Isoniazid Preventive Therapy for the Prevention of Tuberculosis in People Living with HIV/AIDS

Providing isoniazid to prevent tuberculosis among people living with HIV is a proven, internationally recommended strategy that has been effectively implemented in low-resource settings.

This document is part of a series of briefs for health program managers interested in implementing evidence-based programs. With a special emphasis on underutilized interventions, they present evidence on programs that work and provide guidance and resources for replication.

What Works: Clinical Evidence and International Guidance

Isoniazid preventive therapy (IPT) is the provision of the drug isoniazid to people at high risk of developing active tuberculosis (TB). Those with HIV are 20 to 37 times more likely to develop active TB from latent TB than those without HIV, making HIV infection the strongest risk factor for TB.[1] TB is responsible for more than a quarter of deaths of people living with HIV. The World Health Organization (WHO) recommends IPT as part of the *Three I's for HIV/TB*: IPT, Intensified TB case finding, and Infection control for TB. IPT is a proven strategy for reducing TB in individuals and at a community and population level.[2] Despite the strong evidence supporting IPT for TB prevention, it has not been widely implemented outside of the U.S. and other wealthy countries.

RECOMMENDATIONS FROM WHO FOR IMPLEMENTING IPT

The current recommended dose of IPT for adults is 300 mg of isoniazid per day for six months, with 36 months conditionally recommended in areas of high TB prevalence and transmission.[1] Adults and adolescents living with HIV should be screened with the WHO symptom checklist for TB (see box on page 2), to rule out active TB infection. Those reporting one or more symptoms may have active TB and should be further evaluated and then either treated for TB or, once active TB is ruled out, started on IPT. Those reporting none of the symptoms should be started on IPT.

Why IPT Is Underutilized

Fifteen years after WHO recommended IPT for all people living with HIV, less than 1 percent of those living with HIV receive IPT.[3] Supportive policy for IPT exists in 84 countries, yet few are implementing IPT programs.[4] Health systems face several challenges to IPT implementation. Understanding how to address these challenges can open opportunities for the creation of successful programs.

DRUG RESISTANCE

Many TB program officials and health care providers fear that IPT programs will inadvertently lead to the development and worldwide spread of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). Close monitoring of IPT program participants can alleviate this fear, as strong evidence exists that IPT does not increase the risk of developing isoniazid-resistant TB in the absence of active TB. To prevent individuals with active TB from receiving IPT, ruling out active disease at the beginning is most important. If an individual develops new symptoms of TB during IPT treatment, IPT should be stopped and a diagnosis of TB should be confirmed or ruled out. If active TB is

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Symptom checklist to rule out TB

The checklist recommended by WHO involves asking about four symptoms: (1) current cough, (2) night sweats, (3) fever and (4) weight loss. People living with HIV who report an absence of all of these symptoms have a very low probability of having active TB.

WHO recommends that all HIV-positive patients be screened at every visit to a health facility using a symptom checklist.[1] Not only is this important for identifying those who are unlikely to have TB and can be offered IPT, but it also identifies those who may have TB and need referral for diagnosis and treatment.

confirmed, routine treatment should commence, plus culture and drug susceptibility testing or line-probe assay should be performed to assess for isoniazid drug resistance. The development and implementation of national and international drug-resistance surveillance systems can also help to assuage fears through monitoring cases of drug resistant TB and addressing them as they are identified.[1] Experience with and understanding of the benefits of IPT, as well as how to reduce the risk of drug resistance, among health care workers is critical to successful implementation of IPT.[5]

RESOURCE CONSTRAINTS

Resource allocation can be a challenge in the implementation of an IPT program, as it requires a substantial initial investment. However, over time IPT leads to significant cost savings.[6] Initial costs include training of staff and purchase of tuberculin skin-testing (TST) reagent. An additional constraint is the need to purchase isoniazid alone, outside the fixed-dose combination of isoniazid and rifampin typically used in the treatment of TB. Programs may have difficulty acquiring isoniazid outside this combination if national policy does not explicitly provide for isoniazid for IPT.

TOXICITY

When providing any medication, the risk to the patient taking the medication must be taken into account. Isoniazid has known side effects, including liver damage. Even with this risk, the benefits of IPT outweigh the risk of liver damage for people living with HIV.[7] Client monitoring and education can decrease the risk of a severe adverse event.[7] The degree of monitoring that is feasible depends on the setting and ranges from educating clients on symptoms and self-monitoring to monthly check-ups at a health facility.[7]

Two recent studies of IPT for HIV patients in the U.S. reported rates of liver damage of 0.1 percent and 0.3 percent respectively.[8, 9] One hospitalization and no deaths were reported across data that included over 14,000 patients. In both studies, monitoring for potential liver damage included monthly clinical monitoring by a nurse and was required for continued treatment.[8, 9] Patients were also counseled about potential symptoms and side effects at these monthly sessions.[9]

ADHERENCE

Adherence may be a challenge for patients on IPT because they are taking a medication for prevention only, side effects may make them feel sick, and monthly monitoring may feel burdensome. Concerns about low adherence and patients missing monitoring visits feed clinician fears that IPT may lead to drug-resistant TB. However, patient education has been shown to improve IPT adherence.[7]

Where and How IPT Has Worked

Despite the barriers and low uptake of IPT globally, IPT has been successfully implemented in several settings. Experiences from two programs, one in Botswana and one in Brazil, highlight what works and provide guidance for future programs.

Both Botswana and Brazil have programs that provide universal access to antiretroviral therapy (ART). Before implementation of IPT, TB was the main cause of death among people with HIV in both countries. Empirical evidence for the effectiveness of IPT led each country to pursue IPT as a strategy for reducing the incidence of TB. Implementation occurred at different scales (nationally in Botswana and in the city of Rio de Janeiro in Brazil) using different techniques to screen for active TB (a clinical algorithm in Botswana and TST in Brazil). However, the lessons learned from both provide strong recommendations for those who want to implement IPT in local settings. The implementation of IPT successfully reduced the prevalence of TB in Brazil and Botswana. This success in two very different contexts provides evidence that IPT programs may effectively reduce cases of TB and TB-related death globally.

BOTSWANA

Twenty-five percent of people 15-49 years old in Botswana have HIV, and over 80 percent of TB patients are co-infected with HIV. Before IPT implementation, 40 percent of AIDS deaths in Botswana were due to TB.[10] Botswana provides ART free through a program that reaches 90 to 95 percent of people living with HIV who need ART. In 2001 Botswana's Ministry of Health began a national IPT program that used the WHO symptom checklist to screen for active TB infection. By 2006, Botswana's program accounted for 70 percent of people in the world on IPT.

Prior to implementing its national IPT program, Botswana implemented a pilot program that screened for active TB using a symptom checklist (see box on page 2) plus a

chest X-ray for all clients. Following the pilot, the national program — implemented in 2001 — used the symptom checklist alone. The decision to eliminate the X-ray as a part of the screening was based on the high rate of loss to follow-up between checklist screening and chest X-ray (18 percent) and the high sensitivity of the checklist for finding active cases of TB. Only 0.2 percent of cases were missed by the checklist but detected by chest X-ray.[11]

Between 2004 and 2006 a study was conducted within the national IPT program to document the process of running the program. During the study, only three of 1,995 participants developed TB, and isoniazid resistance was not detected in any of them. Eighty-six percent of study participants were adherent (defined as attending all six monthly visits) and severe adverse events occurred in only 1.4 percent of participants.[4] The Botswana experience shows that, contrary to concerns about IPT therapy, IPT can be implemented without leading to resistant TB, most patients will adhere to therapy, and severe adverse events are rare.

A key element in the success of Botswana's national IPT program was the integration of IPT and ART, a recommendation that came from results of the clinical trial. In the pilot study, HIV patients on ART had higher adherence than those not on ART.

BRAZIL

Brazil has the highest number of TB cases in Latin America, with Rio de Janeiro having the second highest TB incidence in Brazil.[12] TB is the leading cause of AIDS-related death in Brazil, even for patients on ART.[12] Brazil provides ART free to all people living with HIV with CD4 counts below 200.[13] The IPT program in Brazil was first implemented in 2005 at 29 clinics in Rio de Janeiro under the control of the City Health Department. These clinics provide services to 57 percent of all HIV patients in Rio. TST is the screening method required by national policy in Brazil.[13] The Rio de Janeiro program was implemented initially as a pilot study, with the hope of generating data and momentum for eventual scale-up to the rest of Brazil.

As in Botswana, the Rio de Janeiro IPT program showed high levels of adherence. Eighty-five percent of all those starting IPT completed the treatment. Higher adherence was also found among those who were already receiving ART.

While TST was used in the implementation of the program, a recommendation from this study was that use of the WHO checklist alone should be explored to decrease the time between HIV diagnosis and the start of IPT.[12]

As a result of the success of Rio de Janeiro's program, the government of Brazil is beginning scale-up of IPT to the rest of the country. Two important strategies have been adopted to increase the success of the national program: advocacy and the training of health care workers. The training curriculum includes the rationale for a national IPT policy, pathogenesis of TB, diagnosis of latent and active TB, TB preventive therapy, and monitoring of patients receiving isoniazid. This training was deemed essential for a successful scale-up.[12] Advocacy includes interventions at several levels. Local advocacy focuses on increasing support for integration of TB and HIV services. National advocacy supports the continuation of scale-up efforts to the whole of Brazil. Advocacy efforts have had political and practical impact. Provision of IPT is now incorporated into Brazil's national TB guidelines, and both TST and IPT appear on all ART therapy prescription forms.[12]

Main Points from IPT Evidence and Experience

- Integration of TB and HIV services is recommended. The integration of TB and HIV services leads to both better services for clients and a greater impact in TB prevention. A first step is the provision of isoniazid at the same clinic where people receive their ART. For those with CD4 counts that makes them ineligible for ART, IPT provided at the ART clinic can serve as an entry point to later care and treatment for HIV.
- The symptom checklist is an effective method of screening for active TB. In the case of Botswana, the symptom checklist was effective in screening for active TB. In Brazil it is recommended that future interventions explore the use of the checklist to decrease the time from HIV diagnosis to IPT provision.
- IPT adherence is high. Despite fears of low adherence leading to drug resistance or low effectiveness, neither was observed in either Botswana or Brazil. Particularly among people on ART, adherence to IPT is high.
- Advocacy to support the integration of HIV and TB services is an important part of an IPT program. Advocacy should be directed toward promoting both local and national goals.
- Include health care worker training in IPT programs. The implementation of IPT requires new competencies from existing health care workers and may require more staff that also need training.

Implementing IPT: How to Get Started

Successful examples of IPT implementation highlight its feasibility in diverse settings. The *WHO Guidelines for Intensified Tuberculosis Case-Finding and Isoniazid Preventive Therapy for People Living with HIV in Resource-Constrained Settings* provides in-depth information on the evidence base for IPT. The target audience for these guidelines includes health care workers, policy makers, health program managers, governments, nongovernmental organizations, funders and patient support groups. The International Training and Education Center for Health (I-TECH) website also provides general information on first steps for implementation of an IPT program.

Below are additional information and resources that provide guidance for those interested in implementing an IPT program.

SITUATIONAL ASSESSMENT

An important first step in implementing an effective IPT program is to understand the local context and tailoring the program appropriately. A situational assessment for IPT should be conducted that gathers information on the prevalence and incidence of HIV, AIDS and TB in the potential catchment area, the number of people currently receiving ART, and the coverage of any current TB or HIV programs. Moreover, information on the current health system capacity in the area is essential. This information will inform program design, including the scope of advocacy and health care worker training needed. The WHO guidelines provide an evidence base for implementation of IPT with options for tailoring the intervention to local context, including choice of screening method(s) and length of treatment.

PROGRAM DESIGN

More information on collaboration between HIV/AIDS and TB programs, advocacy and health care worker training is presented below.

- **Collaborative programs**
  For background on the rationale behind integrating TB and HIV services, as well as guidance for implementing a strategy for collaboration among HIV, TB and IPT programs, see the *WHO Guidelines for Implementing Collaborative TB and HIV Programme Activities*. These are aimed at national and district health planners. For more information on collaborative programming, especially for guidance on engaging both the public and private sectors in collaboration, see the report from a WHO consultation, *Promoting the Implementation of Collaborative TB/HIV Activities Through Public-Private Mix and Partnerships.* This document includes experiences from low-resource settings and includes information for expanding the provision of TB and HIV services to a wider range of providers.

- **Advocacy**
  The Brazil case study emphasized that IPT programs need to include advocacy efforts if scale-up is to be effective. WHO has developed a training manual, *Networking for Policy Change: TB/HIV Advocacy Training Manual*, which was designed to help individuals develop advocacy skills to work for change from the local to international levels related specifically to TB- and HIV-related policy. The Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE) offers additional resources on effective advocacy, based on experiences such as the Brazil case study.

- **Health care worker training**
  Another recommendation from the case study in Brazil was for the need for health care worker training. While specifics of training need to be tailored to the context in which IPT is implemented, CARE has developed a useful training curriculum, *Case-Based Curriculum on the 3 I's*, that can be used and adapted for multidisciplinary, clinic-based teams. Other tools for training are available at the I-TECH website.

- **Monitoring and evaluation**
  Monitoring and evaluation can provide valuable data on program functioning and contribute to global knowledge about effective implementation of TB and HIV programming. The WHO document, *A Guide to Monitoring and Evaluation for Collaborative TB/HIV Activities*, provides guidance on indicators, including an indicator for IPT treatment. The target audience for this guide is anyone from national-level policy makers to HIV or TB program managers. The I-TECH website provides further information on developing indicators for IPT programs.

As outlined above, IPT has proven effective in low-resource settings, and the lessons learned from these programs provide guidance for the development of future programs.

RESOURCES

- WHO Guidelines for Intensified Tuberculosis Case-Finding and Isoniazid Preventive Therapy for People Living with HIV in Resource-Constrained Settings
  Go to: http://www.who.int/en/, click on Programmes and Projects, HIV/AIDS, Publications, under Publications by Type and Date, click on Tuberculosis and HIV

- International Training and Education Center for Health (I-TECH) website
  http://www.tbpreventiontoolkit.org/ipt

- WHO Guidelines for Implementing Collaborative TB and HIV Programme Activities
  Go to: http://www.who.int/en/, click on Programmes and Projects, HIV/AIDS, Publications, under Publications by Type and Date, click on Tuberculosis and HIV

- Promoting the Implementation of Collaborative TB/HIV Activities Through Public-Private Mix and Partnerships
  Go to: http://www.who.int/en/, click on Programmes and Projects, HIV/AIDS, Publications, under Publications by Type and Date, click on Tuberculosis and HIV

- Networking for Policy Change: TB/HIV Advocacy Training Manual
  Go to: www.stoptb.org and search for "Networking for Policy Change"

- Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE)
  http://www.tbhiv-create.org/resources/policy_advocacy

- Case-Based Curriculum on the 3 I's
  Go to: http://www.tbpreventiontoolkit.org, click on Implementing Isoniazid Preventive Therapy, Isoniazid Preventive Therapy Training Tools

- WHO Guidance: A Guide to Monitoring and Evaluation for Collaborative TB/HIV Activities
  Go to: http://www.who.int/en/, click on Programmes and Projects, Tuberculosis (TB), Publications, 2009

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