

hiv & aids treatment in practice

Isoniazid preventive therapy for TB in people with HIV: barriers to national implementation



By Theo Smart

All in all, the studies discussed in part I of this article underscore that enough is known about IPT that its risks can be kept to a minimum in large programmes in resource-limited settings, and that it may markedly reduce active TB and improve survival.

Theoretically, it might even reduce onward transmission, and the overall burden of TB.

So given these benefits, what is holding up national implementation?

Part of the problem has been the tension between HIV/AIDS and TB programme areas that have debated the topic endlessly. In addition to the worries about safety — which one hopes some of the recent studies have assuaged, IPT implementation is primarily being held up by the related fears that IPT may be given to some cases of active TB missed during the screening process (how to exclude active disease), possibly leading to INH resistance, which could in turn contribute to the growing multidrug resistance problem, especially as adherence to preventive medicine is notoriously low.

The example of Botswana

When it started, the programme in Botswana seemed to have all of these angles covered, which is part of why its example is being watched so closely.

“In 1999/2000, there was nothing on the horizon to offer folks in Botswana who had HIV. And the only thing that appeared to have any kind of benefit was IPT — as death from TB was the biggest issue they had with HIV at the time,” said Dr Charles Wells, who formerly provided support for CDC’s international TB/HIV research, including the IPT trial.

Indeed, once upon a time, Botswana was one of the rare countries in Sub-Saharan Africa where TB control strategies appeared to be working. But since the spread of HIV, the TB case rate has tripled to around 603 cases per 100,000 (2005 figures). The estimated TB-HIV coinfection rate is over 80%, and an autopsy study in 1998 suggested that at least 36% of the deaths in people with HIV were due to TB.

The same year, WHO and UNAIDS released recommendations to use preventive therapy for TB in people with HIV. Botswana was quick to act.

The country went about setting up the programme in a very methodical, responsible way: by forming a working group in 1999, and conducting a pilot study in three districts to determine the feasibility of implementing IPT country-wide.

The pilot study was quite successful. It screened over 1000 subjects, and ultimately put over 600 people on IPT with a completion rate of 70% — much better than the adherence reported in other programmes. Notably, at the time, this pilot IPT project also demonstrated that a simple symptom screen (cough, fever) was nearly as sensitive as performing a chest radiograph to rule out active TB (more on this below) (Mosimaneotsile).

On the basis of the feasibility study's success, the Ministry of Health decided to proceed with a national IPT programme for people with HIV and signed a cooperative agreement with the CDC/BOTUSA, which would assist in developing an electronic recording and reporting system, and to help the country perform another national anti-TB drug resistance survey to closely monitor isoniazid resistance trends.

In addition, they planned to launch a study to determine the optimal duration of IPT, and whether testing for latent TB adds any benefit versus simply treating all people with HIV (as the current programme is designed). This was all arranged toward the end of 2001.

The IPT programme would be housed in the TB department at the national level, and staffed with one national coordinator, two regional coordinators, three data officers and a data manager. Implementation, however, would occur in the district (there are 24 health districts in the country), with screening and delivery of IPT by the doctors and nurses working at the country's general clinic network. Support and supervision at the district level were to be provided by district TB coordinators. At that point, the national TB programme was relatively strong, though as anywhere else in sub-Saharan Africa, Botswana had far too few health workers for its needs.

The plan was great. And yet, according to Oaitse Motsamai, programme director: "Actually it has been very difficult to implement this programme in the country."

The current outcome data for the Botswana IPT programme

Over 350,000 people have tested HIV-positive in Botswana. At present, of 71,096 people with HIV have been screened for the programme, and

67,413 started on IPT. 18,121 (27%) are documented as completing their course, 6,779 (10%) are currently on IPT, and 42,513 (63%) are listed as non-completers. They have reasons for 24% and no reasons for 76%.

Of the 24% with recorded reasons for non-completion:

- A few (less than 0.5%) have been due to severe side effects or terminal AIDS,
- 2% were reported to have developed active TB (whether they were adhering to IPT at the time is not clear),
- 10% were discontinued for one reason or another by their healthcare worker,
- 19% are listed as 'other' (it's not clear how many, but for example some could be due to women becoming pregnant),
- 69% are categorised as known to be lost to follow-up (LTFUs). They were only categorised as such when healthcare workers actually visited their homes and found them not to be available or to have moved away.

But for the overall cohort, they aren't sure what happened to about 49% of the people started on IPT. And they have little data on what happened to the TB suspects identified in the screening process (deemed ineligible for IPT) —such as whether they went through the diagnostic process or had active TB.

It's important to reiterate that this is the first time any country has ever tried to run this type of public health intervention, so some problems, and if necessary, course corrections, are to be expected.

"Botswana's the first place globally that's ever tried to deliver this service as an active part of the programme on a large scale," said Dr Wells. "My biggest worry is that people are going to throw the baby out with the bath water, and not look at this as a learning situation."

Indeed, but it may be possible to draw a number of lessons from Botswana's experience, even though some of the challenges were unique to the time and place. There were a number of factors involved in what unfolded.

A delayed implementation

"Unfortunately, the IPT office was not established until late 2003," said Motsamai. "I came into the office almost two years after the inception when there was just somebody picked from NTP to oversee the roll-out. Just one person. And then when the office came up, we started with three persons, me and two data clerks - after two years. My feeling is that the office should have been established first,

protocols, making everything very clear — reporting, monitoring, evaluation, search indicators or whatever.”

Shifting public health priorities

It's important to remember what else was going on in Botswana at the time. In early 2002, the Government of Botswana took the bold step of launching Africa's first national antiretroviral programme — which overnight became the country's number one priority. The country launched four ART sites within the year, and began preparations to rollout ART to all the district hospitals. And in the years since, unlike most other countries, Botswana believes that it has actually put around 85% of its people in immediate need of treatment on ART.

“This was the right thing to do, but there were opportunity costs for doing it,” said Dr Wells. “And one programme in particular that suffered was the TB programme, because before the HIV programme was launched, there was a TB coordinator in every district (except for three). One person dedicated to solely making sure that TB services were delivered and that things run smoothly and that drugs were where they needed to be, smears were being done, and all those things. Well, that model changed with the advent and the launch of the antiretroviral programme... they went from one person who does everything for TB in 21 of the 24 districts, to one public health nurse responsible for six different major programmes, including TB.”

“So the IPT service was being implemented and delivered at a time when there was a huge transition to HIV service delivery at the cost of the rest of the health services.

And also too, to defend the HIV people in terms of taking something like IPT on or making sure it was part of their package — they were told to get antiretrovirals out, and that anything else was background noise. And that's understandable,” he said.

But this massive change in Botswana's public health system impacted heavily on efforts to try to roll-out IPT, which at times must have seemed like a competing vertical programme to the healthcare workers in the clinics.

Overstretched staff

So it was in this context, in the end of 2003, that Motsamai and just two data clerks began trying to roll the IPT programme across the country, training trainers and healthcare workers — until IPT was launched in every district by June 2004. Other staff would be hired to the programme. But the IPT programme found itself distracted by trying to solve the staff shortage in the wider national TB programme.

“At the national level, the IPT programme belongs to the TB programme and the TB programme has been short staffed for many years now. And when we came into the programme, we were looking at all the national TB control strategies and on that endeavour we ended up losing track of our core business that was IPT,” said Motsamai.

But some of this was probably unavoidable, as having a functioning national TB programme was essential to aspects of IPT’s success.

“We had people like community health nurses and other health carers who were tasked with the responsibility of taking care of the TB programme, but we have found that most times they put maybe less than 10% of their effort on TB control activities and that is why we decided to come up with designated TB coordinators, and also this has helped us because we have actually improved on our records,” she said.

But there has also been a high turnover in district health workers, including TB coordinators, so the IPT team has found that they have to train and retrain.

Typical losses to follow-up

Every HIV programme experiences losses to follow-up among people who test positive for HIV, even among those who qualify for ART. But the rates in the IPT programme seem particularly high.

Motsamai listed a number of reasons why clients were getting lost.

Some patients received inadequate counselling and did not know that they had to return regularly for check-ups.

Other reasons were more typical such as transport problems, particularly in the districts, wrong addresses given by clients, and high mobility of clients (in Botswana, it is very common for people to work in the city or mines part of the year, and return to their ancestral village the rest of the year).

But in contrast to ART programmes that tell patients to come back every three or even every six months while they have high CD4 cells, participants in the IPT had to visit the clinic every month. And this is during a period when ART sites in Botswana were packed to capacity, and where doctors and nurses were struggling to put people on ART.

“Sometimes clients are registered and given the first or second doses, then they just disappear. You don’t know what happened to them and nobody bothers to find out where they are. Follow up is very limited and this is what we are trying to push, that all the clients that have been on IPT should be followed up,” she said.

Dr Taraz Samandari of BOTUSA thinks that: "The statistics that Motsamai gave are actually pretty much the worst case scenario because there are many people who got five months of bottles of pills but they just didn't come back for the 6th month to say, 'Okay, I'm done.'"

In other words, if the data were re-analysed looking at subjects who finished five months, Dr Samandari believes the losses to follow-up would be much lower.

Even so, the goal should be to retain people in care. So IPT programmes could benefit by being closely linked into community-based mechanisms of adherence support that the more successful ART programmes use (see HATIP # 90 and 92).

Record keeping/reporting problems

But huge numbers of the non-completers could simply be miscategorised because of poor record keeping and reporting.

The programme started out using a paper-based register and reporting system — separate from the TB register, and from the ART/pre-ART registers — while the electronic database for the programme wasn't rolled out until November 2005. But by then more than 20,000 people had already been put on IPT.

And in the beginning, even with the paper registers, "out of the 24 districts, maybe sometimes six districts would report, sometimes ten but it was very inconsistent," Motsamai said. "We have a lack of timely reporting. I've actually been doing some supervisory visits recently only to find there's a good number within the registers that have completed the 6-month visit. But somebody just failed to pick that up and post this to outcomes."

But again, part of this may be due to competing priorities for the health worker's time.

Motsamai described a typical exchange: "We have a feeling that there are some attitude problems within the health workers themselves because they will complain, 'Oh, workload!' There are too many documents to record and so many initiatives at the same time that they have to take care of. And at the end of the day you come across a situation where somebody has been on IPT, and there aren't clear records/adherence. And then you ask, 'Where is this patient? And they say, 'He has completed treatment.' 'But then, what about the (records)?' 'I know, I'm very sure that they are completed?' they will answer. But there is nothing on record."

Getting the HIV programme, and health providers to 'buy in' to IPT

Taken together, the entire episode illustrates a larger problem about the need to sensitise people working in HIV not only about how IPT can save lives, but why the manner in which it is distributed is extremely important, for the safety of the patient and for TB control in general. There are, after all, dangers related to not investigating TB suspects identified by these programmes, and in releasing large quantities of an important TB drug within the community without properly educating people on how to use it.

The HIV programme bears some responsibility for this. Of course, TB and HIV coordination has been slow in most countries. As a result IPT wasn't emphasised as part of the ART roll-out. A TB/HIV Advisory body was only established a year ago.

Getting people in HIV care to buy-in to IPT has been a problem in many other countries as well.

For instance, one study from the THRio project, identified major differences in IPT usage from clinic to clinic, and then found that the doctors were to blame.

"Doctors' lack of knowledge about the TB prevention protocol in HIV patients was an important reason for different performance among the units," said Dr Betina Durovni during one presentation at the conference. "So after almost two years of implementing this strategy, we are actually revising our strategy and developing new communication strategies for physicians."

Belatedly strengthening TB control

In 2001, it was difficult to predict that the TB programme would be decimated by worker turn over and other health system changes, but it's clear that the scale-up of programmes such as IPT, whether housed in TB or HIV departments, has to go hand in hand with strengthening TB control.

And recently, the Botswana TB programme has been bolstered considerably by recreation of the position of District TB Coordinator, trained to strengthen TB control strategies at the local level.

"Now that we have designated TB coordinators we do have control over them. We do monitor them. We do call them to table more frequently and can see a big difference from the effect. We can see a big difference in the uptake, the monitoring and even the outcomes of the programme". Recently reporting has improved substantially — at least

with the paper-based records. "The average is about 94% on paper-based reporting on a monthly basis which is very good. But we are still only getting five to ten out of the districts to file an electronic report."

Even so, she said the quality of the data that comes out of the programme should start improving soon.

"I'm just coming from a particular district where they were performing very badly and now they have improved a lot. So the outcomes are coming," she added.

A formal review of the programme is slated for next year.

Reactions to the Botswana report

Even though most of the problems in the Botswana IPT programme had more to do with the unique time in history in which it was rolled out (and with a health system trying to do so many things at once), the report has launched a debate between those in favour of IPT and some who think there should be a more cautious approach to scaling it up.

In addition to the traditional worries: how to exclude active disease, prevent INH resistance, and how to ensure adherence, there are operational concerns, including who should really be in charge of running the programme (the TB or HIV department, and how should the data from the programme be recorded and cross-linked between TB and HIV programmes?

Excluding active disease: is chest x-ray necessary?

In a recent TB/HIV newsletter from the TB/HIV Working Group of the Stop TB Partnership, Dr Yibeltal Assefa of the National HIV/AIDS Prevention and Control Office, Ethiopia, said that he is worried that there are no clear guidelines that show how to confidently exclude active pulmonary TB without a chest x-rays. In his setting: "we don't have the infrastructure capacity to confidently rule out active TB in facilities where many PLHIV are seen. I would like to see some well designed studies... and... a locally applicable protocol to exclude active TB that takes the infrastructure development of the country into consideration. More contextual and locally-oriented operational research is needed to scale-up IPT as a practical public health intervention in Ethiopia."

But chest x-rays aren't required in Botswana's programme. So just how safe was the practice?

Results from the IPT study in Botswana presented earlier this year at CROI suggested that Botswana's current algorithm without x-rays misses more cases of active pulmonary disease than originally anticipated.

Out of a total of 4328 adults screened, 2608 patients who were asymptomatic (and thus may have qualified for IPT) had a chest X-ray. 12% (305 subjects) of these had an abnormal chest radiograph as compared to 4% reported in the earlier pilot study, 31 (10%) of those were found to have active TB, and so overall, 1.2% of all the asymptomatic subjects could actually have active pulmonary disease (Samandari). However, that leaves out 38% of the people with abnormal chest x-rays who never came back in for further evaluation and who were lost to follow-up. So 31 out of 190 (17%) of those with abnormal chest x-rays who did come back in were diagnosed with TB, and the number of active cases missed could have been higher.

Notably in the IPT programme, 2% of the non-completers with a known cause were due to breakthrough of active TB.

Although the percentage seems small, the public health consequences of under-treating this small but possibly significant proportion of active TB cases are unclear at present. Notably, in the CDC study, 72 of those with abnormal chest x-rays were known to have initiated a 6-month course of IPT. Four of these developed active TB, one of whom had an INH mono-resistant TB isolate.

It may not be that difficult to treat these cases — if they are captured soon enough. [At least one study has found that patients who do have breakthrough pulmonary TB on IPT respond well to subsequent TB treatment](#) (Mtei).

Including chest x-rays at sites where they are available would decrease the chances of sub-optimally treating active disease. They are certainly included in the CREATE study project algorithms.

But requiring chest x-rays as part of the screening algorithm for active disease for each patient would increase the cost of these programmes substantially — and make it logistically impossible in more peripheral settings.

"Chest x-ray is not accessible to most HIV-infected people who could benefit from IPT in sub-Saharan Africa, so having radiography as an obligatory part of the algorithm will deny people access to an intervention preventing disease and possibly death" said Dr. Kevin De Cock, Director of WHO HIV/AIDS Department.

At least one study at the World Lung Health conference suggested performing chest-x rays makes IPT less cost-effective than intensified

case finding (where cases can often be diagnosed by smear microscopy alone) (Sutton) and one speaker pointed out that what can be detected on x-ray is really in the eye of the beholder: clinicians who know that the patient has TB symptoms are more likely to see (or perceive) evidence of TB on the x-ray than an observer who is off-site (Tamhane).

On the other hand, perhaps we should be thinking outside the box and trying to improve access to chest x-ray at more peripheral levels of the health system in Africa? If money can be found to upgrade laboratory facilities, why not chest x-ray? Small low cost devices have been developed, and nurses could be trained at least to tell the difference between a normal chest x-ray versus an abnormal one. People with a normal chest x-ray could be put onto IPT while the others are referred for more intensive investigations. This would have the added benefit of leading to more TB diagnoses.

But Dr Tony Harries in Malawi isn't sure that it would work.

"I am not convinced about this approach. It is expensive and without maintenance these low cost x-ray machines have the potential to be discarded to the corner of some room, never to be used again once something minor goes wrong," he says.

"With the normal full size chest x-rays and relatively competent clinicians one gets wide variations in interpretation - we tested this many years ago in Malawi! Nurses are not generally used to reading chest x-rays, so I would expect interpretation variation to be quite high with this cadre. Finally, it is well known that a proportion of HIV-infected, immunosuppressed patients with culture-proven TB have completely normal chest x-rays - up to 20%. Thus, having a normal chest x-ray does not rule out active TB!"

What about excluding smear negative (SNTB) and extrapulmonary disease (EPTB)?

But these screening assays mostly focus on typical pulmonary disease, while many people with HIV develop less easy to diagnose forms of the disease that may not always be screened out by a pulmonary disease symptom assessment. In fact, isoniazid treatment in such cases could actually delay diagnosis by partially suppressing the infection.

"My view is that the messages should be simple — only WELL patients should get IPT. Any ill patient (recent weight loss, constitutional symptoms, any impairment of daily function) should not get IPT. Rather defer and investigate and/or monitor for TB in such patients — hopefully this would avoid SNTB and EPTB patients getting IPT," said Dr Graeme Meintjes of GF Jooste Hospital in Cape Town.

“The other message is that there is never an urgency to start IPT... if the patient could have TB but you can't be sure, rather wait and investigate. If they do have TB this will show itself in the next three months in an HIV-infected person with a low CD4 count, and then they should get TB treatment and not IPT.”

“I am nervous that if we don't get these messages out clearly then in operational settings patients with unrecognised active TB will get IPT with adverse consequences for the patient and the programme,” he said.

Resistance

Others are also concerned about resistance, especially in light of the MDR/XDR crisis.

“In an analysis of an MDR cohort in our situation, six out of 140 patients had previous IPT. All six of those patients developed MDR-TB within one year of incomplete treatment with IPT,” said Dr Alistair Calver, who is with AngloGold Ashanti Health (associated with the mining industry in South Africa) during the question and answer session after Motsamai's talk. “So I am concerned about Botswana's figures of high drop out rates from their IPT - that may well be fueling the MDR epidemic.”

But Dr Alison Grant, who is working with miners as well in the Thibela TB project, believes that this could be circumstantial evidence, because the miners might have been newly infected with an MDR strain.

HIV programmes should not be too dismissive of the risk of resistance, and its potential consequences — but at the same time, the roll out of IPT should not be paralysed by this argument either.

Botswana is very much on top of this issue. The country has performed four surveys since 1996, when INH resistance among new patients was 1.6%. That went up to 4.4% in 1999 and remained stable (at 4.5%) in 2002 (it actually decreased in re-treatment cases). MDR resistance in 2002 was 0.8% among new patients. The current review will be finished by March, 2008.

“They have actually put in the appropriate monitoring practices to see how this programme is impacting resistance in the country,” said Dr. Wells.

Adherence

The 27% completion rate in Botswana is a long way from the 70% completion rate reported in the pilot studies. It is more in line with the abysmal adherence seen in ProTest, an initiative that linked an

IPT-containing package of care to HIV counselling and testing, in South Africa, Zambia and Malawi, which ranged from 24% to 59% across the project.

But as previously noted, the large simple trial of IPT in Botswana has had very high completion rates of 94% (of those 1893 who were not discontinued for other reasons) (Chengeta). According to pill count data, 90% of the study participants took 80% or more of their pills. One thing that seemed to encourage them — they gave participants little prizes, like coffee mugs with dancing zebras, when they successfully completed their IPT course.

After conducting focus group discussions to discuss appropriate incentives, the Thibela TB project adopted this strategy as well, by offering various items of small value such as t-shirts, caps, water bottles and key rings (Coetzee). In addition, the project is conducting targeted participant education, individual and peer group support.

“I think there is grassroots resistance and concerns about inducing MDR but I think this can be overcome,” said Dr Venter in South Africa. “We recently analysed our cohort in central Johannesburg, and 94% of them who started ART were on cotrimoxazole. So getting healthcare workers to give prophylaxis is possible, with sufficient training.”

“One of our major problems is the failure of the retention in care of those with good CD4s – the much vaunted wellness [patient education] programmes are empty of content in most cases, and patients feel they get little benefit (which is largely true). We need these fixed, so that TB screening and regular staging actually happens. Paradoxically, providing isoniazid may make these patients more likely to remain in care, as they actually receive treatment beyond a non-evidence based health lecture after sitting in a long primary health queue,” he said.

Where to house an IPT programme

This naturally raises the issue about where IPT programmes should be housed. In the recent TB/HIV newsletter, Dr Mario Raviglione, Director of Stop TB Department of WHO Geneva, Switzerland, argued for putting it in the HIV/AIDS Department. “I am fully convinced that IPT will never be scaled up and accessible to those who need it unless it is taken up by those services handling PLHIV: from VCTs and ARV clinics to general primary care services. Hence, the paramount key strategic move must consist in getting those components of the health sector delivering HIV and primary care services fully engaged in the implementation of IPT.”

“It just seems to me - as an HIV physician, that this fits completely naturally into HIV care and that’s I think how we should be doing it,”

said Dr Grant. "Obviously there are clearly problems where TB Control Programmes are not happy to release isoniazid for this purpose. I think that's clearly something that has to be addressed on a higher level to try to encourage people and reassure them that this is not going to cause a disaster for their TB Control Programme. I think this is part of HIV care and this is how we should be doing it because we are perfectly placed. We've got people coming to be screened for TB and if they don't have TB, they're in a perfect position to go onto IPT. It's a natural synergy - if you like."

However, Dr Halima Dawood of Edendale Hospital in KwaZulu Natal worries about the capacity for programmes to support so many "well" patients.

"First, I think that we need to get our cure rates and interruption rates at a more respectable level before we use IPT, though this intervention has certainly been beneficial in settings in South Africa. But I worry about the follow-up that IPT requires, as the current ARV programmes are saturated and there are some thoughts about extending follow-up intervals already. I am unsure if these programmes can be supported by doctors in the future. We need to start thinking laterally and including communities in the management of HIV/AIDS/TB even more," she said.

Ironically, there was no HIV programme when the IPT programme in Botswana was conceived. Of course, it is only the administration that is housed in TB in Botswana. The delivery is through general care. But would moving it into the HIV programme area increase its uptake?

Dr Wells believes it is actually more appropriate in the TB programme in Botswana:

"I think ironically it was the right decision to have nested it within the TB programme because since that time — especially with the advent of XDR and all of that — there's been a lot more focus put back on the TB programme and people realising to do it all they can't just do one without the other. In retrospect it was the wiser move because it only served to link the programmes better."

Dr Annalies Van Rie thinks that there could be problems putting IPT in either programme area: "If you house it in the TB programme or the HIV/ART programme, it will always be a programme of secondary objective. For the TB programme, TB treatment is the main mission, and for the HIV/ART clinics, getting people on ART and keeping them on ART is the most important task."

Given capacity problems in some HIV programmes, there may not be any one right or wrong answer since different models might work differently in different countries.

For example, in Cambodia's IPT project, they actually attach one or two TB programme officers to HIV clinics that want to do IPT, according to Dr Phalkun Chheng. This actually strengthens linkages between the two programmes, and increases the capacity at the clinic to perform intensified case finding or manage patients on IPT.

"Each country has to look at its own situation and then make that determination," said Dr Riita Dlodlo of Zimbabwe. "Obviously not a separate vertical programme but otherwise, it needs to be negotiated between NTP and NACP."

The focus should be the need of the community and the person with HIV to prevent TB — rather than on the programmes themselves. TB and HIV programmes need to work together to figure out how to deliver IPT in a way that makes sense for the patient and community and then work out the programmatic logistics.

"IPT is currently aimed at those people living with HIV who are well and do not need ART. These are exactly the people who fall out of the boat. They are told they have HIV, are well and asked to come back later. They are probably often perceived as a burden to the system, as they take up time and space of those who really need care," said Dr Van Rie. "We should advocate for better care for those living with HIV but not in need of ART. These individuals need counselling on prevention and how to stay healthy. IPT (and cotrimoxazole) fits into this setting, possibly in general outpatient primary health care clinics."

Staging implementation for the best candidates for IPT

By targeting only the well, as suggested by Dr. Meintjes or people with higher CD4 cell counts, the risk of treating subclinical TB would also be much lower. But another school of thought is that this approach might deny IPT to those patients who would benefit the most (people with a lower CD4 cell count who are at higher risk of TB). Still, either way, it might be possible to stage implementation of IPT by targeting one population at a time.

"Some physicians suggest that probably we should give IPT only to people with high CD4 counts," said a doctor from Kampala, Uganda, following Motsamai's presentation. "But another view is to give it in those with low CD4 counts, give IPT when we give them ARV's. That way, if they are on ARVs and IPT they are closely followed up so if they get active TB it's more likely to be picked up, as opposed to people who are fairly healthy and given treatment and don't complete it and who are more likely to miss having the diagnosis of active TB made because of poor follow up."

“In Malawi, we are wondering about combining IPT with ART but that needs careful thought, especially as many of our patients with unexplained fever and weight loss may have undiagnosed TB,” said Dr Tony Harries, but he added, “we have plans to try scaling up IPT within the context of PMTCT where most HIV-infected women will be WHO Stage 1 and therefore the fear of placing subclinical TB patients on monotherapy is reduced considerably.”

Pregnant women are often excluded from IPT programmes, a [recently published study in India](#) suggests that pregnant women could have a huge unaddressed need for TB preventive therapy and we have to rethink how to handle pregnancy/pregnant women in these programmes.

Children with HIV must also be considered. “For children, you must have the ability to diagnose childhood TB,” said Dr Mark Cotton of Tygerberg Hospital. Exclusion of active disease is even more challenging in children (see <http://www.aidsmap.com/cms1037373.asp> HATIP #32).

But Dr Cotton sees IPT as offering a chance to improve mother-child care overall. “It can be used as an opportunity to improve diagnosis of TB as a preparatory exercise. It should go hand in hand with early HIV diagnosis, access to early HAART and screening pregnant women for TB.”

Separate or integrated registers

Finally, given the problems in record keeping, wouldn't it have made more sense just to combine the IPT register with either the TB or the pre-ART/ART register? Dr Wells isn't sure whether it would have made much difference in Botswana, because of the poor quality of data reporting when it came to TB data overall.

“It's really, really critical to have it linked to the TB case register because what you want to know is: how many cases of TB are we seeing among people who've received IPT?” he added.

However, others think that having too many registers may inevitably lead to problems.

“Registers are like mushrooms, you have to stomp them out,” said Dr Reuben Granich of WHO. “Feasibility is key and must be kept in mind - every new register you implement is a potential recipe for disaster.”

“There is no time to fill in separate registers in sub-Saharan African countries that have one tenth or so of their required health care workers!” said Dr Dlodlo. “Integrate it into pre-ART and ART registers. And to quote Dr. Antony Harries, keep it simple, simple, simple!”

Moving ahead with a simple message

Indeed, keeping it simple is clearly the point of the Core Group of the TB/HIV Working Group of the Stop TB Partnership.

"Accelerating implementation of IPT is one of the major initiatives of the HIV/TB Working Group of the STOP TB partnership," said Dr Diane Havlir, who serves as chair of the group. "Putting the brakes on IPT, an intervention that prevents the leading cause of mortality in persons living with HIV based on the Botswana report is not justified, and certainly not in the best interests of the individual or the public health. Just like ART, IPT has challenges that are surmountable and that will be addressed by ongoing programmatic experience and operational research."

"One of the things that we all need to work on is to make sure we can create systems that are capable of ruling out active TB, of diagnosing active TB so that people can receive appropriate treatment. If people in high HIV burden regions who are HIV-positive don't have active TB, then they are candidates for IPT and they should be given the chance to take it - it can save their lives and prevent them from getting TB," said Mark Harrington, executive director for the Treatment Action Group. "It's a call to arms... and that's going to be a message we are putting out along with the Stop TB working group."

Knowing what we now know about rolling out large successful public health interventions to people with HIV in resource limited countries, it should be possible for programmes to take the model that Botswana developed, take the bits that worked well, and improve upon it substantially.

"It is doable. IPT is no more complex than many other programmes we've rolled out successfully," said Dr Granich.

The technical and logistical challenges can be worked out, but HIV and TB programmes have to get on board together to figure out how to make it happen.

"WHO is really behind this as well and we really want to work with the scientific and programmatic ways to deliver IPT to people with HIV," said Dr Granich.

"My feeling is that widespread use of IPT can only happen through close collaboration between AIDS and TB programmes," said Paul Nunn, Coordinator, TB/HIV and Drug Resistance for the Stop TB Department of WHO.

"My vision is that the best place to start would be in ART clinics, because there you have the infrastructure for identifying those who really need it and for following them up. Then as ART clinics disseminate to the periphery, IPT can go with them. By creatively packaging services together, it should be possible to retain more people in care and on IPT, keep on top of safety and drug resistance issues, and reduce the overall burden of TB disease among people with HIV and their families."

At the policy level, it is essential to ensure the access of HIV stakeholders and service providers to isoniazid through existing systems such as the Global Drug Facility, and also through national level consultation between the two programmes. In most countries, national TB programmes have full control of the purchase and distribution of isoniazid which could prevent its accessibility to HIV service providers.

This would be in the best interest of people with HIV who are more likely to die of TB than anything else.

In the meantime, perhaps programmes should think about a staged roll-out — either beginning first in the healthier people with higher CD4 cell counts before moving into subjects with more advanced disease in whom it may be more difficult to exclude active disease — or perhaps starting first in people on ART in whom it may be easier to ensure closer follow-up. Either way, this would allow programmes to work out some of the logistical issues first, gain experience and then work out how to provide the service to the other populations more effectively.

But we don't have to settle for high losses-to-follow-up or risk potentially misusing an important drug. Today, we should be able to do better than that.

There are successful community-based models that can achieve high-levels of treatment literacy, and provide adherence support that can keep patients in care. IPT should be packaged with something that gives people additional incentive to stay on treatment, perhaps by book-ending IPT between other services that people with HIV and their communities actually want. Of course, that will require the engagement of people with HIV and their communities in the design of these programmes.

But by creatively packaging services together, it should be possible to retain more people in care and on IPT, keep on top of safety and drug resistance issues, saving even more lives, and reducing the overall burden of TB disease among people with HIV and their families.

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*The Global TB/HIV Working Group is one of the seven Working Groups of the Stop TB Partnership established in 2001 to coordinate the global response to the dual TB and HIV epidemic. The Core Group is the decision making body which sets the strategic directions of the Working Group and makes recommendations on the global response to the TB and HIV co-infection epidemic.