

# Scaling-up TB screening and isoniazid preventive therapy among children and adults living with HIV: new WHO guidelines

HIV can be managed, but it requires a proactive approach from the clinician. Delphine Sculier and Haileyesus Getahun introduce the latest guidelines from WHO

## WHY scale-up isoniazid preventive therapy?

Human immunodeficiency virus (HIV) is the strongest risk factor for developing tuberculosis (TB) disease in people with latent or new *Mycobacterium tuberculosis* infection. The risk of developing TB is between 21 and 34 times greater in people living with HIV than among individuals who do not have HIV infection. At least one-third of the estimated 34 million people living with HIV worldwide are infected with *M. tuberculosis*. Yet, only 178 000 were receiving isoniazid preventive therapy (IPT) at the end of 2010 and TB was responsible for a quarter of deaths in people living with HIV.<sup>1</sup>

To reduce the morbidity and mortality from TB in people living with HIV, the World Health Organization (WHO) recommends the following interventions: early provision of antiretroviral therapy (ART) at CD4 count <350 cells/mm<sup>3</sup> and the Three I's for HIV/TB: intensified case-finding of TB (ICF), IPT, and infection control for TB (IC). ICF and treatment of TB interrupts transmission of disease by infectious cases, decreases morbidity, and delays mortality. Most importantly, active TB screening offers the opportunity to provide preventive therapy for people who do not have symptoms and signs of TB. The WHO 'Guidelines for intensified TB case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings' provide guidance to national HIV and TB programmes and to HIV service providers to scale-up the implementation of TB screening and IPT.<sup>2</sup>

## WHAT is isoniazid preventive therapy (IPT)?

IPT reduces the risk of developing TB by 33%.<sup>3</sup> Reduction is even greater in individuals who have a positive tuberculin skin test (TST), up to 74%.<sup>4</sup> Evidence also shows that IPT reduces death from TB by 28% to 49% in people living with HIV who are TST positive.<sup>5,6</sup> Isoniazid at 300 mg/day is as efficacious but safer than rifampicin- and pyrazinamide-containing regimens<sup>3</sup> and remains the drug of choice for preventive TB therapy in adults living with HIV. IPT should be given for at least 6 months.

Evidence from Botswana and South Africa, settings with high TB prevalence and transmission, suggests an

increased benefit with 36 months or longer duration of IPT, particularly in people who are TST positives.<sup>4,7</sup>

In children living with HIV, IPT should be given for 6 months for those who are older than 1 year of age. Findings from a randomised trial conducted in South Africa showed no benefit of IPT in HIV-infected infants when there is no known exposure to a TB source.<sup>8</sup> However, IPT for 6 months is associated with 54% reduction in mortality in older children living with HIV.<sup>9</sup> Isoniazid should be given at a dose of 10 mg/kg body weight and be supplied with vitamin B6 at a dose of 25 mg daily. Available data suggest that isoniazid is not hepatotoxic for children, even in those receiving ART.<sup>10</sup>

## HOW to initiate isoniazid preventive therapy?

All adults and children living with HIV should be regularly screened for TB using simple clinical algorithms wherever they receive care. The clinical algorithm to screen adults includes four symptoms: current cough,



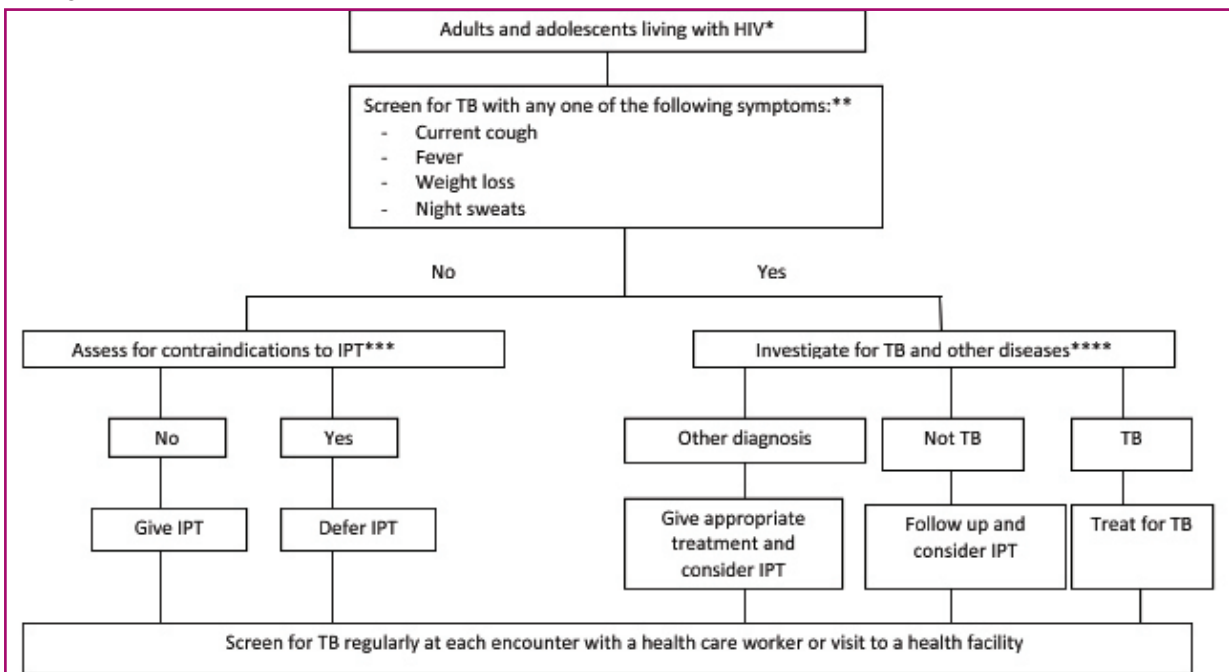
Lung examination. Doctor in Ethiopia using a stethoscope to listen to the lungs of a man who has both tuberculosis and AIDS

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Figure 1 Algorithm for TB screening in adults and adolescents living with HIV in HIV-prevalent and resource-constrained settings



\*Every adult and adolescent should be evaluated for eligibility to receive ART. Infection control measures should be prioritised to reduce *M tuberculosis* transmission in all settings that provide care.

\*\* Chest radiography can be done if available, but is not required to classify patients into TB and non-TB groups. In high HIV-prevalence settings with a high TB prevalence among people living with HIV (e.g. greater than 10%), strong consideration must be given to adding other sensitive investigations.

\*\*\* Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption, and symptoms of peripheral neuropathy. Past history of TB and current pregnancy should not be contraindications for starting IPT. Although not a requirement for initiating IPT, TST may be done as a part of eligibility screening in some settings.

\*\*\*\* Investigations for TB should be done in accordance with existing national guidelines.

fever, weight loss, or night sweats (see Figure 1). The absence of all of these symptoms can identify people living with HIV with a very low probability of having active TB disease. This best screening rule has a sensitivity of 79% and a specificity of 50%.<sup>11</sup> At 5% TB prevalence among people living with HIV, the negative predictive value is 97.7%. Chest radiography is no longer a mandatory requirement for initiating IPT in people living with HIV but its use could be considered to augment the utility of the clinical algorithm in settings with high TB prevalence rates (e.g. greater than 10%).<sup>2</sup> Conversely, adults and adolescents living with HIV who report any one of these four symptoms may have active TB and should be evaluated for TB and other diseases according to national guidelines.

For children, the clinical algorithm relies on the following symptoms: poor weight gain, fever, current cough, or contact history with a TB case (see Figure 2). The absence of all these four symptoms can identify children living with HIV unlikely to have active TB disease, while the presence of any of these symptoms should trigger further investigations for TB and other diseases.

IPT should be given to eligible individuals irrespective of the degree of immunosuppression, the use of

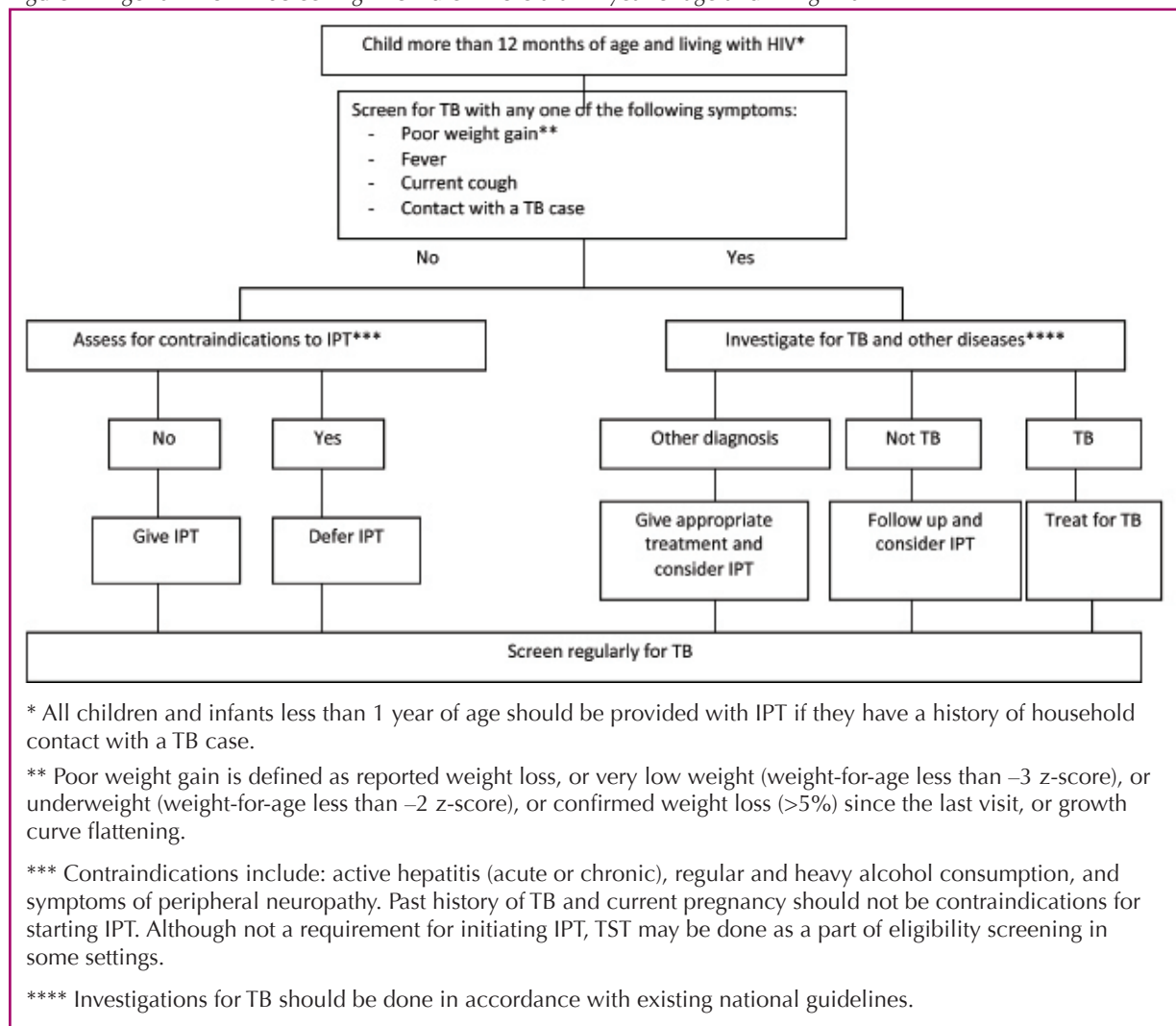
ART, past history of TB, or current pregnancy. Concomitant use of IPT and ART shows additional benefit in reducing TB risk, up to 89%, as demonstrated in studies from Brazil,<sup>12</sup> South Africa,<sup>13</sup> and Botswana.<sup>4</sup> Provision of IPT immediately after successful completion of TB treatment prevents recurrent TB.<sup>14</sup> Active TB has been diagnosed at rates up to 10 times higher in pregnant women living with HIV compared with pregnant women without HIV infection.<sup>15</sup> Maternal TB is associated with 2.5-fold increased risk of vertical transmission of HIV to the unborn baby.<sup>16</sup> TB screening and prevention of TB among pregnant women living with HIV is of utmost importance, and the adult clinical algorithm has been found to have 99.3% negative predictive value among pregnant women with HIV infection.<sup>17</sup>

### Implementation of isoniazid preventive therapy

TB screening should be performed at the time of initial presentation to HIV care and thereafter at every visit to a health facility or contact with a healthcare worker. Screening for TB is important regardless of whether patients have received or are receiving IPT or ART.

IPT is primarily an HIV intervention and is part of high-quality services for people living with HIV.

Figure 2 Algorithm for TB screening in children more than 1 year of age and living with HIV



Therefore, in most settings provision of IPT to people living with HIV should be under the responsibility of national HIV programmes and HIV service providers. National TB programmes may or may not have the ability to reach every person living with HIV in need of IPT and should provide the necessary support to improve access through other programmes. IPT should also be part of a TB prevention package along with infection control for TB, intensified case-finding and provision of early ART to people living with HIV with CD4 count  $<350$  cells/mm<sup>3</sup>. The simple clinical algorithm offers a unique opportunity for HIV programmes to scale-up TB screening and IPT in people unlikely to have active TB. National implementation will need to be monitored and evaluated through appropriate patient monitoring and evaluation systems that should use internationally recommended indicators.

A commonly cited impediment to the provision of IPT to people living with HIV is the fear of development of drug-resistant TB. Studies and meta-analysis have shown that there is no risk of development of drug resistance after provision of IPT.<sup>18,19</sup> Therefore, concerns regarding the development of isoniazid resistance should not be a barrier to providing IPT (see Table 1).

Another obstacle to access the IPT is TST as it has operational and technical limitations such as poor specificity, anergy, cross reactivity with Bacille–Calmette–Guérin vaccination and non-tuberculosis mycobacteria, poor reproductivity, requirement for a cold chain, and price. The WHO recommendations are clear that TST is not a requirement for initiating IPT in people living with HIV but it can be used where feasible to identify people who will benefit most from IPT.

Adherence rates for IPT reported in observational studies and randomised trials varied widely from 34% to 98%. Although it is important for good individual and programme outcomes treatment is completed, the primary objective is to ensure that people do not continue to take IPT in the rare event of active TB. Regular screening using the clinical algorithm at every contact with a healthcare provider is thus important to identify people who may develop active TB on IPT and to stop the prophylaxis. IPT should also be discontinued in cases of toxicity. However, adverse events due to IPT, especially hepatotoxicity, are rare, as observed in a cohort of over 24 000 patients in South Africa (0.54% and 0.07% respectively for adverse events and hepatotoxicity) and can be monitored based on clinical symptoms only.<sup>20</sup>

**Table 1** Key recommendations of the WHO Guidelines for intensified TB case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings

- 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 current cough, fever, weight loss, or night sweats are unlikely to have active TB and should be offered IPT.
- 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.
- Adults and adolescents living with HIV who have an unknown or positive TST status and are unlikely to have active TB should receive at least 6 months of IPT as part of a comprehensive package of HIV care. 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.
- 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. 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.
- TST is not a requirement for initiating IPT in people living with HIV. People living with HIV who have a positive TST benefit more from IPT; TST can be used where feasible to identify such individuals.
- Providing IPT to people living with HIV does not increase the risk of developing isoniazid-resistant TB. Therefore, concerns regarding the development of isoniazid resistance should not be a barrier to providing IPT.
- Children living with HIV who do not have poor weight gain, fever, or current cough are unlikely to have active TB.
- 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.
- 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.
- 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 6 months of IPT if the evaluation shows no TB disease.
- All children living with HIV who have successfully completed treatment for TB disease should receive isoniazid for an additional 6 months.

## Conclusions

IPT is a beneficial intervention to prevent active TB disease among people living with HIV. However, implementation has been slow so far. The WHO 'Guidelines for intensified TB case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings' aims to provide simplified, evidence-based guidance for TB screening and provision of IPT. Success in implementing IPT and reducing the burden

of TB among people living with HIV will depend on the leadership of HIV programmes and service providers to take-up these guidelines and appropriately address perceived barriers to providing IPT. Many countries – such as Ethiopia, Mozambique, and South Africa – have already adopted and implemented the WHO guidelines and demonstrated that rapid scale-up in the provision of IPT to people living with HIV is feasible.<sup>1</sup>

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