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Time for clear and simple messages about delivering isoniazid preventive therapy (IPT)

This HATIP looks at the evidence supporting recent advocacy efforts to increase access to isoniazid preventive therapy (IPT), which, along with cotrimoxazole, is one of the key interventions that should be offered to people with HIV as part of a basic package of care. We investigate what has been working well, and what could have worked better in a public health programme offering IPT in Botswana — as well as what lessons can drawn from the other presentations on IPT at the 38th World Lung Health Conference in November in Cape Town.

Part 1 looks at the efficacy and safety of IPT, part 2 (in a separate email) looks at how to overcome barriers to implementation at national and district level.

Key points

- In countries where TB is common, many people have been exposed to TB and now have a latent infection. But in people with HIV, the infection is much more likely to develop into active TB at some point in the future. TB is the leading cause of death in people with HIV, but taking isoniazid preventive therapy can reduce the risk of TB.
- Isoniazid preventive therapy (IPT) means taking a course of isoniazid treatment in order to stop the development of TB. It can prevent TB in people with HIV regardless of CD4 count or antiretroviral treatment.
- A course of IPT takes at least six to nine months, but studies are investigating whether people with HIV should take IPT longer.
- Taking a six-month course of IPT as directed reduces the risk of TB in people with HIV and latent TB by around 64%, and the risk of death by 26% but the benefit may only last a couple of years in settings where people are frequently re-exposed to TB. In people who receive ART and IPT the risk of TB is reduced by about three-quarters.
- IPT is safe for most people. There is a small risk of hepatitis, which is greater in people who drink a lot of alcohol or have a history of liver disease. The risk is also greater in women during pregnancy and in the three months after delivery. This form of

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hepatitis can be life threatening in people who get symptoms of hepatitis if they continue to take the drug.

- IPT may worsen peripheral neuropathy. Patients should be told about this, and asked to report any increase in nerve pain in the limbs immediately, especially if they are also taking antiretroviral therapy that includes stavudine (d4T), another drug that causes neuropathy.
- The risk of illness and death due to TB is much greater for HIV-positive people who do not take IPT than the risk of severe side effects for people who do take it.

The very first large programme where IPT has been given to people with HIV in Botswana has had trouble getting reliable data on the participants and their outcomes for a number of unexpected reasons. But this has led some countries to hesitate before launching IPT programmes of their own. There are a number of concerns, discussed in more detail in part 2 of this article:

- It can be difficult to detect when latent TB has become active disease by simply screening for symptoms. Chest x rays help but are unavailable or would make programmes unaffordable in many settings. Debate persists about whether chest x-ray is a necessary screening tool for IPT programmes.
- Since isoniazid is a drug used for treating TB, there is a concern that if a person does in fact have active TB, they could develop resistance to isoniazid. So far, there is no evidence that IPT has increased the rate of isoniazid resistance in Botswana. But ongoing surveys should give more information soon.
- In order to avoid the risk of giving isoniazid to people with active TB, the most simple rule is: only give it to well patients. If they have cough, fever or recent weight loss, watch for the development of active TB. If the patient might have TB but you can't be sure, wait and investigate.
- IPT has the potential to retain in care people with HIV who do not need antiretroviral therapy, and may encourage earlier HIV diagnosis if people know that something is available that could prevent one of the most common opportunistic infections in people with HIV.
- However, IPT requires monthly follow-up, and programmes are looking for creative ways to keep patients on IPT coming back to the healthcare workers for monitoring and new supplies.

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- IPT could also protect the families, households and communities of people with HIV, by reducing the risk that TB will spread, especially to other people with HIV.
- There are questions about who should run IPT programmes, and how to best collect patient outcome data, however it is clear that communities, primary care and nurses can have a role in IPT.

Part 1: efficacy and safety of IPT

"Isoniazid Preventive Therapy (IPT) works; is safe; and works with antiretroviral therapy (ART) or by itself," according to the Core Group of the TB/HIV Working Group of the Stop TB Partnership (see resources at end of this article), which has put out a call to make certain that IPT is part of the preventive package of care routinely offered to people with HIV.

Although offering IPT for people living with HIV/AIDS when active tuberculosis is safely excluded has been WHO policy since 1998, the statement from the Core Group represents the first wave of a new effort from both the TB and HIV worlds to get countries to implement IPT in their HIV programmes.

Still questions remain about how best to scale up IPT from pilot projects to the national level.

Before taking the leap themselves, many HIV and tuberculosis (TB) programmes have been waiting to learn from the experience of the IPT programme in Botswana, which, in 2001, became the first and only country thus far to start giving IPT to adults with HIV as a public health measure.

But at the Stop TB Symposium, in the run-up to the 38th World Lung Health Conference in Cape Town, a report on the first few years of the country's IPT programme made it sound like a mixed success at best.

"Since the inception of the programme, we have screened over 71,000 HIV positive people, and have started 67,413 on IPT," said Oaitse Motsamai, director of the Botswana IPT Programme. However, of those put on IPT, only 37% are either currently on treatment or have been reported as finishing the six-month course of IPT, while as many as 63% are listed as "non-completers."

In other words, 42,513 people who were given a supply of isoniazid may have never completed it.

"We know why they did not complete in 24%, but don't have the reasons for 76%," she said. "This means that we know the outcomes of

about 51% of our clients who were enrolled in the programme. So the question is, where is the other 49%?"

Of course, there's much more to the story in Botswana, as we will explain below. But at first glance, this may not be the sort of report that encourages other countries to start up IPT programmes of their own.

"I'm trying to get South Africa to start IPT, how can I convince them —the healthcare workers, the doctors — when the figures I'm giving them are 63% non-completers?" said Lorna Nshuti, a TB/HIV advisor working with the International Center for AIDS Care and Treatment Programs (ICAP) in the Eastern Cape of South Africa.

Yet the Botswana IPT programme shouldn't be counted out just yet — it was after all conceived of and launched as a separate vertical programme just before Botswana's massive ART roll-out became the country's overwhelming primary public health concern — and recently Botswana and BOTUSA (the CDC/Botswana partnership) have taken steps to significantly strengthen the programme. Plus, it is important to note that some sites within the country are having remarkable success.

In fact, another ongoing large research trial in Botswana, which is looking at the optimum duration of IPT, has had very high treatment completion rates of 94%, according to another report made during the World Lung Health Conference.

But the fact remains that IPT has the potential to reduce the burden of TB among people with HIV — and save many lives —so it is crucial that we learn as much from the experience in Botswana as possible.

So after looking at the evidence supporting the statement from the Core Group of the TB/HIV Working Group of the Stop TB Partnership, this HATIP investigates what worked well, and what could have worked better in the Botswana IPT programme— as well as what lessons can be drawn from the other presentations on IPT at the 38th World Lung Health Conference.

IPT works

That's the easy part.

But how well it works depends upon the risk of active TB, duration of treatment, adherence and other factors.

Over forty-five years of clinical research have demonstrated that taking 5 mg/kg (usually 300 mg) isoniazid daily reduces the risk of active disease in people with latent TB. In one early pivotal study (published in 1982 by the International Union Against Tuberculosis Committee on Prophylaxis (IUATCP)) in 28,000 people, the preventive effect became

evident after the first 12 weeks on treatment with a 31% reduction in incidence of active disease, but the effect increased to 69% after 24 weeks of IPT, and to over 93% at 52 weeks in adherent/completer patients (on treatment analysis).

Partly because the intent-to-treat analysis showed less difference between six and twelve months of IPT, and because of a risk-benefit analysis taking into account the risk of cumulative liver toxicity (more on this below), the study concluded that taking IPT for six months was better, and that is what the 1998 WHO policy recommended.

But some countries reached different conclusions.

"US public health officials revisited the combined data on IPT and determined that the best risk benefit ratio for duration was nine months (and that's for a low burden setting such as the US)," says Dr Charles Wells, who was formerly Chief of the International Research and Programs Branch in the Division of Tuberculosis Elimination with the CDC. "Subsequently, the CDC/ATS guidelines were changed and nine months is now the practice in the US. It stands to reason that if the US analysis was on target, then six months is way low for a high burden setting."

The fact is, the optimum length of time for IPT has never really been established in people with HIV, who have a dramatically greater risk of developing active disease in their lifetime. In countries with a high burden of both diseases, as many as one-third to one-half of people with HIV are coinfected. The annual risk of developing TB while HIV-positive is 5-10% compared to a lifetime risk of only 10% in HIV-negative people with latent TB.

But it can be difficult to recognise latent TB infection in someone with HIV, because the tuberculin skin test (TST) (or purified protein derivative, PPD) for latent disease can be difficult to interpret. Advancing HIV disease causes some people to be anergic on TST (without substantial reactions) so some experts recommend using a lower cut-off (a reaction 5mm rather than 10mm) as a positive result. But at least one study by Cobelens et al, has found that this makes the test much less specific for TB — particularly in areas where BCG vaccination and exposure to cross-reactive non tuberculous mycobacteria are frequent (like in sub-Saharan Africa)—and not that much more sensitive.

So TST interpretation isn't perfect, and in many resource-limited settings performing TSTs can be challenging from an operational perspective. One issue is that people simply don't return to the clinic to have their TST response measured. "Whoever came up with the PPD requirements as an entry to care clearly didn't ever work in the services

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– it's a ridiculous requirement, screening must be done early in the week and then read later, and adds little to efficacy," Dr Francois Venter, of the Reproductive Health and HIV Research Unit in Johannesburg, South Africa, told us recently in reference to recommendations in South Africa.

Thus, where the risk of TB exposure is considered very high, many programmes, such as the one in Botswana, just don't see the point in doing TST. Likewise, in settings of high TB infection (>30%), current WHO policy is that a TST isn't necessary — preventive therapy should be provided to all eligible people with HIV (WHO/UNAIDS 1998).

In part because they included people with and/or without latent TB, clinical trials in people with HIV have reported somewhat variable success rates using IPT. But according to a Cochrane meta-analysis of these studies published in 2004, IPT reduces the risk of developing active disease in people with HIV and a positive TST by about 64% (which is remarkably consistent with what the IUATCP found) and the risk of mortality by 26% (Woldehanna and Volmink).

The analysis did not find IPT to be of benefit to people without positive TSTs — even where the risk of exposure to TB is high. However, when the data from all participants (those with and without latent TB) were pooled, IPT still significantly reduced the risk of active TB by 33%.

Since the Cochrane analysis, another study looked at the introduction of IPT into a workplace HIV clinic at a mine in South Africa. The researchers enrolled 1655 HIV-positive men; 679 of those who had no signs of active tuberculosis started isoniazid therapy. TSTs were not routinely performed because the majority of employees were assumed to have latent TB infection.

After a median follow-up of 22 months, the clinic saw a 32% overall drop in the number of active cases (for the entire population, both on and not on IPT). In a multivariate analysis, if men with a history of TB (who were not eligible for IPT in the programme) were excluded, IPT treatment led to a 46% drop in the incidence of active TB. But "despite our intervention, the TB incidence rate in the post-clinic phase remained unacceptably high at 9 per 100 person-years," the authors wrote. They came up with a number of potential reasons for this, one being that adherence "may have been less than that in clinical trial conditions, which may have resulted in a reduced effect." (see http://www.aidsmap.com/en/news/A82A1807-EF2A-4188-A2F2-FECE67524FDF.asp , Grant). But more on adherence later in the article.

IPT works with ART

Another recently published report suggests IPT also works with ART. This was a retrospective chart review comparing TB rates in 11026

people with HIV who received care 1) without ART or IPT, 2) with ART alone, 3) with IPT alone, 4) with ART plus IPT at 29 public clinics in Rio de Janeiro, Brazil between September 2003 and September 2005 (Golub). Out of the total cohort, 1,096 patients (~10%) started IPT and 834 (76.1%) completed six months. The majority (though not all) of those who started IPT had had a positive TST.

For the cohort overall, the incidence of active TB was 2.28 cases/100 person-years (PY) [95% confidence interval (CI) 2.06–2.52] — twenty times higher than for the general population in Brazil. The incidence was highest, at 4.01/100 PY, among those who didn't take ART or IPT, 1.90/100 PY (95% CI 1.66–2.17) on ART alone, and 1.27/100 PY (95% CI 0.41–2.95) on IPT alone. The incidence among patients who were on both ART and IPT was 0.80/100 PY (95% CI 0.38–1.47).

In a multivariate analysis, after adjusting for age, previous tuberculosis diagnosis, and CD4 cell counts at baseline, ART alone was independently associated with a 59% reduction in tuberculosis incidence, P<0.001), while the effect of IPT alone was no longer significant (adjusted relative hazard 0.57; P=0.34). The ability to accurately gauge IPT's effect could have been limited by the small proportion of people taking IPT — and the way doctors prescribe IPT in Brazil (more on this below). However, the use of both IPT and ART together significantly reduced the incidence by 76% (p<0.001). Similar benefits were observed in people with CD4 cell counts below and above 350 cells.

As a retrospective chart review, the study is limited in some respects. For instance, the authors wrote: "We do not know why some patients underwent TST and why some patients began IPT or ART whereas others did not."

Of note, about 40% of people who had positive TSTs were not put on IPT. Only 13 TB cases were diagnosed among 815 patients with a positive TST who started IPT (1.6%) versus 63 of 548 patients not starting treatment (11.5%; P<0.01). But it is not clear whether these two groups should be compared because doctors may have been using the TST as a part of the process to diagnose TB in people who may have had signs or symptoms of TB.

The study from Brazil also included those with a previous TB diagnosis (17% of the total patients) who were at a very high risk of recurrent or reactivated TB. Guidelines do not currently recommend giving IPT to people with HIV previously treated for TB. However, three small studies provide rather consistent findings that it could also have significant benefit in this population (see

http://www.aidsmap.com/en/news/5486E157-F95A-4A0C-818C-9641294FA515.asp (Churchyard 2003).

But this brings up one other problem — that it is quite easy for people with HIV to become re-exposed in regions with a high burden of TB. Therefore, the benefit of a course of IPT doesn't necessarily last all that long. Clinical studies report mixed results following six months of IPT — one study in Zambia suggested that the protective effect could last up to three years (Quigley 2001), but a study from Uganda found the effect only lasted one year (Johnson 2001).

So again, perhaps IPT needs to be given longer in people with HIV — which is part of what the BOTUSA IPT trial is currently investigating.

IPT is safe

Isoniazid, like any other drug, has side effects. It can cause nausea, which can be reduced by taking it with food (unless it is severe and associated with other symptoms of hepatitis; see below), rash, fever, mild central nervous system effects and peripheral neuropathy, the risk of which may be attenuated somewhat by taking vitamin B6. However, this condition is a particular concern in people with HIV on ART, especially taking drugs such as d4T or ddI, which can cause peripheral neuropathy as well. In addition, the safety of isoniazid during the first trimester of pregnancy has not been absolutely established.

But most of the worry centres on hepatitis. During the 1970s, reports of fatal liver damage in some patients surfaced (Riska). In the IUATCP study, hepatitis occurred in 0.5% of the people on isoniazid versus 0.1% of the people on placebo, with two-thirds of the serious events happening within the first 24 weeks on treatment. Three cases resulted in death (0.14 per 1000 persons on the drug). Each of these three had continued taking isoniazid after liver problems had been recognised, and the study's authors concluded the risk of hepatitis and subsequent death might have been avoided "by the knowledge available today."

Twenty-five years later, the risks are much better characterised. Many of the early reports of hepatitis included findings of elevated liver enzymes, in particular transaminase, which are asymptomatic and tend to resolve spontaneously. Serious events were more likely in older patients, people with pre-existing conditions, and people who drink to excess (although definitions for this vary widely).

With proper management, most serious events can be averted. But there is some disagreement about how the drug should be monitored. In the US, the American Thoracic Society/Centers for Disease Control and Prevention Guidelines recommend performing baseline liver function tests in anyone with HIV, a history of liver disease, "persons who use alcohol regularly," and pregnancy, with ongoing monitoring if the liver

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enzyme results come back abnormal. It also states that some experts recommend stopping the drug and that they consider elevations over five times the upper limit of normal as cause to discontinue the drug (or three times above normal when there are symptoms).

But a study in a public health setting in Seattle, Washington, forgoing laboratory monitoring, reported only 11 cases of hepatitis in over seven years in a cohort of 11,141 people on isoniazid— and only one of the cases required hospitalisation (Nolan). The clinic kept incidents to a minimum by relying on careful patient selection (avoiding IPT in older patients unless the risk of TB was considered high), patient education and clinical monitoring. Patient education consisted of telling the patients to stop taking isoniazid immediately and to report promptly to their clinic if symptoms of hepatitis develop (a progressive onset of anorexia, nausea, vomiting, and jaundice).

Despite coming from Seattle, this seems like a monitoring model that could be used in resource-limited settings — although the frequency of clinical monitoring may be limited in clinics that are already operating beyond capacity. So in resource-limited settings, community-based organisations working on treatment literacy and adherence support should be engaged in the rollout of IPT from day one.

Safety studies at the 38th World Lung Health Conference

Studies at the 38th World Lung Health Conference reported findings in people with HIV consistent with what's been published in the literature showing that IPT is generally well tolerated, most of the hepatitis is indeed related to asymptomatic transaminase elevations, but also, in at least one unfortunate case, failing to discontinue the drug immediately when symptoms of hepatitis appear can lead to death.

Several reports came from study projects associated with the Consortium to respond effectively to the AIDS/TB epidemic (CREATE), a Bill and Melinda Gates Foundation supported consortium of international researchers and advocates in TB and HIV seeking to identify effective public health strategies in the fight against TB. CREATE's Project Director, Dr Lois Eldred, presented retrospective data showing no difference in the rates of liver toxicity in patients on IPT plus ART and ART alone at Johns Hopkins Moore Clinic, and low rates in patients on ART plus IPT in the retrospective study described earlier on ART and IPT in Rio (part of the THRio project in Brazil).

The case control study at the Johns Hopkins Moore clinic matched 70 cases receiving isoniazid and ART together to 95 controls (by date) starting on ART alone. Liver toxicity was defined as a change in AST/ALT from baseline to the last date of receiving isoniazid, and data were excluded if the last liver enzyme test was more than sixty days

before or after the last reported IPT dose. Liver toxicity was graded 0-1, if either ALT or AST were elevated up to three times baseline levels; grade 2, 3-5 times baseline; and grade 3-4, more than five times baseline.

At baseline, CD4 cell counts were significantly lower in cases on IPT/ART (median 116 vs 252 cells; p-value 0.01); they had higher median viral loads ($p<0.01$), higher baseline AST ($p=0.04$) though there was no difference in ALT, and were more likely to be HCV coinfected (98% vs. 66%, $p<0.001$ — though test results were unavailable for a third of the cases).

Despite these factors, which might have predisposed the IPT/ART group to have more liver toxicity, there were no significant differences between the two groups: five out of 70 (7.1%) had grade 2 events (and four out of those five were HCV coinfected) vs four out of 95 (4.2%) on ART alone ($p=0.41$); while two out of 70 (2.9%) had grade 3-4 events on IPT/ART vs four out of 95 (4.2%) on ART alone ($p=0.65$).

Meanwhile, in the THRio study, 291 patients have been put on both ART and INH, 163 have completed six months as of September 30, 2007. Only one of these has developed hepatitis (grade 3). Overall, taking ART with IPT was not associated with hepatotoxicity.

Another Create study project, Thibela TB ('prevent TB' in Sotho), operating in the gold mines in South Africa, offered more prospective safety data (as well as a wealth of operational expertise) in a number of posters presented at the conference. The Thibela TB study is randomising clusters (15 gold mine shafts and their employees) rather than individuals to receive either community-wide TB screening plus nine months of IPT vs. routine TB control programme activities. When it has completed enrolment, the study could involve around 70,000 miners, about half of whom will be in the intervention sites and eligible to volunteer for TB screening and IPT.

One poster by Mngadi et al. described the adverse event data to date from four of the intervention clusters that have begun enrolling participants (with 11,293 enrolled, 9626 who have started IPT as of September this year). 98% of the participants are male with a median age of 40. They have monthly scheduled visits, and make unscheduled visits as necessary. At enrolment and at each visit to the clinic, participants are educated about side effects and encouraged to report them promptly. Adverse events are as reported by the participant or gauged by a symptom screen at each visit. Routine laboratory tests to confirm side effects are considered logistically impossible.

In the fourteen months since the study began enrolling, only 76 adverse events have been recorded. Most were graded mild or moderate: 43 hypersensitivity reactions, 29 cases of peripheral neuropathy, and four cases of hepatitis though one of these cases was severe.

A high proportion of these participants are receiving care for HIV, so only the case of hepatitis was considered 'definitely related' to IPT, while most of the adverse events were considered only 'possibly related.' Although median time for most of the reported events was within 27 days of starting IPT, this ranged between 1 to 212 days. However, the median time to hepatitis was 35.5 days (range 19-99).

"This confirms the safety profile of IPT, thus far," the poster's authors concluded.

Of course, there is no comparison arm in this analysis, but the event rate seems rather low. One of the reasons for this could be that, like the clinic in Seattle, the investigators believe in careful patient selection — in other words, as reported in a poster by Popane et al, "use of eligibility criteria ensures the safety of IPT." The poster described these criteria, which might be useful for other programmes considering implementing IPT on a large scale.

Permanent ineligibility criteria in the Thibela TB study include:

- IPT inappropriate
- Increased risk of adverse events
- Other
- on TB treatment or IPT
- Alcohol intake >28 units/wk (men) and > 21 units/wk (women
- History of chronic liver disease
- History of epilepsy or psychosis
- Peripheral neuropathy of grade 2 or greater
- Rash suggestive of hypersensitivity
- Possible pregnancy or < 3 months post partum, contraindicated medications, being on investigational drugs, or weight < 40 kg

Temporary ineligibility criteria include:

- TB suspects (who then should go through the diagnostic process)
- Suspected hepatitis
- Women at screening who are not on reliable contraception but are willing to use contraception
- Suspected hypersensitivity rash

For the programme overall, so far, about 5.3% of the over 11,500 volunteers have been deemed permanently ineligible, mostly because of heavier alcohol use, while around 10% were temporarily ineligible, mostly because they were TB suspects. However, if after examination these participants are found not to have active TB, or sort out their other issues, they will be given IPT.

The BOTUSA study of IPT also excludes TB suspects and people with a history of hepatitis, pregnant women, etc — but it also has the capacity to rigorously monitor liver function tests for any hint of hepatitis. A poster at the conference presented a safety analysis looking just at IPT-associated hepatitis in the trial (Nyirenda). As part of this study, all participants receive open-label isoniazid 300 or 200 mg per day (depending upon weight) plus 25 mg of vitamin B6 for six months. People were excluded from the safety analysis if their liver enzymes were abnormal at baseline. Hepatitis was defined as any elevation of one grade or more of liver enzymes or bilirubin.

The study has enrolled 1,998 subjects; 1,768 who attended at least 5 of 6 monthly visits for follow-up and to pick up their medications, were included in the safety analysis. In contrast to Thibela TB, the majority were female (74%), median age was 33 (range 19-70), and median CD4 cell count, 303. 28% had CD4 cell counts below 200, and 27% were on ART. 13% reported that they drink alcohol.

There were 54 cases of hepatitis (3% of the cohort). As consistent with the literature on IPT, the vast majority of these were transient asymptomatic liver enzyme elevations that occurred within the first month and resolved on their own. Only 19 were severe (> grade 2), 1.1% of the entire cohort.

Sadly, there was one hepatitis-related death in a woman without any other easily identifiable risk factors: no hepatitis B coinfection, and she did not report drinking alcohol and was not also on ART. The authors wrote, "After developing jaundice, she did not stop IPT and was unfortunately given acetaminophen" [which can aggravate hepatitis].

In analyses looking at risk factors in all the patients for developing severe hepatitis, the investigators found no association between hepatitis B coinfection and hepatitis on IPT, but noted a four-fold increased risk of hepatitis in patients who had less than 200 CD4 cells or who were on ART. They concluded that "hepatic enzymes should be more closely monitored in persons on both IPT and ART."

However, as noted by the Thibela TB study, this would be logistically impossible in most settings, and it is not clear that this would necessarily avert the risk of these events occurring any better than

monitoring symptoms. It would not have prevented the death in this study.

Nor would she have been screened out using Thibela TB's eligibility criteria, underscoring that some severe liver toxicity on IPT may be unavoidable, and it is absolutely essential to educate patients to immediately discontinue treatment and seek medical attention when they experience symptoms of hepatitis.

That being said, it is important to remember that the risk of morbidity and mortality for people living with HIV is higher for those not taking IPT, so this risk should not be a barrier to rolling out an IPT programme. People have hepatitis, or lactic acidosis or other unexpected reactions and die on ART as well. But the benefits to the community of IPT for people with HIV as a whole are too great to not offer the intervention.

Of note regarding liver enzyme monitoring, in the ongoing double-blind portion of the study, which is assessing continuous IPT (36 months versus 6 months), the Data Safety and Monitoring Board recommended performing an extra liver enzyme assessment on all patients still on treatment (active or placebo).

"The results were reassuring and did not suggest evidence of increased risk in this population," said Dr Andrew Nunn of the Medical Research Council who sits on the study's DSMB. Final judgements about the relative safety of three years versus just six months of IPT, and the relative risks and benefits to this population will have to wait until the trial's conclusion in 2009.

Part 2 of this article follows in a separate email, and discusses the challenges of implementing IPT at national and district level, drawing on the experience of the Botswana programme and the views of experts in the field. Part 2 also includes full references for this article.