This case study explains how key stakeholders in Cambodia have effectively scaled up the provision of isoniazid preventive therapy to prevent tuberculosis among people living with HIV.

Isoniazid preventive therapy (IPT) is the provision of the drug isoniazid to people at high risk of developing active tuberculosis (TB). Research shows that IPT can reduce the overall risk of active TB among people living with HIV (PLHIV) by up to 62 percent. In 1998, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) began recommending IPT for all PLHIV as part of their global guidance for reducing the burden of TB among PLHIV. Although 84 countries have policies that support IPT, fewer than 1 percent of PLHIV are receiving IPT today. Very few countries outside of the United States and other developed countries have implemented national IPT programs. Cambodia is an exception.

This case study explains how key stakeholders in Cambodia have effectively scaled up the provision of IPT to prevent TB among PLHIV. The case study reviews the TB and HIV burden in Cambodia, the key institutions collaborating to promote national scale-up and the role of research and global guidance in this effort. It also describes the development of national policies and frameworks to support the launch and scale-up of IPT and outlines the key facilitators and challenges of national implementation. The case study is intended to serve as an example for other countries interested in scaling up IPT — whether they are in the planning stages, are conducting IPT research or are initiating national IPT programs.

Background on TB and HIV
When a person is exposed to the bacterium *Mycobacterium tuberculosis*, he or she may become infected with TB. This type of infection can be controlled and remain latent for years, but it can also progress to active TB, which produces symptoms and can be contagious. PLHIV are 20 to 37 times more likely to develop active TB than people who are not infected with HIV, making HIV infection the strongest risk factor for TB.
Coordinating TB and HIV Services

As early as the 1990s, national and international interest in coordinating TB and HIV services was growing, and overlap between the two epidemics in Cambodia prompted a collaboration between the country’s separate national programs for TB and HIV. Under the Cambodian Ministry of Health (MOH), the National Center for TB and Leprosy Control (CENAT) was overseeing all TB services in Cambodia and the National Center for HIV/AIDS, Dermatology and Sexually Transmitted Disease (NCHADS) was overseeing all HIV services.

In 1999, the TB and HIV programs — CENAT and NCHADS — established a subcommittee on TB/HIV to begin exploring the possibility of integrating TB and HIV services at a national level. The subcommittee developed a TB/HIV Country Framework to address how the two national programs should treat patients co-infected with TB and HIV, including diagnosis and referral. Both CENAT and NCHADS approved the framework in 2002. Around the same time, NCHADS separately developed a Continuum of Care for People Living with HIV/AIDS Operational Framework to define the comprehensive care that should be provided to PLHIV, including treatment for opportunistic infections such as TB.

In 2003, CENAT and NCHADS released a joint statement to define the roles and responsibilities of each national program and to introduce joint training activities. CENAT and NCHADS released a second joint statement in 2005 to reaffirm their collaboration and to announce that all new HIV patients in Cambodia should be screened for TB and all TB patients should be screened for HIV.

As the collaboration between CENAT and NCHADS grew stronger, the subcommittee on TB/HIV also identified several international partners that could supply technical assistance to improve provider capacity for screening PLHIV for TB and for providing IPT to those who screen negative for TB. These partners, many of which were represented on the subcommittee, included the Japan International Cooperation Agency, FHI 360, the Gorgas TB Initiative at the University of Alabama at Birmingham, WHO and the Global AIDS Program of the U.S. Centers for Disease Control and Prevention (CDC).

Demonstrating the Feasibility of IPT

A research study known by many as the Gorgas study helped reinforce Cambodia’s general commitment to implementing IPT for PLHIV. In 2003, FHI 360, the Gorgas TB Initiative and other partners began the four-year study, which demonstrated the effectiveness of IPT for preventing TB among PLHIV at two sites in Cambodia.

In brief, 2,420 HIV-positive individuals were screened for TB for the Gorgas study, and 202 were eligible for IPT (as they did not have active TB and did not have any contraindications to using isoniazid). Of these individuals, 153 were enrolled in the study. Each participant received a one-month supply of isoniazid and was asked to return to the study clinic monthly for nine months. After nine months of treatment, the participants were followed every six months for an additional three years.

Final results, which were available for 130 participants, showed high rates of adherence and effectiveness. Among the 130 participants, 113 (87 percent) completed a full course of IPT, and only one participant (1 percent) developed active TB. No complications of treatment were reported.

The thorough documentation and subsequent global dissemination of the study results informed both national IPT strategies and international IPT initiatives. The positive study results also encouraged the establishment of a cross-referral system between the TB and HIV programs in Cambodia, increased the capacity of health care providers to deliver TB and HIV services, increased community knowledge about the link between TB and HIV, and increased community participation in TB, HIV and AIDS care.

Regional Evidence and Global Guidance

A regional study conducted from 2006 to 2008 by the CDC in Cambodia, Thailand and Vietnam also contributed to the growing enthusiasm for implementing IPT in Cambodia. The results of the study suggested that health care providers could use a simple checklist to ask PLHIV about three symptoms — cough, night sweats and fever — to determine their likelihood of having active TB. PLHIV who reported an absence of all three symptoms had a very low probability of having an active infection and were thus eligible for IPT.

Simultaneously, in 2008, WHO released a new global policy called the Three Is for HIV/TB, which recommended intensified TB case finding, initiation of IPT and TB infection control to prevent active TB among PLHIV. The policy suggested that all PLHIV in areas of high TB prevalence...
Launch and Scale-Up of IPT

In 2010, the heads of NCHADS and CENAT issued the new SOPs and officially launched the Three I’s for HIV/TB policy in Cambodia. IPT implementation began in July 2010 at six pilot sites. These were the two Gorgas study sites and four additional pre-antiretroviral (ART)/ART sites. NCHADS was in charge of implementing IPT for eligible patients at the sites. CENAT was responsible for providing isoniazid and vitamin B1, as well as TSTs where needed. All six of the pilot sites originally used TSTs to screen PLHIV for TB.

With the launch of the new policy, scale-up of IPT implementation began. By June 2012, IPT was being provided in 36 national pre-ART/ART sites. According to statistics from the sites, 3,589 (91 percent) of 3,946 new pre-ART patients were screened for TB in 2011. A total of 768 of these new patients, plus 1,305 continuing patients at the sites, initiated IPT that year. Plans are under way to expand the program to all 60 national pre-ART/ART sites in Cambodia.

Facilitators of Scale-Up

Despite global recommendations for implementing IPT, few countries have been successful in initiating national scale-up. Early political commitment and the development of supportive policies were important factors in making national scale-up in Cambodia possible. External funding, local and national collaboration among providers of TB and HIV services, and a willingness to simplify procedures were other important factors. Updates to the national policy have helped ensure that the policy continues to meet the needs of patients and the health care workers providing IPT services.

POLITICAL COMMITMENT

Political commitment to implementing IPT was perhaps the most important factor leading to national scale-up in Cambodia. Encouraged by global evidence, regional evidence and local experience with IPT provision, CENAT and NCHADS were both in favor of implementing IPT at the national level. Their establishment of a subcommittee on TB/HIV and the development of the TB/HIV Country Framework helped prove their commitment to this issue and to strengthen their collaboration.

The development of the Continuum of Care for People Living with HIV/AIDS Operational Framework further showed the commitment of NCHADS for reducing TB among PLHIV. Because IPT is primarily an intervention for PLHIV, WHO places great importance on national HIV programs spearheading IPT efforts. As a result, NCHADS came forward as the leader for national implementation of IPT after the two WHO meetings in Geneva in 2009 and 2010. The director of NCHADS also emerged as a key champion for IPT in Cambodia.

Developing Standard Operating Procedures

In 2008, the Cambodian MOH appointed a technical working group to develop standard operating procedures (SOPs) for implementing the Three I’s for HIV/TB policy, including IPT based on WHO guidelines. The technical working group was made up of representatives of CENAT, NCHADS and their partner organizations. The SOPs would provide guidance on the necessary systems for implementation, including referrals and indicators for monitoring. The working group developed them specifically to help district-level managers and health care workers implement the policy in continuum of care settings.

Also in 2008, the national government standardized the implementation of TB and HIV activities by developing an integrated TB/HIV training curriculum, a manual for providers and monitoring tools. Both CENAT and NCHADS also participated in a regional workshop in Phnom Penh to discuss a revised framework on co-infection with TB and HIV for the Western Pacific Region.

Over the next two years, CENAT and NCHADS participated in two meetings hosted by WHO in Geneva to further discuss integrating TB and HIV services. The first meeting, in 2009, was a core group meeting of WHO’s TB/HIV technical working group. The second, in 2010, was a global policy meeting to review evidence about intensified TB case finding and about IPT. Following these meetings, CENAT and NCHADS finalized the Cambodia-specific Three I’s for HIV/TB SOPs to include use of the tuberculin skin test (TST) to screen PLHIV for TB. Where the TST was not available, use of the three-symptom checklist was recommended.

The Original Three I's for HIV/TB

Intensified TB Case Finding
All PLHIV and people at high risk of HIV should be screened for TB and promptly diagnosed and treated if needed.

Initiation of IPT
IPT is safe for PLHIV who do not have active TB. All PLHIV who live in areas with a high prevalence of TB and all PLHIV who have a latent TB infection or have been exposed to an infected person should begin IPT.

TB Infection Control
HIV programs and other health facilities should use infection control measures to prevent the spread of the bacterium that causes TB, especially in areas with a high HIV prevalence.

should be screened for TB and either diagnosed with TB or put on IPT. (A later version of the global policy, not published until 2011, incorporated lessons learned from the regional CDC study, including using the symptom checklist to screen for TB.)

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The existence of a national Three I’s for HIV/TB policy has clarified which procedures providers should perform on patients requiring both TB and HIV services. Also, national support for IPT has allowed providers from across the country to share challenges and successes and to work together to improve services.

**EXTERNAL FUNDING**

External funding was crucial to implementing IPT in Cambodia. Initially, FHI 360 and the Gorgas TB Initiative supported many of the costs associated with IPT provision during the Gorgas study, including those for ensuring sustainability after the study was over. A combination of funders — including FHI 360, CDC and the Global Fund — provided support for launching the Three I’s for HIV/TB policy and for training workshops, technical assistance and monitoring visits during the pilot and scale-up phases. This external funding for one-time costs enabled ongoing costs, such as drugs and other supplies, to be covered by CENAT and NCHADS.

**COLLABORATION AMONG PROVIDERS**

Collaboration at the provider level has been key to the continued functioning of Cambodia’s IPT program. With guidance from the SOPs, joint training of TB and HIV providers was initiated during IPT implementation. Although initially difficult for providers, this joint training led to mutual respect, understanding and an increased willingness to collaborate. Higher-level providers, community volunteers, community health workers who specialize in TB and providers of home-based care were all trained on the co-treatment of TB and HIV. Regular meetings were also held at all levels to discuss cases and resolve challenges of implementing a national IPT program.

**SIMPLIFICATION OF PROCEDURES**

While Cambodia’s Three I’s for HIV/TB SOPs were being designed, those involved made an effort to streamline the protocol for providing IPT. Although complex algorithms that included both the TST and the three-question checklist could be used to screen PLHIV for TB, the new policy in Cambodia recommended using the three-question checklist alone when the TST was not available. If a given site had the clinical and technical capacity to use the TST, the site was still advised to use the TST. Use of the checklist alone, however, has two advantages. Because patients don’t have to wait for TST results, they can start IPT immediately, which saves time for health care providers. Also, using the checklist alone reduces the amount of time patients need to stay on IPT. Those who test positive for TST must be on IPT for 36 months, but those who screen positive by the three-question checklist alone need be on IPT for only six months.

**UPDATES TO THE NATIONAL POLICY**

As international guidance on IPT evolves, the MOH in Cambodia is making an effort to keep the national Three I’s policy updated. In 2011, WHO updated its global guidance on intensified TB case finding and initiation of IPT. The new guidance recommends referral to IPT for all PLHIV and removes the requirement that the TST be used to guide IPT use. As a result, the requirement for use of the TST has also been removed from Cambodia’s policy. Also, the three-question checklist for screening PLHIV for TB has been changed to a four-question checklist, based on a WHO recommendation to add weight loss as another important symptom of TB.
symptom of disease. Finally, the Cambodian national policy has been changed from the Three I’s for HIV/TB to the Fives I’s for HIV/TB, with the addition of immediate ART and integration of HIV and TB services. These additional measures were added in response to the challenges of integrating services, including confusion about CD4 count requirements for beginning ART. As these policy changes are being implemented, the accompanying SOPs are being updated to reflect them.

**Challenges of Scale-Up**

CENAT and NCHADS have had laudable success in rolling out IPT for PLHIV at the national level, but the scale-up process has not been without challenges. Difficulties when screening by TST, provider resistance, variation in quality among sites, data management issues and inconsistent funding continue to require targeted responses from the national TB and HIV programs.

**Difficulties When Screening by TST**

A variety of providers, including providers of home-based care and community health workers who specialize in TB, were among those trained on co-treatment of TB and HIV. However, providers had difficulties implementing IPT when patients were screened by TST rather than by the symptom checklist. Because a TST requires a 72-hour waiting period before it can be read, many patients screened by TST never return for test results or to begin taking isoniazid. Three of the six pilot sites that opened in 2010 had to be closed because of these difficulties. After those closures, none of the new implementation sites required screening by TST.

**Provider Resistance**

Just after the launch event for the Three I’s for HIV/TB policy, many health care providers were not convinced that IPT was an accepted practice because of national concerns about drug-resistant TB and local concerns about the adverse effects of isoniazid. In response, CENAT and NCHADS held meetings with implementing institutions, including directors of provincial health departments and provincial AIDS coordinators, to discuss the Three I’s. Although this made some difference, provider resistance remains an issue at some sites.

**Variation in Quality**

Another challenge to scale-up is variation in quality of care among the sites implementing IPT. For example, the quality of TB screening varies greatly from site to site. Such variation might be due in part to differences in program support. The sites that receive additional technical assistance and monitoring visits from nongovernmental organizations tend to have better diagnostic accuracy and treatment follow-up than other sites.

**Data Management**

Cambodia has a national database for tracking HIV activities that integrates information about TB, including IPT. The database, however, contains data only on output (the number of patients who begin IPT), making it difficult to monitor the outcomes and impact of IPT implementation. In addition, CENAT and NCHADS have different mechanisms for collecting data and different reporting requirements for the sites they oversee. Individual patient records capture the details required by both programs, but these data are held at individual sites and are not recorded in national registers or databases. This issue is currently being discussed at the national level.

**Inconsistent Funding**

External funding allowed some flexibility and facilitated the launch of the Three I’s for HIV/TB policy. A dependence on this type of funding, however, makes continuing national scale-up difficult. Scale-up was also challenged by the rejection of the TB component of Global Fund Round 10 funding for Cambodia. More recently, activities such as meetings and home-based care visits have been affected by the cancellation of Global Fund Round 11 funding. Lack of funding for training, supervision and activities aimed at launching new sites and improving service delivery has slowed the scale-up process. In addition, the Cambodian MOH had been offering financial incentives to providers who deliver priority programs such as HIV or TB programs. Because this money is no longer available, quality of care, including that for IPT, may be reduced in some settings.

**Conclusion**

In a relatively short time, Cambodia has gone from no mention of IPT in its national policies to a clear plan for implementing IPT nationwide. Through strong global support and the combined efforts and commitment of CENAT and NCHADS, substantial progress has been made toward universal provision.

Collaboration and technical assistance from international partners has been crucial in building a more robust Three I’s for HIV/TB program. These partnerships have filled gaps in funding and helped build the capacity of health care providers to screen patients for TB and provide IPT according to the new national policy. The program has not been without challenges, such as difficulties implementing IPT when the TST is used for screening. However, the flexibility of CENAT and NCHADS in understanding and addressing these challenges has enabled the program’s continued growth.
About FHI 360: FHI 360 is a nonprofit human development organization dedicated to improving lives in lasting ways by advancing integrated, locally driven solutions. Our staff includes experts in health, education, nutrition, environment, economic development, civil society, gender, youth, research and technology — creating a unique mix of capabilities to address today’s interrelated development challenges. FHI 360 serves more than 60 countries, all 50 U.S. states and all U.S. territories.

REFERENCES


9 Battambang Provincial Health Department (KH); Family Health International/Cambodia; Gorgas TB Initiative at UAB. TB screening and IPT initiation among HIV-infected persons, experience from Battambang Province [Internet]. Poster session presented at: National Aids Conference; 2008 Sep 10 [cited 2012 Sep 5]; Phnom Penh, Cambodia. Available from: http://www.nac3.hacccambodia.org/documents/nac/Battambang_IPT_NAC_10Sep08-LF.pdf


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