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New joint guidelines on IPT and intensified case-finding from WHO

By Theo Smart

New guidelines on key approaches to TB prevention in people living with HIV

New [guidelines on Intensified TB Case Finding and the provision of Isoniazid Preventive Therapy \(IPT\)](#) (henceforth the ICF/IPT guidelines) were formally launched by WHO on December 1st.

“What’s new in these 2010 guidelines? One is that screening for TB by using only a symptom-based algorithm is sufficient to start IPT for people living with HIV – and we believe this is based on very solid and thorough evidence and will address much of the anxiety and the concerns of programme managers and implementers,” said Dr Haileyesus Getahun of WHO’s STOP TB Department at the South African TB Conference earlier this year. “Second, there is no need for a chest x-ray and tuberculin skin tests (TST) shouldn’t be a requirement for putting someone on IPT,” he went on.

Other recommendations, such as screening the patient (including those on IPT) for TB at every clinic visit, and a recommendation to consider offering a longer course of IPT (36 months) in settings where the risk of TB transmission between people with HIV is particularly high, are also new.

Additionally, it should be stressed that the ICF/IPT guidelines are one joint policy: intensified case finding should no longer be seen as something that can be divorced from IPT – IPT provision should follow as the consequence of intensified case finding whenever someone with HIV screens negative for active TB.

Joining ICF to IPT has been made possible by the identification of a simplified clinical algorithm – does the patient report having a cough currently, or a fever, weight loss or night sweats –with a high negative predictive value. (A negative predictive value is the proportion of patients with negative results on a test or algorithm who are correctly diagnosed).

In other words, according to WHO, trained staff should now be able to confidently exclude active TB in a substantial number of people living with HIV – even without a chest x-ray – and flag the remaining individuals with positive results for further diagnostic evaluation.

Relatively few active cases would be missed by the clinical TB screen (and continued screening – which should occur in people who are taking IPT as well – should identify any breakthrough cases quickly and these cases should still respond to standard treatment anyway).

Thus, the guidelines stress that one of the most commonly cited barriers to IPT implementation – the difficulty of detecting active TB in some individuals– is really no excuse for failing to offer IPT to the many thousands of people who are likely to benefit from it – clinically ‘well’ people with HIV. Symptom-free people living with HIV are at a high risk of contracting and dying from TB because they have either already been exposed, or are at high risk of being exposed to it in their communities or clinical care settings. Programmes *have a responsibility to routinely screen* people living with HIV for TB, offer a course of IPT to those who clearly don’t have it, and make certain that the rest receive further diagnostic evaluations.

But how programmes respond to other aspects of the guidance and their implementation– such as how long IPT should be given, the role of tuberculin skin testing, and how best to retain and monitor patients on IPT– may vary by context and setting as described below.

The new adult recommendations

Key recommendations for adolescents and adults with HIV	
Recommended actions	(Editor’s note: Note that WHO recommendations are now graded, based upon the confidence of an expert committee in the recommendations, in light of in the strength of the evidence. See footnotes for clarification).
1) Adults and adolescents living with HIV should be screened for TB with a clinical algorithm and those who do not report any one of the symptoms of <ul style="list-style-type: none"> • current cough, • fever, • weight loss or • night sweats are unlikely to have active TB and should be offered IPT.	<i>Strong recommendation, moderate quality of evidence</i> ¹
2) Adults and adolescents living with HIV and screened with a clinical algorithm for TB, and who report any one of the symptoms of current cough, fever, weight loss or night sweats may have active TB and should be evaluated for TB and other diseases.	<i>Strong recommendation, moderate quality of evidence</i>
4) Adults and adolescents living with HIV who have an unknown or positive TST status and who are unlikely to have active TB should receive at least 36 months of IPT. ² IPT should be given to such individuals irrespective of the degree of immunosuppression, and also to those on ART, those who have previously been treated for TB and pregnant women.	<i>CONDITIONAL recommendation, moderate quality of evidence</i> ³ [emphasis added]
5) TST is not a requirement for initiating IPT in people living with HIV.	<i>Strong recommendation, moderate quality of evidence</i>
6) People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals.	<i>Strong recommendation, high quality of evidence</i>
7) Providing IPT to people living with HIV does not increase the risk of developing isoniazid (INH)-resistant TB. Therefore, concerns regarding the development of INH resistance should not be a barrier to providing IPT.	
<small>1 A strong recommendation is one for which the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects. 2 The considerations for implementation should include the local context such as the epidemiology of TB and HIV, and settings with the highest rates of prevalence and transmission of TB among people living with HIV. 3 A conditional recommendation is one for which the panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects and data to support the recommendation are scant. Therefore, the recommendation is only applicable to a specific group, population or setting, or new evidence may result in changing the balance of risk to benefit, or the benefits may not warrant the cost or resource requirements in all settings.</small>	

Background

Globally, one third of the world is latently infected with TB, though roughly 90-95% of people without HIV will never go on to develop active disease. But HIV increases the risk of developing active TB dramatically — people living with HIV have between 20-37 times higher risk of TB. Consequently, TB is the leading cause of death among people with HIV in most of the world.

Preventing illness and death due to TB should therefore be one of the highest priorities of HIV programmes and care providers. Along with the provision of antiretroviral therapy (ART), WHO has promoted three interventions, the 'Three I's', as essential TB-fighting activities for HIV programmes to implement. The Three I's include adopting good *Infection Control* practices to reduce the likelihood of exposure to TB bacilli, in clinical, congregate settings and in the community (IC); *Intensified Case Finding* to increase the early identification of TB disease (ICF); and the provision of Isoniazid Preventive Therapy (IPT) to reduce the risk of TB to those in whom active TB disease can be excluded (See [HATIP #112](#)).

"It's very clear that IPT decreases the incidence of tuberculosis for people living with HIV," said Dr Reuben Granich, of WHO's HIV Department, who described the new guidelines at this year's Union World Conference on Lung Health in Berlin. A course of IPT reduces the risk of active TB by about a third in people living with HIV overall — though the reduction in risk is as high as 64% in those who have a positive TST result, indicating prior exposure to TB. Notably, in the BOTUSA study, [people with a positive TST who took IPT for 36 months experienced a 92% reduction in the risk of IPT](#).

Gradually, HIV programmes have taken up most of WHO's recommendations on TB/HIV. But for reasons that HATIP has addressed in a previous issue ([HATIP 96](#)) including the lack of an accepted approach to excluding active TB (and whether a chest x-ray is necessary), confusion over the necessity of conducting tuberculin skin tests to confirm latent infection, fears of isoniazid resistance, and coordinating stocking and other issues with national TB control programmes, IPT implementation has lagged.

According to Dr Granich, some countries erected ridiculously high requirements before it was considered 'safe' to implement IPT. He gave the following example of one country's IPT policy:

Barriers to IPT: an example

Eligibility criteria for a facility to offer IPT in Country X in 2006
<p>Human resources:</p> <ul style="list-style-type: none"> • Medical Officer • Laboratory assistant • Trained counselor • Pharmacy technician • Adherence supporters
<p>Infrastructure:</p> <ul style="list-style-type: none"> • Functional laboratory • X-ray or access to x-ray services • Counseling room/space and consultation room
<p>Equipment and logistics:</p> <ul style="list-style-type: none"> • Facilities for TB microscopy • Facilities for skin testing (mantoux) • Cold chain system • Facilities for HIV testing • Sustainable supply of anti-TB drugs including Isoniazid • Sustainable supply of HIV test kits
<p>Other key issues:</p> <ul style="list-style-type: none"> • If an organisation has a TB default rate of greater than 5 percent, it will not be eligible to provide IPT

"You had to have all of these things in place, including a default rate below 5%," said Dr Granich. "So needless to say, this country has not implemented much."

At least some of the delay in implementation could be due to a lack of consistent technical guidance. So when WHO convened the Three I's meeting in April 2008, it was recommended that WHO produce clearer guidance reflecting the most recent scientific evidence to expedite the implementation of IPT in tandem with ICF.

The simplified TB screening algorithm (and the risk of resistance)

As already noted, WHO undertook a comprehensive systematic meta-analysis of primary patient data from 12 TB screening studies, including over 8000 patients, in order to identify the best screening algorithm for excluding active TB.

The studies looked at TB symptom screening algorithms that included all of the main TB symptoms, but the meta-analysis concluded that a combination of four had the highest negative predictive value: a current cough (on the day of screening), or a reporting fever, weight loss or night sweats.

The screening algorithm has a sensitivity of 79% for TB and a specificity of 50%. Assuming a 5% TB prevalence among people living with HIV, the negative predictive value was 97.7% (95% confidence interval 97.4–98.0).

If a person living with HIV doesn't report having any of these symptoms, they have a very low probability of having active TB.

Many programmes have been slow to implement IPT because they concluded that it was necessary to perform a chest x-ray to exclude active TB in patients who do not report any symptoms. This, of course, would make IPT implementation impossible in settings without access to chest x-rays, and increase the cost of implementation everywhere else.

"The whole focus is not whether somebody has TB, but whether they don't have TB and whether you can feel safe giving them IPT," commented Dr Getahun.

However, although the meta-analysis found that the addition of the chest x-ray improved the sensitivity of screening for active TB somewhat, it only increased the negative predictive value marginally.

Another important point made by the panel reviewing the guidelines concerns the frequency of screening for TB symptoms. The panel concluded that this should happen each time a person with HIV visits a health facility or has contact with a health worker, including those patients who have received or are receiving IPT or ART. This should greatly decrease the likelihood of a breakthrough case of active TB escaping detection while someone is taking IPT and the subsequent risk of developing resistance to isoniazid. However, it should also be pointed out that a meta-analysis of eight IPT studies conducted for the ICF/IPT guidelines found no statistically significant increase in isoniazid resistance (relative risk, 95% confidence interval= 1.87 [0.65–5.38]). Additionally, a recent review of data from the Thibela TB study in a very large cohort of South African gold miners has also found no significant evidence of resistance.

Who should be offered IPT and for how long?

What is the role of TST?

The guidelines also make some important clarifications about which people living with HIV should be offered a course of IPT (provided they report none of the four TB symptoms). In short, the guidelines recommend that everyone should receive IPT (at least in

resource-limited settings), regardless of their CD4 cell count, whether they are on ART, have previously been treated for TB or are pregnant women.

Guidance regarding people on ART had previously been unclear (indeed, at the South African TB Conference, Dr Getahun pointed out that “the quality of evidence in support of concomitant IPT and ART is very low because there is no study that directly addresses this question and from the published literature the results are contrasting.”)

Meanwhile, people who previously had TB and pregnant women have often been excluded from IPT programmes, despite reason to believe that they may benefit.

In addition, the guidelines state a TST is not necessary before offering IPT. The requirement to perform TST has long proven a barrier to IPT implementation in many settings, partly because it requires maintaining a cold chain system and refrigeration to stock the tuberculin (very difficult in some settings) and also because reading the test requires that the patient make a repeated clinic visit just days after it is administered. Many simply cannot return to the clinic so soon, so IPT programmes requiring TST tend to miss many people who might benefit from IPT.

At the same time however, the guidelines note that IPT is much more beneficial for those who test TST positive, which becomes important when considering how long the course of IPT should be.

The guidelines review group were absolutely clear that people should be offered at least six months of IPT. However, one of the key findings from the BOTUSA IPT study, mentioned earlier, was the limited durability of the short course of IPT's benefit in that setting — it began to wear off within six months of completing treatment — versus the profoundly greater benefit of 36 months of IPT, essentially, for the purpose of that study, continuous treatment.

So the guidelines group also made a conditional recommendation that IPT should be offered for 36 months — with small print noting that this was based on less data, and may be specific to settings in which people with HIV are at high risk of being exposed (or rather re-exposed) to TB.

But this recommendation presents something of a quandary for programmes and patients. Even though a short course of isoniazid, when given consistently with vitamin B6 (pyridoxine) to reduce the risk of peripheral neuropathy, is ‘safe’ (there are relatively few serious adverse events or deaths on treatment), the drug is not without side effects. There are really no data at all on the long-term safety of continuous IPT, and safety may be a particular concern for people who have to take lifelong ART concurrently, especially given that some antiretrovirals and isoniazid have overlapping toxicities (including neuropathy and hepatitis).

But also of concern is that the BOTUSA IPT study also showed that 36 months of IPT offered no statistically significant benefit over 6 months of IPT in people who were TST-negative at baseline — the vast majority of people in the study.

For people who have not been exposed to TB, the risks of continuous treatment could well outweigh the benefits. On the other hand, people may eventually go on to be exposed to TB, especially in very high TB burden settings (in fact, someone should conduct a study on the rate of TST conversion among people with HIV attending clinics in different settings).

But if countries decided to require TSTs, as some do, before offering continuous IPT, it would present the same barrier to IPT implementation that these guidelines seek to avoid, and very few people would get IPT at all.

Ultimately, until there are more data on long-term IPT (or whether those taking ART, or at what point after taking ART, it might be safe

to discontinue IPT), people living with HIV may have to weigh the evidence and make the choice for themselves.

“PLHIV and AIDS, we are the people who are faced with death of TB,” said Carol Nyirenda at this year’s Union World Conference on Lung Health. “I don’t think some of you can actually imagine - when you are adhering to treatment; I’ve been adhering religiously to my HIV treatment for seven years. But then TB could come, within two weeks I’m dead. I could be speaking to you today, by the time I get home I catch TB and I’m dead. So I don’t think you can imagine how we sit and watch our friends die and think, ‘When is this going to happen to me?’ But with clear and accurate information - as has been with ART - we take our treatment for life.... We should ask our governments in the South to offer us this service of IPT. For me what I push for is that I should be offered this service - at least on an ‘opt-out’ basis: Let ME see whether I want to take it or not. I should be given the choice... What we are saying is: *‘don’t close us out of the deal!’*”

At the same time, it is important to note that it’s highly unlikely that any person living with HIV in a well-resourced setting with a low risk of TB would volunteer to take IPT, not to mention three or more years of it, unless they discovered they were TST-positive. Why should people in resource-limited settings not have the same access to information to guide their treatment decision? So activists in settings considering continuous IPT may want to demand developing the capacity to screen for latent TB — either with TSTs, or the gamma interferon release assays (such as *Quantiferon*), or some new diagnostic tool.

ICF/IPT in infants and children with HIV

“Children are a group often forgotten in the broader context... of TB and TB/HIV. The data, as it applies in this context [to ICF/IPT]- are limited,” said Dr Helen Menzies who spoke about the ICF/IPT guidelines in infants and children with HIV (see box) at the Union Conference in Berlin. “In terms of programmatic implementation, probably the most important take-home point is that children should be regularly assessed for contact [with an active TB case]. The question needs to be asked carefully and often, and with a wide scope.”

The number of studies looking at the use of IPT in children is indeed limited as described in HATIP’s series on Childhood TB. The case for IPT in older children is much stronger, but the data conflicting in infants. For instance, some studies in which IPT and ICF were given to infants, famously found that the interventions reduced the risk of death — and this did not appear to be driven by differences in TB outcomes. However, a more recent study found benefit from giving IPT to HIV-exposed children — however, the children participating in the study were regularly screened for TB contacts in their family — and those with contacts were quickly removed from the study and provided with treatment (which could have reduced the power of the study to reach any conclusions about TB-related endpoints).

Dr Menzies urged the audience to try to generate more data on IPT, especially from other parts of the world. “I would encourage all of you to take on evaluating this area as you roll out IPT programmes. Please include the children. I think we need data from different kinds of settings so we can really understand the best approach and the impact that we’re having.”

“We need to understand TB and TB/HIV as family diseases where we understand the whole context of the family, looking at the points of entry that give us the opportunity to screen mothers and children, pregnant women, and how we reach out to other family members as well,” she concluded.

ICF/IPT Guideline's Key Recommendations in Infants and Children Living with HIV	
1) Children living with HIV who do not have poor weight gain, ¹ fever or current cough are unlikely to have active TB.	<i>Strong recommendation, low quality of evidence</i>
2) Children living with HIV who have any one of the following symptoms – poor weight gain, fever, current cough or contact history with a TB case – may have TB and should be evaluated for TB and other conditions. If the evaluation shows no TB, such children should be offered IPT regardless of their age.	<i>Strong recommendation, low quality of evidence</i>
3) Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive six months of IPT (10 mg/kg/day) as part of a comprehensive package of HIV prevention and care services.	<i>Strong recommendation, moderate quality of evidence</i>
4) In children living with HIV who are less than 12 months of age, only those children who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB disease.	<i>Strong recommendation, low quality of evidence</i>
5) All children living with HIV who have successfully completed treatment for TB disease should receive INH for an additional six months.	<i>Conditional recommendation, low quality of evidence</i>
1 Poor weight gain is defined as reported weight loss, or very low weight (weight-for-age less than -3 z-score), or underweight (weight for-age less than -2 z-score), or confirmed weight loss (>5%) since the last visit, or growth curve flattening.	

Operationalising the guidelines

The guidelines contained little information on how programmes should put them into implementation. Logistical challenges with the increased workload for clinics, adherence support staff and pharmacies, and the implementation of wellness programmes (getting and keeping healthy people not yet on ART into care) remain. These might only be addressable by making the community of people living with HIV partners in implementation as well as patients (this was a topic of a recent ARASA meeting in South Africa that will be discussed in an upcoming HATIP).

In addition, CREATE has recently published a series of articles in a supplement published Nov. 18 in the journal AIDS on its experience implementing IPT. According to CREATE, a link to download these articles will be posted soon on their website (<http://www.tbhiv-create.org>) or on their [Facebook Group Page](#).

There is also the question of government commitment to providing IPT within public health systems. As TB/HV activist Carol Nawina Nyirenda said at the 41st Union World Conference on Lung Health in Berlin:

"It is really wrong that people living with HIV should still be dying of TB, which is a curable disease, especially when there are [interventions] like IPT (isoniazid preventive therapy), which can help people living with HIV. But most of our governments in the South do not want to implement IPT."

about HATIP

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