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TB Preventive Therapy for People Living with HIV – Key Considerations for Scale-Up in Resource-Limited Settings

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SUMMARY

Tuberculosis (TB) is the leading cause of death for persons living with HIV (PLHIV). TB preventive therapy (TPT) works synergistically with, and independently of, antiretroviral therapy (ART) to reduce TB morbidity, mortality and incidence among PLHIV. However, although TPT is a crucial and cost-effective component of HIV care for adults and children, and has been strongly recommended as an international standard of care for over a decade, it has remained highly underutilized. If we are to end the global TB epidemic, we must address the significant reservoir of TB infection, especially in those, such as PLHIV, with highest risk of progression to TB disease. In order to do so, we must confront the pervasive perception that barriers to TPT scale-up are insurmountable in resource-limited settings.

In this article, we review available evidence to address several commonly stated obstacles to TPT scale-up. These include the need for tuberculin skin testing, limited diagnostic capacity to reliably exclude TB disease, concerns about creating drug resistance, suboptimal patient adherence to therapy, inability to prevent and monitor for adverse events, a “one size fits all” option for TPT regimen and duration, and uncertainty about TPT use in children, adolescents, and pregnant women. We also discuss TPT delivery in the era of differentiated care for PLHIV, how to best tackle advanced planning for drug procurement and supply chain management, and how to create an enabling environment for TPT scale-up success.

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TB prevention; isoniazid preventive therapy; TB/HIV

BACKGROUND

Tuberculosis (TB) is the leading cause of death for all people from a single infectious organism, and the leading cause overall in persons living with HIV (PLHIV).[1] Regular screening for TB disease among PLHIV is a standard of care and a critical component of HIV care and treatment because it can be effectively treated, especially when diagnosed early. TB case detection remains low worldwide, with the number of reported new cases only 61% of the estimated TB incidence in 2016.[1] Finding and treating people with TB disease, and thus interrupting further transmission, remains a top global health priority. However, treating patients with TB disease is a downstream intervention. It has been estimated that nearly a quarter of the global population is infected with TB, the vast majority of whom do not have active disease.[2] Without detecting and treating TB infection and halting its progression to disease, the TB epidemic will not end. An emphasis on TB prevention not only spares individuals the burden of TB-associated morbidity and mortality, but it also reduces the economic impact of the disease on the health system as a whole.

Antiretroviral therapy (ART) is a critical TB prevention intervention for PLHIV, and alone can reduce the likelihood of developing TB disease by up to 65%. However, PLHIV remain at substantially increased risk for TB even when on ART and with high CD4 cell counts.[3–4] TB preventive therapy (TPT) is an instrumental component of HIV care because it has a synergistic effect with ART and also independently lowers the risk of TB disease among PLHIV.[5–6] Multiple studies have demonstrated unequivocally that TPT reduces TB incidence among PLHIV and that it is cost-effective.[5–13] Recently, researchers from the prospective, randomized TEMPRANO study published follow-up data demonstrating that six months of isoniazid (INH) — a frequently used TPT regimen — reduced mortality by 39% at 78 months after enrollment, independent of ART.[14] Taken together, ART and TPT can have a substantial and sustained epidemiological impact by reducing the risk of TB disease among, and therefore transmission from, PLHIV.

Although INH preventive therapy (IPT) specifically has been a priority World Health Organization (WHO) recommendation for PLHIV for over a decade, uptake has been slow. As of 2016, only 940,269 newly enrolled PLHIV (42%) had started any form of TPT in 23 high TB or TB/HIV burden countries reporting to WHO.[1,15] If we are to end the global TB epidemic, we must address the significant reservoir of TB infection, especially in those most likely to progress to TB disease (such as PLHIV). In order to do so, we must confront the pervasive perception that barriers to TPT scale-up are insurmountable in resource-limited settings.

COMMONLY STATED OBSTACLES TO TPT SCALE-UP

The Need for Tuberculin Skin Testing (TST) to Confirm Latent TB Infection (LTBI)

A positive TST or interferon-gamma release assay (IGRA) indicative of LTBI has been shown to identify PLHIV most likely to benefit from IPT.[7,16] However, requiring LTBI testing in resource-limited settings can be a prohibitive barrier due to financial costs, the need for trained technicians (for appropriate administration and interpretation), a reliable tuberculin supply chain, and repeat patient visits within a narrow time frame for results reading. In addition, its value is limited by poor specificity and sensitivity among PLHIV.[17] Authors of a 2010 Cochrane meta-analysis reported that IPT lowers the risk of TB disease in PLHIV with a positive TST as well as for all PLHIV (regardless of TST status), and a subsequent study from South Africa also demonstrated benefit for adults with a negative TST.[7,10] Additionally, a modelling study comparing a “TST-positive only” to a “treat all” approach demonstrated that the latter prevented substantially more TB cases among PLHIV with a minimum decrease in cost-effectiveness.[13] These observations support WHO’s recent strong recommendation that LTBI testing should not be a requirement for use of TPT scale-up in PLHIV.[16]

Inability to Reliably Rule Out TB Disease and Selective Pressure for TB Drug Resistance

A common concern among clinicians is limited capacity to reliably exclude TB disease. Indeed, researchers from multiple studies, including TB prevalence surveys in Asia and Kenya, have found a substantial proportion of TB cases with a negative symptom screen.[17–22] However, these surveys were not designed to investigate the sensitivity of clinical screening. Other research has shown that clinical screening performs well for ruling out TB disease among PLHIV in most settings: the four-symptom TB screen recommended by WHO has a negative predictive value (NPV) of 97.7% among adult and adolescent PLHIV at a 5% TB prevalence, and 90% NPV at a 20% prevalence.[17,23] This NPV increases to 94% when combined with chest radiography. However, given the cost, workload, infrastructure, and staffing requirements of using chest radiography, not to mention potential lapses in machine functionality in resource-limited settings, WHO’s current TB screening recommendations do not require its use (though they suggest incorporation in screening algorithms where feasible to implement).[16] This is supported by a modeling study that compared symptom screening alone to symptom screening with chest radiography prior to IPT. The authors concluded that although use of chest radiography might reduce new cases of potential INH resistance, it paradoxically could result in increased numbers of TB cases and deaths due to patient attrition during the radiography process, with fewer people ultimately benefiting from TPT.[24] Clearly, the costs and benefits of chest radiography for initial TB screening must be weighed in terms of a country’s TB burden and resources. If chest radiography is not available, screening may be optimized in other ways. In the South African XPHACTOR study, adult clinic attendees were screened using the WHO-recommended four-symptom screen and then Xpert MTB/RIF if they were designated “high risk for TB” according to a new algorithm (any of the following: cough, BMI<18.5, CD4<100, weight loss ≥10%). In this setting, the NPV was greater than 98% for both ART-naïve and experienced patients.[25]

Healthcare workers' concern about creating selective pressure for emergent drug-resistant TB by providing TPT to PLHIV with undiagnosed TB disease can be a barrier to TPT scale-up. While researchers from multiple studies have demonstrated the practicality of IPT, none have shown a statistically significant increase in INH resistance, leading to WHO's strong recommendation that this concern should not be a barrier to IPT provision.[26–31] However, many of these studies used laboratory or radiologic tests to rule out TB disease before starting IPT, so it is yet unknown whether widespread programmatic scale-up of TPT using only clinical symptom screening will result in increased TB drug resistance. This is of particular concern for rifamycins; however, no published data have assessed the impact of the new, shorter-duration rifamycin-containing TPT regimens (already being implemented in some settings) on emerging drug resistance. Theoretically, asymptomatic disease may be associated with low bacterial burden that can be eradicated by one or two agents and, based on modeling data, the very clear benefits of TPT will likely outweigh a potential risk of drug resistance, especially in countries with a decreasing TB incidence overall (as has been demonstrated where ART coverage has expanded among PLHIV).[19,32–36] Nevertheless, programs should be prepared to conduct active surveillance for resistance to drugs included in their TPT regimens, and also to perform drug susceptibility testing for patients who develop TB disease after receiving TPT.

Patient Adherence and Treatment Completion

Adhering to preventive medical regimens can be difficult, especially when patients feel well and regimens require months to complete. Reported adherence rates to TPT are highly variable in adults, pregnant women, and children living with HIV, and range from under 37% to greater than 95%.[37–39] The consequences of diminished adherence to preventive therapy are not the same as for treatment of disease: poor adherence to preventive therapy essentially means that the person is not protected against the possibility of future disease and is not in itself harmful. Nevertheless, program personnel and clinicians should make every effort to promote adherence to maximize its efficacy. There is evidence that TPT adherence and satisfaction can be improved with integration of TB and HIV services, and with INH co-formulated with cotrimoxazole and vitamin B6.[40–46] This fixed dose combination pill has now received WHO pre-qualification and inclusion on the Essential Medicines List, and several countries have begun registration in advance of procurement.[47] In one Botswanan study where men and younger patients had low IPT adherence, patients cited work commitments as the reason; targeted health outreach to these patient groups and expansion of locations or hours for accessing TPT (and ART) could improve completion rates.[48] In Swaziland, patients demonstrated very high adherence when they self-selected their IPT service delivery model, and when their healthcare workers were trained in motivational interviewing techniques.[49] In South Africa, a similar study reported that patients welcomed positive provider messaging on IPT, counselling, and short message service (SMS) messaging for treatment support.[45] Lastly, patients who are given in-depth counselling including explanation of IPT and it's possible side effects are also more likely to adhere to therapy.[50] Additional operational research on methods to improve adherence will help identify impactful, culturally sensitive interventions, and should be encouraged. Anecdotally, providers have reported better treatment adherence when IPT is described as treatment for

latent infection (rather than prevention of disease), and the effect of this subtle but important distinction merits further investigation.

Inability to Prevent and Monitor for Adverse Events

Clinicians and program personnel frequently express concern about the potential toxicity of TPT medications, especially for patients who are also receiving ART. Neuropathy is associated with INH, but is also seen with certain antiretrovirals (ARVs) and HIV infection itself, making it difficult sometimes to determine the causative agent. It is more frequent in PLHIV who are undernourished, and can be prevented with concurrent prescription of pyridoxine (vitamin B6).[51] However, the adverse event that may be of greatest concern to clinicians is INH-associated hepatotoxicity. In the vast majority of cases, elevation in liver enzymes as a result of INH therapy is mild (less than 3 times the upper limit of normal), has no clinical consequence, and resolves spontaneously or with the cessation of therapy. The reported prevalence of hepatotoxicity in people given IPT has varied. In the TEMPRANO study of PLHIV, INH was not associated with any increase in Grade 3 or 4 adverse events.[6] In a meta-analysis of data from seven studies (not restricted to PLHIV), a median of 1.8% of persons given IPT developed an elevation in liver enzymes (variably defined as greater than three to five times the upper limit of normal),[52] although in other studies rates of hepatotoxicity have been higher.[53–54] In 1982, authors from the largest trial of IPT published to date reported 95 cases of hepatitis in 20,840 persons receiving INH in European countries (0.5%); however, the definition of hepatitis and the method and frequency of screening were not described. Of those 95 cases, three were fatal (0.0001% of total enrollees), all three of whom had continued to take INH after elevations in liver enzymes were recognized.[55]

The risk of INH-induced hepatotoxicity can increase markedly with age, consumption of alcohol or other potentially hepatotoxic substances, concomitant nevirapine administration, active hepatitis, or severe immunosuppression.[56–57] Although the prevalence of alcohol use and chronic viral hepatitis is often unknown in many TB endemic areas,[58–60] the risk of INH-associated hepatotoxicity among PLHIV who drink alcohol or who have active hepatitis can be mitigated with careful screening and exclusion of potentially high-risk individuals, thorough patient and provider education, and appropriate monitoring (direct or remote review of symptoms) for adverse reactions. WHO recommends that patients be monitored routinely and counseled to contact health providers if they develop any symptom or adverse event. However, given limited data, the rarity of clinically relevant adverse events, and the poor predictive value of baseline liver enzyme testing for treatment-associated adverse events, such testing prior to TPT initiation should not be a barrier to overall TPT scale-up where not routinely feasible.[61] Programs should be prepared, however, to offer clinical management guidance and liver function testing in patients who report symptoms. Clinicians should discontinue TPT if the elevation is severe (above five times the upper limit of normal). As with all medications, any serious adverse events should be reported to national surveillance systems per country-specific protocols.

“One Size Fits All” Option for Regimen and Duration

Investigators from the landmark BOTUSA trial reported that 36 months of INH (as a proxy for life-long INH) was cost-effective and reduced TB incidence and deaths (the latter only if

TST-positive) compared to a standard six-month course.[29,62] Largely based on these results, WHO guidelines included the conditional recommendation that adults and adolescent PLHIV with unknown or positive TST status and unlikely to have TB disease should receive at least 36 months of IPT.[63] Authors of a subsequent 2016 systematic review reported that the risk of TB in high TB and HIV prevalence settings was 38% lower among participants receiving 36 months of IPT compared with six months, with no significantly increased risk for drug resistance.[64] Investigators from one of the included studies (from South Africa) noted more Grade 3 or 4 elevations in liver enzymes among patients receiving continuous IPT up to six years, with no increase in hospitalizations or death. However the review concluded that the overall benefits of IPT for at least 36 months probably outweighs the risk of increased adverse events in settings of high TB prevalence and transmission.[28,64] In addition, while a long-lasting protective effect of IPT was noted by researchers in the moderate TB incidence setting of Rio de Janeiro, the protective effect waned quickly in Botswana (after 36 months of treatment) and South Africa (after six), likely due to reinfection after successful IPT completion in areas with high TB endemicity.[9,28,65–67] Given this concern, there is increasing global interest in the utility of continuous or recurrent IPT in settings with high rates of TB transmission, and additional data on these regimens is currently needed.

Some drop-off in IPT efficacy after course completion may also be due to incomplete treatment of latent TB.[68] While INH is bactericidal against rapidly replicating organisms (such as in TB disease), it is only bacteriostatic against latent, non-replicating organisms characteristic of LTBI. As a result, some researchers advocate for use of rifamycin-based regimens for LTBI treatment instead.[68–69] WHO already recommends several options for TPT in low TB burden settings and their recent guidance also included an option for three months of rifapentine (RPT) with INH (3HP) for high burden settings. 3HP is a shorter regimen than six to nine months of INH, has reduced risk of hepatotoxicity, and has been shown to have higher treatment completion rate, thus making it a potentially useful TPT option for PLHIV in resource-limited settings in the near future.[28,70] In addition, results from a recently completed Phase three trial comparing nine months of INH to one month of INH and RPT (1HP) demonstrated non-inferiority of 1HP.[71] Based on recent evidence, we know that rifamycins can be used effectively with efavirenz 600 mg and other ARVs such as raltegravir. However, they may be problematic for PLHIV on protease inhibitors, efavirenz 400 mg, or – somewhat concerning given its likely widespread scale-up in the near future – dolutegravir (DTG).[28,72–75] In particular, rifamycins induce metabolism of DTG, so dose adjustment will be required. Additionally, RPT may have a specific interaction with INH: a small open-label study evaluating the pharmacokinetics of DTG with RPT-INH in four HIV-negative health volunteers was terminated early due to the development of flu-like symptoms and Grade 2–4 transaminase elevations in two subjects, who were found to have higher than expected INH exposure.[76] Additional pharmacokinetic investigations are ongoing and results are expected by the end of 2018.

Uncertainty about TPT Use for Infants, Children, Adolescents, and Pregnant Women

INH is safe for use and generally has lower toxicity in children than in adults. As children and adolescents living with HIV and LTBI are at particular risk for rapid progression to TB

disease,[77] WHO strongly recommends six months of INH for all children living with HIV (CLHIV) 12 months and older who live in a setting with a high prevalence of TB, and those less than 12 months with a known TB exposure, in whom TB disease has been excluded. Conditionally, they also recommend six months of additional INH for all CLHIV who have completed TB treatment, regardless of age.[16,78–80] In CLHIV aged 12 months or older with a negative TB screen (i.e., no evidence of poor weight gain, fever, current cough, or TB contact), IPT can and should be started immediately.[81,82]

TB/HIV is a major non-obstetric cause of maternal mortality in resource-limited settings and also increases the risk of infant mortality and mother-to-child transmission of HIV.[83,84] Given that the risk for progression from LTBI to TB disease appears to be higher during pregnancy and the postpartum period,[85] the 2018 WHO guidance on LTBI explicitly includes pregnant women living with HIV as an IPT-eligible population.[16] As of the last WHO policy review, eleven countries in sub-Saharan Africa had included pregnant women living with HIV in their guidelines for TPT in PLHIV. While the performance of the WHO-recommended four-symptom screen has been documented to have a low sensitivity (28-55%) in pregnant women, the NPV has been shown to be high for ruling out TB disease.[86–89] In addition, while there have been reports of hepatotoxicity in pregnant women receiving INH, in the one study that compared rates of INH-related hepatitis and associated mortality in pre- and post-partum women to rates in non-pregnant women there was no statistically significant difference.[90] In a nested study of pregnant women receiving INH in the BOTUSA trial, authors also did not find adverse pregnancy outcomes, nor an elevated risk of INH-associated hepatitis when used in pregnancy.[91] However, recent findings from a Phase four randomized trial in Africa, Asia and Haiti reported a statistically significant increase in a composite measure of adverse pregnancy outcomes (including preterm delivery, low birth weight, congenital anomaly or fetal demise) with IPT initiated during pregnancy compared with delay to 12 weeks postpartum; the impact of these new findings on global recommendations is yet to be determined.[92]

TPT Delivery in the Era of Differentiated Care for PLHIV

In the era of “Test and Start”, ART programs are increasingly moving towards offering differentiated models of service delivery in order to deliver patient-centered care more efficiently and effectively.[63] As part of these models, many programs are increasing the interval between clinic visits and ARV pickups for PLHIV on ART and deemed to be “stable”. TB screening along with prescribing and dispensing practices for TPT and cotrimoxazole could be modified to align with those for ARVs in these contexts where possible. As care for PLHIV stable on ART moves increasingly into communities, programs will need to train patients, community health workers, and/or ART club members to distribute TPT and monitor for side effects and/or TB symptoms.[93]

Planning, Drug Procurement, and Supply Chain Management

The vast majority of PLHIV, numbering in the millions, are candidates for TPT. If TPT scale-up is to occur rapidly, advanced planning for procurement and supply management will be essential to avoid drug stock outs. TB and HIV programs, including prevention-of-mother-to-child transmission programs, should forecast anticipated needs (including

pediatric dosage forms), and arrange to procure their chosen TPT regimens (+/− vitamin B6). If multi-month prescribing in alignment with ART delivery is to be used, adequate supplies should be available in advance. Indeed, programs should consider setting aside and labeling a full regimen of TPT for each patient at ART initiation. Mechanisms could also be instituted for sites to request TPT "pulls" if they ever anticipate running out of stocks. In many cases, TPT is best procured from the Global Drug Facility (GDF), an initiative of the Stop TB Partnership that already provides quality-assured TB drugs at low cost, and provides technical assistance in TB drug management and monitoring. Additionally, by creating a large and stable pooled market for TB drugs, the GDF incentivizes a secure global supply and, if provided with accurate national forecasts of TPT needs, should be able to manage increased demand in the context of global TPT scale up.[94] Since National TB Programs may already be procuring TPT for children with known TB exposure (and often have a history of working with the GDF), it may be easiest for them to continue to procure TPT and transfer stocks to HIV programs for disbursement to PLHIV. There are, obviously, alternative procurement paths, and each country will need to determine what is best and most reliable for them. Ultimately, the logistical aspects of TPT should foster close collaboration between national TB and HIV programs, which will help programs to improve WHO-recommended service integration.

The Need for an "Enabling Environment" for TPT Scale-up

We recommend that National TB and HIV programs engage in technical cooperation with international donors and partners to ensure that specific recommendations and/or strategies for TPT are in place before widespread scale-up. Once these recommendations are in place, advocacy and education efforts will be important to ensure successful scale-up of TPT. As part of the Brazilian THRio study, participants attending clinics where healthcare workers received specific training on IPT administration had a 31% reduction in TB or mortality compared with clinics where healthcare workers had not received this training.[95] In 2014, investigators from a pilot IPT program in Zimbabwe speculated that only half of patients received IPT due to several factors, including inadequate advocacy, community sensitization, formally trained staff, education and communication materials, and IPT stocks.[96] Planning for and addressing each of these components will be critical for successful TPT scale-up. In addition, coordinated efforts of the HIV and TB programs will not only result in better patient-centered care, but has also been shown (through the IeDEA Consortium of 26 low-income countries) to improve the implementation of TPT for PLHIV.[15,46] Lastly, in order to adequately monitor and evaluate TPT scale-up, programs may need to adapt current data collection registers to capture TPT duration, completion, outcomes, and monitoring for adverse events. In addition to routine data collection, regional implementation science or situational assessments may shed light on the types of TPT service delivery models and interventions that should be implemented at scale in a given setting.

CONCLUSION

TPT is a standard and crucial component of HIV care for adults and children but, although it has been strongly recommended as an international standard of care for over a decade, it has remained highly underutilized. While there are some legitimate areas of concern, notably the

hepatotoxic effects of INH and the possibility of engendering resistance, TPT has been demonstrated to be a cost-effective method to reduce morbidity, mortality, and TB incidence among PLHIV. Most national HIV programs do have a policy for TPT, but very few of them have developed the programming to turn it into a practical reality. Among other donor agencies, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) has recently emphasized the importance of TPT, and now requires implementing partners to report on its initiation and completion among PLHIV under HIV care and treatment.[97] The recognition that TPT provision for PLHIV is an integral part of quality HIV care is the first step required by national programs and their partners. However, serious commitments should continue to be made to address anticipated barriers and scale-up TPT in a meaningful way. It is inexcusable that TB remains the leading cause of death among PLHIV when we have an evidence-based method of prevention but have failed to implement it. Now is the time for HIV programs to assume greater leadership and, in coordination with TB programs, place the same emphasis on TPT scale-up that was placed on HIV testing for all people with TB and, more recently, Test and Start for all PLHIV.

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Table

Commonly Stated Obstacles to TPT Scale-Up and Evidence-Based Recommendations

Perceived Obstacle	Reality	Recommendations
Need for LTBI testing	• LTBI testing requires financial investment, trained technicians, reliable supply chain and repeat patient visits • IPT benefit demonstrated in absence of TST testing	• TPT scale up regardless of TST/IGRA availability
Inability to reliably rule out TB disease	• 4 symptom screen has reasonable sensitivity among PLHIV in most settings, and can be optimized further (e.g., XPHACTOR study) • Sensitivity increases with CXR, but this increases cost, workload and infrastructure and staffing requirements	• 4 symptom screen of all PLHIV at every encounter (consider XPHACTOR algorithm) • Weigh utility of CXR in terms of country's TB burden and resources
Creation of TB drug resistance	• No evidence of increased INH resistance with IPT, but unknown what will occur with programmatic scale up and use of new drugs	• Close patient follow up, and drug susceptibility testing in unlikely event of a patient developing TB disease while on a TPT regimen • Periodic national TB drug resistance surveillance
Patient adherence and treatment completion	• Reported adherence rates to TPT are highly variable, but adherence is required for efficacy	• Integrated TB/HIV services, and INH co-formulation with CTX/B6 • Differentiated service delivery • Use of shorter TPT regimens where appropriate • Positive provider messaging, patient education, in-depth motivational counselling, and SMS treatment support • Documentation of TPT completion in programmatic reporting
Inability to prevent and monitor for adverse events	• INH-associated LFT elevations usually have few clinical consequences, but risk increases with age, alcohol, nevirapine, immunosuppression, etc. • Neuropathy can occur, especially in undernourished PLHIV	• Careful screening for TPT exclusion criteria • Patient education and appropriate monitoring for adverse events • Adverse event reporting to national surveillance systems
One size fits all option for regimen and duration	• 36 months of INH can be more effective than 6 months, but its protective effect wanes quickly in high TB prevalence settings	• Other regimens (e.g., 3 months rifapentine + INH) may be recommended options for high-burden settings (shorter, better tolerability, but requires caution with some ARVs)
Uncertainty about use in children/adolescents	• INH is safe and generally has lower toxicity in children than adults	• TPT provision for all children living with HIV ≥12 months, or <12 months with a known TB exposure, after exclusion of TB disease
Uncertainty about use in pregnancy	• INH has not been shown to result in statistically significant increases in hepatotoxicity; however, recent data identified a statistically significant increase in any adverse pregnancy outcome compared to deferring INH until the postpartum period	• Pregnant women living with HIV should be routinely screened for TB • Pregnant women living with HIV who do not have TB disease should be counseled about the individual risks and benefits of INH. Clinicians may consider deferring INH until the postpartum period • Inclusion of pregnancy status in data collection tools
TPT delivery in the era of differentiated care for PLHIV	• Many HIV programs are increasing the interval between clinic visits and ARV pickups for stable ART patients	• Alignment of prescribing practices for TPT with those for ARVs • Programs could train patients, CHWs, and ART club members to distribute TPT and monitor for TB symptoms and/or side effects
Planning, procurement and supply chain management	• Adequate advanced planning for procurement and supply chain management will be essential to avoid TPT stock outs	• TB and HIV program coordination to forecast anticipated needs • Setting aside full courses for patients at initiation • Mechanisms for sites to request TPT "pulls"
No enabling environment for TPT scale up success	• Enabling policies, guidance, advocacy and education are needed for successful TPT scale up • Current M&E tools not often adequate to measure TPT scale up successes and challenges	• Collaborative assurance of appropriate policies and guidance • Advocacy and education efforts • Adaptation of current data collection tools to capture TPT regimen, duration, completion, outcomes, and adverse events • Regional assessment of best models of TPT service delivery

TST: tuberculin skin testing; IPT: isoniazid preventive therapy; TB: tuberculosis; PLHIV: people living with HIV; CXR: chest X-ray; INH: isoniazid; TPT: TB preventive therapy; CTX: cotrimoxazole; LFT: liver function test; WHO: World Health Organization; ARV: antiretroviral; CHWs: community health workers; ART: antiretroviral therapy; M&E: monitoring and evaluation