headache (5.6%), itchy skin (4.3%) and joint pains (3.7%) were the most common symptoms reported by those interviewed after one month of IPT, and increased appetite during the first month was reported by 101/162 (62.3%) participants. This was seen as an advantage by 99, who reported feeling better on IPT and a disadvantage by two, who reported feeling worse. Increased sexual drive was reported by 62/162 (38.3%) participants during the first month and decreased sexual drive by 3/162 (1.9%). The period prevalence of ever having experienced a specific symptom while on IPT, combining participants interviewed at months three and six, was 5.7% for headaches, 5.4% for itchy skin, 2.1% for joint pains 0.9% for stomach pains, 0.9% for diarrhoea and 0.6% for nausea. Increased appetite was reported as an advantage by 201/336 (59.8%) of participants at visit three or six and as a disadvantage by three (0.9%). At visits three or six, increased sexual drive was reported by 142 (42.3%) participants and decreased sexual drive by 10 (3.0%). Point prevalence of specific symptoms at the end of months 1, 3 and 6 were consistently lower than period prevalence (data not shown). All symptoms that were enquired about specifically were more common among participants interviewed prior to starting IPT (table 4): for example, 34/337 (10.1%) reported headache and 26/335 individuals (7.8%) reported joint pains; interestingly 81.6% reported increased appetite and 86.4% reported increased energy levels in the two weeks prior to IPT.

Beliefs about and attitudes towards IPT

In response to the open question “What do people here say about IPT?”, 173/498 (34.7%) individuals taking IPT reported that they had heard that IPT caused a deterioration in sexual function, for example “They say it affects their manhood” (quote translated by interviewer). 123/498 (24.7%) reported that they had heard that IPT caused an increase in appetite (“Most of them claim

that IPT makes them eat a lot"); 81/498 (16.3%) improved energy and general health ("People are very happy about Thibela, they say it makes them healthy because they eat better and are no more sick") and 9/498(1.8%) that IPT would kill them or make them sick in some unspecified way ("[They say] that Thibela tablets make them sick that they are killing them").

Discussion

Adverse events reported in the main Thibela TB study

Our results provide reassurance that IPT can safely be delivered with clinical monitoring by trained nursing staff. Overall, very few study-defined adverse events were reported. We asked about symptoms suggesting study-defined adverse events at each visit, and thus ascertainment of these events is as complete as possible, but we cannot exclude underreporting. Conversely, assessment of possible hypersensitivity and peripheral neuropathy was largely based on clinical assessment by study nurses, and it is likely that we have overestimated the true risk of these events attributable to IPT. By using company employment records to ascertain death, we believe it is unlikely that we missed any isoniazid-related deaths. The death which occurred underlines how important it is that IPT is stopped immediately in the event of symptoms suggesting hepatotoxicity.

Comparison of the frequency of adverse events with other published studies of IPT is difficult because it is often unclear whether ascertainment was based on specific enquiry or on spontaneous report; some studies only report the frequency of events resulting in discontinuation of IPT; and case definitions are inconsistent. The frequency of suspected hypersensitivity in our study (0.25%) is very similar to the frequency of rash in studies of IPT among people with HIV infection in African countries [8,9], but lower than recent studies in Thailand and the United States [10,11]. Clinical hepatotoxicity, recorded in 0.07% of participants starting IPT in our study, was very unusual, despite our relatively liberal inclusion criteria, particularly no age restriction; this risk was substantially lower than reported in historical large IPT cohorts in the United States (risk of clinical hepatotoxicity

around 1% [12]) and Europe (0.5%, among individuals of median age 50 years [13]). The risk of clinical hepatitis will inevitably be lower than that of biochemical hepatitis in studies where liver function tests are performed routinely, since asymptomatic low grade liver function abnormalities are well documented to occur soon after starting IPT. However the relevance of asymptomatic biochemical hepatotoxicity is questionable [14], and recent studies among individuals with HIV in African settings have reported low risks of hepatotoxicity, even with routine liver function monitoring [9,15,16]. The risk of hepatotoxicity may be lower in black vs. white people [17] which could partly explain these differences. Our data suggest that clinical monitoring for IPT-related adverse events, and specifically for hepatotoxicity, is adequate providing people taking IPT are educated to discontinue their medication and seek advice if they have symptoms suggesting adverse events.

Our analysis of risk factors for hepatotoxicity identified alcohol use (any vs. none) as the only factor predisposing to hepatotoxicity, but this must be balanced against the possible benefit from IPT; in our study, the absolute risk of hepatotoxicity was low even among those who drank alcohol. Many guidelines suggest that individuals over 35 should not be offered IPT on the basis of a higher risk of hepatotoxicity. Our study suggests that older individuals should not necessarily be excluded from receiving IPT given their low overall risk of hepatotoxicity. There was no evidence of an increased risk of hepatotoxicity among individuals taking antiretroviral therapy. Our risk factor analysis is limited by the small number of cases of hepatotoxicity, resulting in relatively low power to detect such associations. However strengths include the very large number of participants and the estimation of risk of hepatotoxicity by alcohol intake quantified in units per week, a major advantage compared with many previous studies.

Sub-study of minor adverse effects

Specific minor symptoms, potentially attributable to IPT, were relatively rare, and, reassuringly, were less frequent among individuals already taking IPT compared to those at enrolment. Increased appetite was reported frequently, both spontaneously in response to open questions, as well as on specific enquiry; the higher frequency reported prior to IPT is hard to explain, and qualitative studies may help to understand this. Anecdotally, increased appetite on IPT has been reported previously among adults in Zambia (V. Bond, personal communication) and among children [18]. However, this is, to our knowledge, the first time increased appetite on IPT has been reported in a relatively large, representative sample. For the majority of Thibela TB participants, the increased appetite was reported positively, as an improvement in wellbeing. This may not be the case in lower resource settings or regions of food scarcity and may threaten adherence to IPT in such settings. If so, there may be a need to consider food supplementation where IPT is implemented.

Many individuals reported that others said that IPT caused deterioration in sexual function; far fewer (1.9% in the first month) reported this experience themselves. This is not a generally-recognised adverse effect of IPT but we anticipated rumours of negative health effects in the context of mass treatment. Such rumours have potential to influence uptake and retention to mass treatment programmes, and must be countered promptly with accurate information.

As for major adverse events, comparison with other studies is difficult because of inconsistent methods. Among 565 HIV-infected individuals taking IPT in Tanzania, low numbers of participants stopped IPT due to nausea (2.1%), peripheral neuropathy (0.5%) or psychiatric illness (0.2%) [19]. Other studies reported similarly low proportions of participants stopping IPT because of rash, gastrointestinal symptoms and peripheral neuropathy [9,20-22]. Among HIV-infected individuals in Brazil, 17/138 had adverse effects including nausea, pruritus, xerostomia and hepatotoxicity [23]. Other studies also report a low prevalence of minor adverse effects [24-28], but many apparently rely on spontaneous report of symptoms, likely to underestimate the true prevalence. Most recent

studies of IPT have been among HIV clinic attendees, who may experience and report minor adverse effects differently from this mining workforce. However, our population has a high HIV prevalence, and our results are relevant to wider use of IPT both among clinic attendees with HIV and to settings where community-wide IPT may be considered.

Most of the loss of Thibela TB participants occurred during the first month, and could have been due to very early minor adverse effects that would have been missed in this study; individuals who were symptomatic prior to IPT could have been more likely to drop out. Defaulters were traced, but it was not feasible to get information on reasons for dropping out.

In conclusion, data from this study of over 24,000 individuals starting IPT provide reassurance that IPT-related adverse events, and particularly hepatotoxicity, are very rare, even among older individuals. In a subset of participants, minor adverse effects were rare, though increased appetite was frequently reported. People taking IPT must be educated to recognise and act appropriately on early symptoms suggesting hepatotoxicity. Clinical monitoring for adverse events can safely be undertaken by trained nursing staff.

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Author contributions

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Conflict of interest

All authors: no conflict

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Table 1: Features of common adverse events reported among 24221 Thibela TB participants

	Suspected hypersensitivity	**Peripheral neuropathy**	**Hepatotoxicity**	**Convulsions**
Number of events (% total study participants)	61 (0.25%)	50 (0.21%)	17 (0.07%)	4 (0.02%)
Male: number (%)	60 (98%)	45 (90%)	16 (94%)	4 (100%)
Age, years: median (range)	42 (19-56)	40.5 (22-59)	42 (23-56)	25 (19-41)
Days from IPT start to event: median (range)	20 (0-223)	34 (1-212)	117 (2-263)	99 (23-176)
Severity				
mild	31	44	10	1
moderate	29	6	2	3
severe	0	0	4	0
potentially life-threatening	0	0	1	0
ungraded	1			
Fulfilling criteria for a serious adverse event	0	0	2	2
Relationship to IPT				
definitely related	0	0	2	0
probably related	6	4	1	2
possible related	51	46	12	0
not related	4	0	2	2

Table 2: Univariable analysis of risk factors for hepatotoxicity among Thibela TB participants

Variable	Category	Hepatotoxicity/total (%)	Odds ratio (95% CI)
Sex	Male	14/23038 (0.06%)	1
	Female	1/1168 (0.09%)	1.4 (0.2-10.7)
Age group (years)	<35	3/7763 (0.04%)	1
	35-44	7/8203 (0.09%)	2.2 (0.6-8.5)
	45+	5/8201 (0.06%)	1.6 (0.4-6.6)
Ethnic group	Black	14/23794 (0.06%)	1
	Other	1/425 (0.24%)	4.0 (0.5-30.5)
Baseline weight (kg)	<60	2/4234 (0.05%)	1
	61-80	8/14700 (0.05%)	1.2 (0.2-5.4)
	81+	5/5275 (0.09%)	2.0 (0.4-10.4)
History suggesting HIV care*	No	15/23584 (0.06%)	1
	Yes	0/618 (0%)	-
Antiretroviral therapy	No	15/23654 (0.06%)	1
	Yes	0/544 (0%)	-
Alcohol use (units/week)	0	4/14139 (0.03%)	1
	1-14	10/7760 (0.13%)	4.6 (1.4-14.5)
	15+	1/2321 (0.04%)	1.5 (0.2-13.6)

* history of antiretroviral therapy or previous isoniazid preventive therapy

Table 3: Reasons reported on open questioning for feeling better or worse since starting isoniazid preventive therapy

Reasons for feeling better (n=324)			
Reason given	number	% of those feeling better (n=324)	% of total participants (overall prevalence) (n=498)
Increased appetite	180	55.6	36.1
Improved energy levels/general health	126	38.9	25.3
Improvements in specific symptoms[1]	26	8.0	5.2
Improvements in sleep/reduced tiredness	26	8.0	5.2
Improvements in sexual function	13	4.0	2.6
Reasons for feeling worse (n=17)			
Reason given	number	% of those feeling worse (n=17)	% of total participants (overall prevalence) (n=498)
Worsening of specific symptoms[1]	8	47.1	1.6
Increased appetite	3	17.6	0.6
Increased tiredness/worsening sleep	3	17.6	0.6
Worsening sexual function	2	11.8	0.4
Other reasons	1	5.9	0.2

[1]Symptoms described in table 4

Table 4: Prevalence of specific symptoms before isoniazid preventive therapy (IPT) and during the first month, three months or six months on IPT

Symptom reported	Period prevalence during first month on IPT (n=162)	Period prevalence at visits 3 and 6[1] (n=336)	Period prevalence during two weeks prior to IPT start (n=337)
Headache	9 (5.6%)	19 (5.7%)	34 (10.1%)
Itchy skin	7 (4.3%)	18 (5.4%)	28/336 (8.3%)
Joint pains	6 (3.7%)	7 (2.1%)	26/336 (7.7%)
Diarrhoea	3 (1.9%)	3 (0.9%)	15 (4.5%)
Nausea	3 (1.9%)	2 (0.6%)	10 (3.0%)
Stomach pains	2 (1.2%)	3 (0.9%)	19 (5.6%)
Increased appetite	101 (62.3%)	204 (60.7%)	275 (81.6%)
Decreased appetite	0	0	47 (14.0%)
Increased energy levels	102 (63.0%)	295 (61.1%)	291 (86.4%)
Decreased energy levels	1 (0.6%)	0	30 (8.9%)
Increased sexual drive	62 (38.3%)	142 (42.3%)	216 (64.1%)
Decreased sexual drive	3 (1.9%)	10 (3.0%)	99/336 (29.5%)

[1]Total number reporting experiencing the symptom at any time since the start of IPT, combining individuals at the 3- and 6-month visits