Policies, practices and barriers to implementing tuberculosis preventive treatment—35 countries, 2017

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BACKGROUND: Tuberculosis preventive treatment (TPT) reduces the development of tuberculosis (TB) disease and mortality in people living with human immunodeficiency virus (HIV) infection. Despite this known effectiveness, global uptake of TPT has been slow. We aimed to assess current status of TPT implementation in countries supported by the US President's Emergency Plan for AIDS Relief (PEPFAR). METHODS: We surveyed TB-HIV program staff at US Centers for Disease Control and Prevention (CDC) country offices in 42 PEPFAR-supported countries about current TPT policies, practices, and barriers to implementation. Surveys completed from July to December 2017 were analyzed.

RESULTS: Of 42 eligible PEPFAR-supported countries, staff from 35 (83%) CDC country offices completed the

IN 2014, TUBERCULOSIS (TB) surpassed human immunodeficiency virus (HIV) as the leading infectious cause of death worldwide and remains the top cause of death among people living with HIV (PLHIV).^{1,2} Isoniazid preventive therapy (IPT), the most common type of TB preventive treatment (TPT), was first shown to reduce TB disease in PLHIV in the 1990s before the widespread use of antiretroviral treatment (ART).³ Since then, studies have shown that IPT has an additive TB preventive effect compared to ART alone.4-7 Furthermore, IPT has recently been shown to reduce the risk of death in PLHIV by 37% at about 5 years of follow-up, independent of ART.8 Despite the evidence, global uptake of IPT has been slow. Only 36% of people newly enrolled in HIV care reported from 59 countries in 2017 were started on TPT.² Furthermore, the extent to which the estimated 36.9 million people with HIV9 worldwide have received TPT in previous years is unknown.

Since 1998, the World Health Organization (WHO) has repeatedly recommended programmatic use of IPT in PLHIV as a TB preventive measure,

survey. TPT was included in national guidelines in 33 (94%) countries, but only 21 (60%) reported nationwide programmatic TPT implementation. HIV programs led TPT implementation in 20/32 (63%) countries, but TB programs led drug procurement in 18/32 (56%) countries. Stock outs were frequent, as 21/ 28 (75%) countries reported at least one isoniazid stock out in the previous year.

CONCLUSION: Despite widespread inclusion of TPT in guidelines, programmatic TPT implementation lags. Successful scale-up of TPT requires uninterrupted drug supply chains facilitated by improved leadership and coordination between HIV and TB programs.

KEY WORDS: isoniazid preventive therapy; acquired immunodeficiency syndrome; surveys and questionnaires; policy; leadership

including in the most recent guidelines on latent TB infection (LTBI) released in 2018.10,11 Standard guidance prior to 2018, which remains consistent with current guidelines, is that *all* PLHIV—including children with HIV as well as pregnant and breastfeeding women with HIV-in whom active TB disease has been ruled out should receive at least 6 months of IPT or an equivalent TPT regimen.¹¹ Additional eligible populations include HIV-negative children aged ≤ 5 years who are household contacts of a person with TB.11 Neither PLHIV nor child household contacts aged ≤ 5 years require testing for LTBI prior to receiving TPT.¹¹ Populations can be screened using a clinical algorithm alone. Negative clinical screening has a high negative predictive value, indicating that the person is unlikely to have active TB and should be offered TPT instead.11,12

In 2018, the WHO expanded eligible populations to include *all* household contacts of a person with TB regardless of HIV status or age.¹¹ Another important update in 2018 was that newer, shorter TPT regimens were included for the first time for high TB incidence settings.¹¹

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In 2003, the US President's Emergency Plan for AIDS Relief (PEPFAR) was created to deliver lifesaving services in countries hardest hit by HIV/ AIDS (acquired immune-deficiency syndrome). While the primary focus of PEPFAR was to scale up ART in countries, IPT has been a component of PEPFAR's strategy since inception. However, in 2017, PEPFAR began prioritizing TPT as a critical component of comprehensive HIV care by introducing a new indicator that required countries to set targets for the number of PLHIV who complete TPT at PEPFARsupported sites.¹³

We aimed to obtain a baseline assessment of TPT policies, practices and barriers to programmatic TPT implementation from which to measure and respond to ongoing progress toward TPT scale-up in PEPFAR-supported countries. As this survey was conducted in 2017 before the 2018 WHO LTBI guidelines were released, these findings also serve as a baseline prior to guideline change.

METHODS

We developed a survey to collect data about current policies, practices, and barriers to successful TPT implementation. We reviewed the literature and consulted subject matter experts to develop questions. The survey was pilot-tested with Centers for Disease Control and Prevention (CDC) headquarters staff.

Countries were eligible for participation in the survey if they 1) received PEPFAR funding, and 2) received TB-HIV technical assistance from the US CDC in Atlanta, Georgia. Surveys were emailed to TB-HIV program staff at eligible CDC country offices for completion. These staff work closely with national HIV and TB programs in countries. Surveys were emailed in July 2017, and all surveys returned by 31 December 2017 were included in this analysis.

The survey was divided into two main sections: 1) policies and guidelines, and 2) current programmatic practices. Answer choices were in categorical, ordinal, or free-text formats. Categorical and ordinal data were summarized as frequencies and proportions. Free-text responses to the "Other" category were reviewed and either re-classified according to existing categories or reported as individual responses.

We asked countries about barriers to TPT implementation. Respondents could select barriers from a list of eight options and also provide additional barriers, if needed. We ordered barriers by frequency of countries that reported each barrier.

We organized countries included in this survey into WHO regions and described them by TB incidence and by proportion of TB cases with HIV using data from the 2018 WHO Global TB Report.² We reported survey results in aggregate, by three broad regional classifications, to maintain confidentiality of individual country responses. The three regions used to report survey results were as follows: 1) Africa (WHO African Region); 2) Asia (WHO South East Asia and Western Pacific Regions); and 3) Other regions (WHO Americas Region, European Region, and Eastern Mediterranean Region).

The protocol for the survey was reviewed by the Center for Global Health at the CDC, and was determined to be a public health program evaluation and not human subjects research.

RESULTS

Of 42 PEPFAR-supported countries eligible to participate in the survey, 35 (83%) responded (Figure 1). Table 1 shows characteristics of all 42 eligible countries by those that did and did not respond to the survey. Responding countries were mostly from the WHO African region (n = 22, 63%) with high burdens of TB and TB-HIV co-infection (Table 1). The median TB incidence in responding countries was 201 cases per 100 000 population (interquartile range [IQR] 144–326). The median proportion of reported TB cases with known HIV was 18% (IQR 7–40).

Inclusion and content of tuberculosis preventive treatment in guidelines

TPT had been included in either HIV or TB national guidelines in 33/35 (94%) countries that responded to the survey (Table 2). Two countries lacked formal guidance on TPT, one in Africa and one in Asia. Most countries reported including PLHIV (31/35, 89%) and child contacts of a person with TB (30/35, 86%) among populations eligible to receive TPT; however, sub-populations of PLHIV (e.g., children with HIV [23/35, 66%]), as well as pregnant (26/33, 79%) and breastfeeding (20/31, 65%) women with HIV were less often explicitly specified in guidelines as eligible to receive TPT.

Isoniazid (INH) daily for 6 months was the most common TPT regimen recommended in country guidelines (31/35, 89%). In general, guidelines in countries in the African region included a greater variety of TPT regimens than those in Asia; this included different regimens and different durations of IPT (Table 2). Three (9%) countries overall reported using the tuberculin skin test to determine eligibility for TPT.

Implementation of tuberculosis preventive treatment

Twenty-one (60%) countries reported nationwide programmatic implementation of TPT. Similar proportions of nationwide programmatic TPT implementation were reported in Africa (12/22, 55%) and Asia (4/7, 57%). Of the remaining 14 countries, 12 (86%) reported some degree of TPT implementation that was either limited to a geographic area, to child contacts of persons with TB, or to a pilot or research



Figure 1 PEPFAR-supported countries that completed the TB preventive treatment survey (black). PEPFAR = President's Emergency Plan for AIDS Relief; TB = tuberculosis.

project. Of all 35 countries, two (6%), both in Africa, reported no implementation of TPT at all.

In 32 countries that responded to a question related to which program —HIV or TB—leads TPT implementation, 20 (63%) reported that the HIV program leads TPT implementation for PLHIV in their country. Of these, 11 (55%) also reported that the TB program leads TPT drug procurement in their country (Figure 2). Among these 11 countries, eight (73%) reported at least one TPT stock out in the previous year.

Table 1 Characteristics of PEPFAR-supported countries thatresponded and those that did not respond to the TB preventivetreatment survey

	Responded (n = 35) n (%)	Did not respond (n = 7) n (%)	Total eligible countries (n = 42) n (%)
WHO Region African Region Americas Region Eastern Mediterranean Region European Region South-East Asia Region Western Pacific Region	22 (63) 4 (11) 0 1 (3) 3 (9) 5 (14)	3 (43) 2 (29) 0 1 (14) 1 (14) 0	25 (60) 6 (14) 0 2 (5) 4 (10) 5 (12)
TB incidence, /100 000* <100 100−200 ≥200	6 (17) 11 (31) 18 (51)	3 (43) 1 (14) 3 (43)	9 (21) 12 (29) 21 (50)
Proportion of reported TB cases w <10 10-30 ≥ 30	vith HIV, %* 10 (29) 13 (37) 12 (34)	1 (14) 6 (86) 0	11 (26) 19 (45) 12 (29)

* Data source: WHO 2018 Global tuberculosis report.²

PEPFAR = President's Emergency Plan for AIDS Relief; TB = tuberculosis; WHO = World Health Organization; HIV = human immunodeficiency virus.

Of the 28 countries that responded to a question about TPT stock outs, 21 (75%) reported having at least one TPT stock out in the previous year. These are most likely INH stock outs, since IPT is the primary TPT regimen included in all national guidelines (Table 2). Eleven (39%) countries reported having TPT stock outs 1–2 times a year, while 10 (36%) countries reported having \geq 3 stock outs in a year. Stock outs were reported more frequently in Africa than in Asia, with 14/18 (78%) countries in Africa reporting at least one TPT stock out in the previous year compared to 3/ 5 (60%) countries in Asia (Table 2).

Barriers to tuberculosis preventive treatment

Among eight answer options for barriers to TPT implementation, the most frequently reported barrier was "no funds to buy TPT medications," which was



Figure 2 Venn diagram showing differences in program leadership for TPT implementation and drug procurement. Eleven countries differ in the program that leads TPT implementation and drug procurement. HIV = human immunodeficiency virus; TPT = TB preventive treatment; TB = tuberculosis.

Table 2 Country responses to TPT survey, by region (n = 35)

	All countries $(n = 35)$	Africa [†] ($n = 22$)	Asia [‡] ($n = 7$)	Other countries [§] (n = 6)
Survey question (summarized)	n (%)	n (%)	n (%)	n (%)
TPT included in any national guidelines	33 (94)	21 (95)	6 (86)	6 (100)
Populations eligible to receive TPT in current guidelines PLHIV in whom TB disease has been excluded Children with HIV aged ≥12 months Child contacts (<5 years) of a person with TB Pregnant women Breastfeeding women	31 (89) 23 (66) 30 (86) 26/33* (79) 20/31* (65)	19 (86) 14 (64) 20 (91) 17/21* (81) 13/20* (65)	7 (100) 4 (57) 5 (71) 5 (71) 4 (57)	5 (83) 5 (83) 5 (83) 4/5* (80) 3/4* (75)
Regimens currently recommended for TPT in guidelines INH, daily for 6 months INH, daily for 9 months INH, daily for 12 months INH, daily for 36 months INH, continuous INH and RPT, weekly for 12 weeks INH and RMP, daily for 3 months RMP, daily for 4 months Tuberculin skin test is used to determine TPT eligibility	31 (89) 6 (17) 1 (3) 2 (6) 1 (3) 0 1 (3) 3/34* (9)	20 (91) 3 (14) 1 (5) 1 (5) 1 (5) 1 (5) 0 0 2/21* (10)	6 (86) 3 (43) 1 (14) 0 0 0 0 0 0 1 (14)	6 (100) 1 (17) 0 1 (17) 0 0 0 1 (17) 0
Extent of programmatic implementation of TPT TPT implemented nationally TPT implemented in a limited geographic area or implementation limited to child contacts TPT implemented as a pilot or research project TPT has not been implemented	21 (60) 6 (17) 6 (17) 2 (6)	12 (55) 5 (23) 3 (14) 2 (9)	4 (57) 0 3 (43) 0	5 (83) 1 (17) 0 0
National program that leads TPT implementation HIV program TB program Both Neither	15/32*# (47) 7/32* (22) 9/32*# (28) 1/32* (3)	9/19* (47) 6/19* (32) 3/19* (16) 1/19* (5)	4 (57) 1 (14) 2 (29) 0	2 (33) 0 4 (67) 0
National program that leads TPT drug procurement HIV program TB program Both Neither	4/32* (13) 18/32* (56) 5/32* (16) 5/32* (16)	3/19* (16) 11/19* (58) 2/19* (11) 3/19* (16)	1 (14) 5 (71) 0 1 (14)	0 2 (33) 3 (50) 1 (17)
Frequency of TPT stock outs Never Rarely (1–2 times a year) Sometimes (3–4 times a year) Often (≥5 times a year) Currently performing adverse event monitoring	7/28* (25) 11/28* (39) 7/28* (25) 3/28* (11) 18/33* (55)	4/18* (22) 5/18* (28) 7/18* (39) 2/18* (11) 12/20* (60)	2/5* (40) 2/5* (40) 0 1/5* (20) 3/7* (43)	1/5* (20) 4/5* (80) 0 3/6* (50)

* Denominators represent number of countries that responded to the question.

[†] Responses from countries in the WHO African Region (n = 22). [‡] Responses from countries in the WHO South-East Asia and Western Pacific Regions (n = 7).

 $^{\$}$ Responses from countries in WHO Americas Region, Eastern Mediterranean Region, and Europe Regions (n=6).

Five countries in the "Both" category reported that the HIV program leads TPT implementation for PLHIV, whereas the TB program leads TPT implementation for children. After reclassification of these responses, 20/32 (63%) countries reported that the HIV program leads TPT implementation for PLHIV

TPT = tuberculosis preventive treatment; PLHIV = people living with HIV; TB = tuberculosis; HIV = human immunodeficiency virus; INH = isoniazid; RPT = rifapentine; RMP = rifampin

reported by 16 (46%) countries (Table 3). Additional frequently reported barriers included "concern for IPTrelated toxicities" (n = 15, 43%), "no dedicated staff to lead TPT implementation" (n = 14, 40%), "HIV program thinks TPT is a TB issue" (n = 14, 40%), and "TB program thinks TPT is an HIV issue (n = 13,37%). Among responses to the "Other barrier" option, the most frequently reported barrier was "TPT stock outs or supply chain issues" (n = 10, 29%).

DISCUSSION

TPT, specifically IPT, has been widely included in national guidelines among the 35 PEPFAR-supported countries surveyed. Common reported barriers to

implementation were interrupted TPT supply chains, inadequate funding and staffing, and coordination between HIV and TB programs. These barriers likely contribute to the underutilization of TPT among persons in high-risk groups recommended to receive TPT.^{2,11}

Providing clear and consistent guidance at the national level on the appropriate use of TPT is the first step towards programmatic implementation of TPT. Our survey results showed that most countries have successfully included at least a section on TPT in HIV and/or TB national guidelines; however, opportunities to strengthen the content of these guidelines exist. For example, several countries did not specifically mention that children with HIV, as well as

Table 3	Barriers to	TPT imp	lementation	in 35	PEPFAR
supported	countries,	2017			

Barrier	Countries that reported barriers* (n = 35) n (%)
No funds to buy TPT medications Concern for IPT-related toxicities	16 (46) 15 (43)
No dedicated staff to lead TPT implementation	14 (40)
TB program staff thinks TPT is a HIV issue	13 (37)
Lack of political will	12 (34)
Concern for lack of evidence of efficacy of TPT	10 (29)
Absent, outdated or complex TPT guidelines Other	9 (26)
TPT stock outs or supply chain issues Fear of creating isoniazid monoresistance	10 (29)
or inadequately ruling out active TB	5 (14)

* We asked countries about barriers to TPT implementation. Respondents could select barriers from a list of eight items and also provide additional barriers, if needed. Barriers were ordered according to the frequency with which they were reported.

TPT = TB preventive treatment; PEPFAR = President's Emergency Plan for AIDS Relief; IPT = isoniazid preventive therapy; HIV = human immunodeficiency virus; TB = tuberculosis.

pregnant or breastfeeding women with HIV, are eligible for TPT. Explicitly stating these populations as eligible for TPT and providing population-specific guidance is important to promote clinician awareness and ensure appropriate use of TPT in these vulnerable populations.¹¹

The lag between including TPT in guidelines and actually implementing TPT nationwide may be explained in the context of key barriers reported in this survey. Most countries reported that HIV programs lead TPT implementation, whereas TB programs were more frequently reported to lead TPT drug procurement. This split in responsibilities could lead to misaligned forecasting and supply chain management for TPT drugs. An alarming proportion (75%) of countries reported having at least one IPT stock out in the previous year. As an anti-TB drug, INH is often under the control of national TB programs, which have historically been tasked with conducting procurement and supply chain management of IPT for PLHIV.14 However, as IPT and TPT regimens increasingly become part of routine HIV care, aligning TPT procurement and delivery mechanisms with those of ART may limit interruptions in TPT stocks. Although our survey did not investigate causes of stock outs, given the history of disruptions in the manufacture and supply of INH active pharmaceutical ingredient (API), similar above-country issues may have also contributed to these stock outs.15,16 Such above-country challenges with INH API would not be addressed by only aligning TPT with ART systems for forecasting and logistics.

Several countries also reported lack of funding and staff to lead TPT implementation. The initial phase of TPT implementation requires a period in which healthcare workers are trained in country-specific guidelines, monitoring and evaluation practices, and medication management.¹⁷ However, as TPT becomes integrated into routine HIV care, existing ART providers will likely be able to adopt TPT as part of daily practice without the need for additional staff, similar to the adoption of cotrimoxazole into routine HIV care.

Our survey is subject to limitations. First, responses were based on self-report without objective validation. Second, respondents to our survey were TB-HIV staff at CDC country offices who may not have had complete and updated information regarding TPT implementation in host countries. Responses represent views of technical agency staff, which are likely different from views of other important stakeholders such as healthcare workers, patients, and staff at HIV and TB programs. Furthermore, respondents' views may be shaped by the funding and political climate in which they operate. Third, there may have been ambiguity in the interpretation of terms used, such as "nationwide implementation". However, we used terms that are routinely used in PEPFAR contexts to allow for consistent interpretations as much as possible. Fourth, reporting of TPT stock outs in the question that asked about barriers to TPT implementation is likely an underestimate because TPT stock outs were not a pre-specified answer option to this question. Despite this omission, the issue of TPT stock outs emerged as a clear barrier in responses to a separate question that asked specifically about frequency of TPT stock outs. Finally, responses to questions earlier in the survey could have influenced responses to questions later in the survey.

Several of the barriers reported in this survey have been previously reported, including shortages of INH, limited funding and staff to lead TPT implementation, and inadequate coordination between HIV and TB programs.¹⁸ The persistence of these barriers suggests a need to change the ways in which the global community conceptualizes and addresses TPT for PLHIV. As a routine component of HIV care, funding and implementation of TPT for PLHIV should be administered through HIV programs. Donors and implementers could exercise more flexibility and coordination to facilitate TPT implementation for PLHIV through HIV programs. Recent experience has shown that when governments, partners, and other stakeholders commit to TPT as a priority, impressive action follows. After the Ministry of Health in Kenya committed to supporting IPT in 2015 and set bold targets, IPT uptake among PLHIV in Kenya increased almost 50-fold from 9981 at the end of 2014 to 493 436 in December 2016.19

As TPT becomes increasingly recognized as a critical, underutilized tool to reduce morbidity and mortality and provide optimal care for PLHIV, expansion of TPT is expected. At the first high-level meeting of the United Nations General Assembly on the fight against TB held on 26 September 2018,

national representatives committed to placing six million PLHIV on TPT by 2022.²⁰ PEPFAR is helping countries that receive its support to achieve-and surpass-this goal by integrating TPT implementation into existing platforms for HIV program planning and monitoring. Parlaying TPT into existing PEPFAR infrastructure allows for synergistic, instead of parallel systems, to assist with barriers related to funding, staffing, and logistics. For example, reliable systems used for ART delivery can be leveraged to assist with challenges related to TPT stock outs. Furthermore, PEPFAR's market share can be used to negotiate lower drug prices for the newer, shortcourse TPT regimens, which hold promise for increasing TPT uptake and completion. Lastly, PEPFAR's data systems can be used for routine monitoring of programmatic data to help countries make timely adjustments to their programs to achieve targets. Examples of such programmatic data include the care cascade from TB screening to either completion of TPT or to TB diagnosis and treatment initiation using indicators recommended by a board of scientific advisors.

Ensuring that every eligible PLHIV, newly or currently enrolled in care, receives and completes an appropriate course of TPT could be a realistic, not aspirational, goal.

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__ R É S U M É

CONTEXTE : Le traitement préventif de la tuberculose (TPT) réduit le développement de la tuberculose (TB) maladie et sa mortalité chez les personnes vivant avec le virus de l'immunodéficience humaine (VIH). En dépit de son efficacité connue, la couverture mondiale du TPT a été lente. Nous avons voulu évaluer le statut actuel de la mise en œuvre du TPT dans les pays soutenus par le President's Emergency Plan for AIDS Relief (PEPFAR) des États Unis.

MÉTHODE : Nous avons fait une enquête auprès du personnel du programme TB-VIH dans les bureaux nationaux du CDC (Centers for Disease Control and Prevention des Etats Unis) dans 42 pays soutenus par le PEPFAR à propos des politiques et pratiques actuelles en matière de TPT et d'entraves à sa mise en œuvre. Les enquêtes achevées entre juillet et décembre 2017 ont été analysées.

RÉSULTATS : Sur 42 pays éligibles soutenus par le

MARCO DE REFERENCIA: El tratamiento preventivo de la tuberculosis (TPT) disminuye la aparición de enfermedad tuberculosa y la mortalidad por esta causa en las personas con infección por el virus de la inmunodeficiencia humana (VIH). Pese a su efectividad comprobada, la aceptación mundial del TPT ha sido baja. En el presente estudio se evaluó la situación actual de la ejecución del TPT en los países que reciben apoyo del Plan de Emergencia del Presidente (de los Estados Unidos) para el Alivio del Sida (PEPFAR).

MÉTODO: Se llevó a cabo una encuesta a funcionarios del programa de tuberculosis (TB) y VIH en las oficinas del país de los Centros para el Control y la Prevención de Enfermedades (CDC) en 42 países que reciben ayuda del PEPFAR, sobre las políticas vigentes, las prácticas y los obstáculos a la ejecución del TPT. Se analizaron las encuestas completadas de julio a diciembre del 2017.

RESULTADOS: De los 42 países idóneos que recibían

PEPFAR, le personnel de 35 (83%) bureaux nationaux du CDC ont achevé l'enquête. Le TPT a été inclus dans les directives nationales dans 33 (94%) pays, mais seulement 21 (60%) ont fait état d'une mise en œuvre nationale du programme de TPT. Les programmes VIH ont mené une mise en œuvre du TPT dans 20/32 (63%) pays, mais les programmes TB ont dirigé l'approvisionnement en médicaments dans 18/32 (56%) pays. Les ruptures de stock ont été fréquentes puisque 21/28 (75%) pays ont rapporté au moins une rupture d'isoniazide au cours de l'année précédente. CONCLUSION : En dépit d'une large inclusion du TPT dans les directives, la mise en œuvre programmatique du TPT traîne. La réussite de l'expansion du TPT requiert un approvisionnement ininterrompu de médicaments facilité par une amélioration du leadership et de la

coordination entre les programmes VIH et TB.

RESUMEN

apoyo del PEPFAR, los funcionarios de 35 oficinas de país de los CDC (83%) completaron la encuesta. El TPT estaba incluido en las directrices nacionales en 33 países (94%), pero solo 21 (60%) referían una ejecución del TPT a escala nacional. Los programas del VIH dirigían la ejecución del TPT en 20/32 países (63%), pero los programas de TB tenían a su cargo la adquisición de los medicamentos en 18/32 países (56%). Los desabastecimientos eran frecuentes, pues 21/28 países (75%) informaron al menos un desabastecimiento de isoniazida durante el año anterior.

CONCLUSIÓN: Pese a la inclusión del TPT en las directrices nacionales, existe un retraso en su ejecución programática. La ampliación de escala del TPT exige una cadena de abastecimiento de medicamentos ininterrumpida, facilitada por una dirección reforzada y mejor coordinación entre los programas contra la infección por el VIH y la TB.