Questions (with Answers!) from the 2019 Good COPs vs. Bad COPs Webinar on Advocacy to Ensure the Prioritization of TB in 2019 PEPFAR Country Operational Plans (COPs)

TB Preventive Therapy (TPT) Questions

1 **Should TPT be included in routine care of people with HIV?**
YES! The PEPFAR COPs guidance clearly states: "TPT for all PLHIV (including pregnant women and children) must be scaled-up as an integral and **routine part** of the HIV clinical care package." TB remains the leading cause of death of PLHIV, and we know that TPT reduces the risk of TB among PLHIV and saves lives. PEPFAR put it this way: "The evidence base for TPT is clear—it can reduce incident TB among PLHIV by up to 64% when used alone (and substantially more when combined with ART) and has been shown to reduce long-term mortality by almost 40%" (COPs guidance p. 64). The bottom line is that all PLHIV have the right to access TPT.

2 **Is there any news of co-formulation of 3HP (or at least co-packaging)?**
Currently, 3HP is only available in standalone formulations of rifapentine (150 mg tablets) and isoniazid (300 mg tablets). This is a challenge because it contributes to the high pill burden of the regimen: a single dose of 3HP requires swallowing 10 tablets (6 rifapentine tablets; 3 isoniazid tablets; and 1 vitamin B6). Generic manufacturers are developing new formulations of rifapentine, and we expect to see a fixed-dose combination (FDC) of 3HP and a 300 mg tablet of rifapentine enter the market in the next one to two years. In addition, Sanofi has developed a child-friendly FDC of 3HP that dissolves in water and tastes like mango. This pediatric 3HP FDC is being evaluated in a clinical trial and is not yet on the market. Until this product becomes available, health care providers must crush rifapentine in order to give it to children who are unable to swallow tablets.

3 **What about the use of 3HP with TLD?**
TLD = Dolutegravir, Lamivudine, and Tenofovir Disoproxil Fumarate, and is the first-line ARV regimen in PEPFAR-supported programs. Information on using

3HP with TLD will become available as soon as early March 2019 at the CROI Conference where investigators from the IMPAACT4TB consortium will present results of a study evaluating the safety and pharmacokinetics (PK) of giving 3HP with dolutegravir in PLHIV. In addition to assessing safety, the study will answer the question of whether dolutegravir must be dosed at a higher level in the presence of rifapentine. (Dosing is an important question since rifapentine, like other rifamycin agents such as rifampicin, speeds up the body's metabolism of many drugs, including dolutegravir). TAG will share results from this study with advocates and communities following the presentation at CROI.

Here is PEPFAR's take on whether 3HP can be used with TLD: "The safety of co-administering rifapentine and dolutegravir in PLHIV is currently being investigated, but results are expected in early 2019. If pharmacokinetic results show that rifapentine can be safely co-administered with dolutegravir (as expected), then rifapentine-based regimens will be preferred for TPT, pending availability at a competitive price" (COPS guidance p. 396).

4 **Do the guidelines say to eliminate the possibility of active TB before starting TPT?**

Yes—it is important to rule out active TB disease before starting someone on TPT. According to World Health Organization (WHO) guidelines, adults and adolescents living with HIV should be screened for TB according to a clinical algorithm; those without any TB symptoms (e.g., fever, night sweats, weight loss) are unlikely to have active TB and should be offered TPT. A chest X-ray may be offered to PLHIV, and TPT given to those without any abnormal radiographic findings. People with symptoms should be further evaluated for TB and placed on treatment if diagnosed with active TB disease.

TB screening is an important PEPFAR indicator and reporting requirement. PEPFAR COPs guidance describes TB screening as having two outcomes: "Countries are now required to report on TB screening of patients on ART, and the two mutually exclusive clinical decisions made from that screening: 1) initiation of TB treatment, or 2) initiation and completion of TPT" (COPs guidance p. 245).

5 **Can we recommend 3HR for children <2yrs and pregnant women?**

Yes—the 3HR regimen can be safely used in children and pregnant women. Use of 3HR should be the preferred option for all children who weigh <25 kg because of the availability of a pediatric dispersible HR FDC that is already available in countries. For children with HIV and on ART, use either 3HR or IPT based on the antiretroviral regimen. Children on efavirenz-based therapy should receive 3HR and the pediatric dispersible FDC should be used for all kids <25 kg. Children on nevirapine, lopinavir-ritonavir, or dolutegravir should take IPT. As noted above, a clinical trial evaluating the safety and optimal dosing of 3HP in children under age two will begin enrolling soon. This study is being conducted using a child-friendly, water dispersible 3HP FDC.

6 **What are advocates doing to reduce the price of rifapentine? Is 3HP currently funded in any PEPFAR country?**
One powerful action advocates can take to lower the price of rifapentine is to **start building demand** for the drug now. This includes ensuring that every PEPFAR supported country is using at least some rifapentine to reach its TPT scale-up targets in COP19. The current price of rifapentine—set by an agreement between Sanofi and the Global Drug Facility—is volume dependent. That means that if volumes reach certain thresholds, the price of the drug will come down. Demand generation for rifapentine will also help build a market for generic manufacturers that are preparing to introduce new formulations of rifapentine and rifapentine-isoniazid in the next year or two. In the meantime, there is much more than Sanofi can do to make rifapentine available and affordable. Advocates should **call on Sanofi to reduce the price of rifapentine** for the global health market and **register the drug in more countries**.

In short, advocates can: 1) build demand for rifapentine by ensuring PEPFAR countries include 3HP in COP19 and budget for buying rifapentine; 2) support the entry of generic manufacturers; and 3) call on Sanofi to further reduce the price of rifapentine and register the drug widely.

When it comes to using rifapentine in PEPFAR programs, the only way to go is up: a review of 16 PEPFAR countries conducted by TAG found that almost no countries included 3HP in COP18 strategic direction summaries. As of Q3 2018, no PEPFAR countries had procured rifapentine using PEPFAR funding.

7 **Is there any reason why 1HP was not included in the previous presentation?**
Thank you for mentioning the 1HP regimen (one month of daily isoniazid and rifapentine). A clinical trial studying the safety and efficacy of 1HP in PLHIV reported results last year. The trial found that 1HP was noninferior to (no worse than) 9 months of isoniazid (9H) in preventing TB, death from TB, or death from unknown cause. The 1HP regimen was safe and more likely to be completed by participants than 9H. The World Health Organization has yet to issue guidance on 1HP. While waiting for a recommendation from WHO, countries can start using 1HP under operational research conditions, and this is something advocates can push for in COPs development.

Other TB Prevention Questions

8 **Workers in dusty workplaces (e.g. miners and stone crushers) are at high risk of developing silicosis and TB. In high burden silicosis and HIV communities, their risk of acquiring active TB is 15 times greater than in individuals without silicosis and HIV. Health workers in high burden countries have a 2 to 3-fold higher risk of contracting TB. Experts are**

available to assist countries and workplaces to put controls in place in these workplaces, PEPFAR funding would enable countries to implement and evaluate workplace primary prevention measures to prevent new TB cases among these workers? This would prioritize TB prevention in these workplaces, a complementary approach to the also needed focus on vaccines and new drugs. Might PEPFAR funding be available for this approach?

The short answer is, yes—infection control and primary prevention measures are supported by PEPFAR, and the activities you outline are things advocates can push for. Regarding TB prevention among mine workers, section 5.2.1.3 of the COPS19 guidance includes "services that target TB/HIV activities in special populations such as pediatrics, prisoners, miners, migrants, and pregnant women or women at antenatal clinics." See answer to the next question for more information on PEPFAR support for primary prevention in healthcare settings.

9 **Many COPs include funding for additional health care workers. What is being done to train them in how to protect themselves from TB and HIV infection and supplying them with appropriate personal protective equipment?**

Great question. The PEFPAR COPs guidance recognizes infection control in healthcare settings as an important part of preventing TB: "All program systems investments should include provisions for TB infection control. Facility-level and administrative infection control measures should be prioritized. Facility measures constitute the framework for setting up and implementing the other controls (administrative, environmental, and personal protective equipment) at the level of the facility and include the development of policies and procedures for rapid identification and isolation of individuals with TB, the appointment of a facility-based Infection Control officer and annual surveillance of staff for indication of TB infection and/or disease" (COPS guidance p. 394). Figure 9.9.1 in the COPs guidance provides additional information infection control measures supported by PEPFAR that advocates can take forward into COP development meetings.

10 **Is anything being done to support R&D for the development of a vaccine that would prevent the progression to active TB from latent TB?**

Yes. Research to develop new TB vaccines is underway and made several major advances in 2018. Most notable was the publication of positive results from a phase IIb trial of TB vaccine candidate M72/AS01E in the New England Journal of Medicine. The trial found that M72/AS01E provided 54.0% protection to adults with TB infection from developing active TB disease. This positive signal must now be confirmed in a phase III trial before the vaccine can be licensed and used. For more information on TB vaccine research and development, you can read TAG's TB Prevention Pipeline Report, which provides a comprehensive review of the clinical pipeline for new TB vaccines.

Pediatric TB Questions

11 **How can COPs strengthen the implementation of home-based care for pediatric TB?**

The optimal package for home-based care for pediatric TB should include the following core elements:

- Sensitization and information sharing about pediatric TB and the importance of getting children screened;
- Contact tracing i.e., children who are contacts of adult pulmonary TB cases (or who have siblings diagnosed with TB) should be screened for TB through household-based visits performed by community health workers (CHWs);
- Treatment adherence support: CHWs should visit the household and provide treatment adherence support to patients and caregivers;
- Referral and patient follow-up to ensure children identified at the community level are linked to facilities (including, for example, m-health solutions such as SMS reminders);
- Pill refills for children on TPT or treatment for active TB disease.

In order to implement this optimal care package, it is crucial that COPs include the following components:

- Human resources for community activities for both TB and HIV;
- Job descriptions for cadres responsible for community linkages and community-based provision of care must include TB activities (e.g., contact investigation and screening);
- Budget to develop pediatric TB training materials specifically targeting CHWs (e.g., slide decks, job aids for pediatric TB screening).

12 **What are the best models of integrating and scaling-up TB preventive therapy within existing programs?**

Among children, the two priority target populations for TPT are: HIV-positive children and child contacts under five years of age.

Regarding children with HIV: the best model is a facility-based model that builds on the regular visits that HIV-positive children in care should access through HIV services. Children with HIV should be screened for TB at each visit. In crowded HIV services, it is strongly advisable to introduce cadres (i.e., cough monitors) who can perform TB screening in the waiting area while patients wait before they are screened by the healthcare worker (either a nurse or clinician). Human resource for TB screening in HIV services should be included in COPs.

Regarding child household contacts: Several lines of evidence show that the community-based model is the most efficient in reaching out to children and family members of people who have been diagnosed with TB. This implies that CHWs need to be linked to the TB clinic, get the names of adult TB patients identified, and plan visits to their households. An important consideration for

COPs is building synergies between HIV and TB services in the same facility. If there are CHWs attached to the HIV services who are tasked with household visits, the same CHWs should also be attached to the TB clinic, and community visits should include both HIV and TB activities. Community contact tracing activities need to be well prepared through community sensitization toward TB and pediatric TB in order to improve acceptance and mitigate stigma.

TB LAM Questions

13 **Does PEPFAR support the procurement of consumables that are to be used with the diagnostic tools (e.g. urine cups and pipettes needed to implement TB LAM testing)?**
Yes, PEPFAR does fund the procurement of consumables. Section 5.2.1.3 (TB/HIV) of the FY2019 PEPFAR COPs Guidance lists the following among items that may be covered using PEPFAR funds: *"Laboratory costs for TB/HIV, including GeneXpert MTB/RIF cartridges (including MTB/RIF Ultra cartridges), TB Lipoarabinomannan (LAM) Ag urine assays, other TB-specific diagnostics and consumables (e.g., specimen cups, biosafety cabinets, supplies and equipment for AFB smear microscopy and culture, supplies for drug susceptibility testing), personnel training and specimen transportation for TB diagnostic testing."*

14 **How do we counter arguments from donors that TB LAM testing has not been shown to reduce overall mortality in all HIV-positive inpatients, rather only some high risk groups?**
Multi-country, randomized, controlled trials have demonstrated the ability of TB LAM testing to allow for earlier TB diagnosis in people with HIV in both inpatient and outpatient settings, and to reduce TB mortality. The Cochrane review, which led to WHO guidance in 2015, estimated TB LAM to have a sensitivity of 56 percent and a specificity of 90 percent in HIV-positive patients with a CD4 count<100 cells/mm3.

The multi-country STAMP trial showed that using TB LAM testing in addition to GeneXpert MTB/RIF in all HIV-positive, hospital-admitted adults resulted in a survival benefit in the most at-risk sub-populations, and an increase in TB diagnosis and treatment initiation in the general study population. These data expand the previous evidence to indicate the value of using TB LAM testing as a TB screening test in all hospitalized patients with HIV. Further, a separate prospective observational cohort study of both ambulatory and hospitalized HIV-positive adults in Kenya indicated the utility of expanding TB-LAM testing to people with CD4<200/mm3 to increase diagnostic yield.

These data underscore the importance of TB LAM testing for PLHIV. The available evidence demonstrates the potential benefits of using the TB-LAM test in high TB/HIV burden settings for all people with HIV admitted to a hospital regardless of CD4 count or symptoms (plus GeneXpert

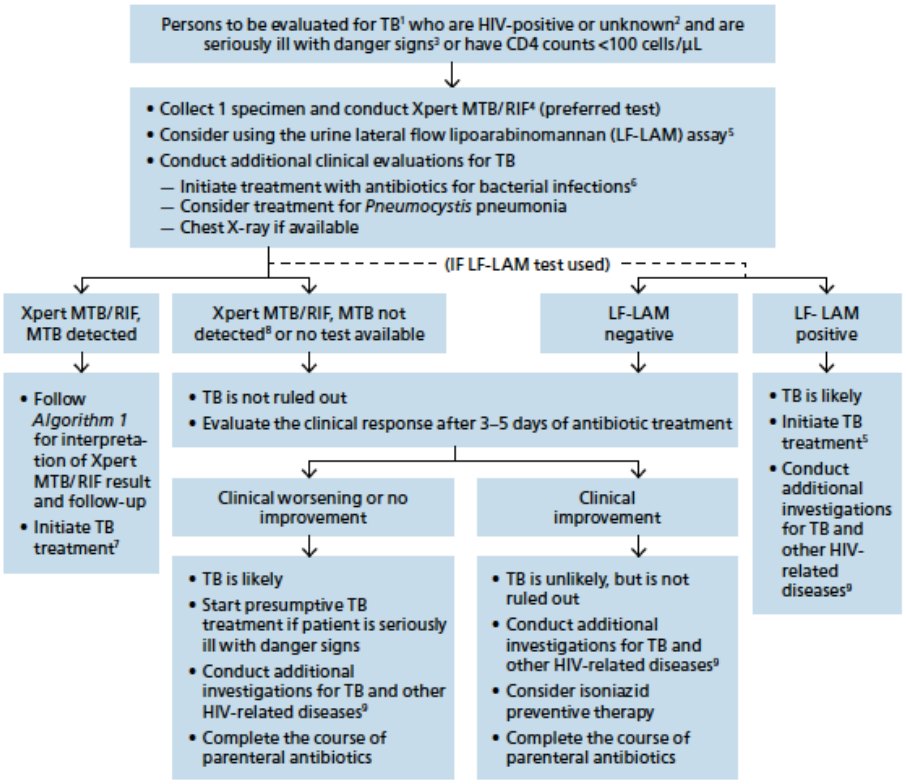
MTB/RIF Ultra), and for all people with HIV with CD4<200 cells/mm3 presenting to ambulatory care.

Other TB LAM tests are in development and may have improved sensitivity in all people with HIV (not just advanced disease). The WHO is expected to review in 2019 available evidence for the current TB LAM test, as well as a new LAM test by FujiFilm. This may result in a broader indication for LAM testing. In the meantime, TB and HIV programs should not wait to roll out the existing test, given its high potential to save lives.

15 **Where in the diagnostic algorithm would the LAM test be ideally placed?**
According to the Model TB Diagnostic Algorithms published by the Global Laboratory Initiative (GLI), TB LAM testing belongs in the algorithm for TB screening among PLHIV who are seriously ill with danger signs or have CD4 counts ≤ 100 cells/μl (page 24).

As described above, the latest evidence suggests that TB LAM testing should be provided for all people with HIV admitted to a hospital regardless of CD4 count or symptoms (plus GeneXpert MTB/RIF Ultra), and for all people with HIV with CD4<200 cells/mm3 presenting to ambulatory care. The GLI's model TB diagnostic algorithms are available at the following link: http://www.stoptb.org/wg/gli/assets/documents/GLI_algorithms.pdf.

Algorithm 4: Algorithm for evaluating persons for TB, among PLHIV who are seriously ill with danger signs or have CD4 counts ≤ 100 cells/µl



Stigma, Human Rights, and Legal Barriers Questions

16 **How do we put activities on stigma reduction, human rights and removing legal barriers that hinder access to HIV services in COPs?**
PEPFAR remains committed to addressing stigma, human rights violations, and legal barriers that undermine an effective HIV/AIDS response: "COP19 continues to…demand that COP planning consider issues of stigma, discrimination, and human rights" (COP19 guidance, p. 23). Section 2.5.4 of the PEPFAR COP19 guidance addresses "stigma, discrimination, violence, and human rights." This section calls for addressing stigma "at all points in the service-delivery cascade" and acknowledges the need to "address the structural- and policy-level barriers that perpetuate discrimination" (COP19 guidance, p. 117). This section mentions a number of tools that advocates can use in COPs development, including a Stigma Index 2.0, legal environmental assessments, gender and sexual diversity training, and a CSO and human rights matrix.

17 **In terms of resistance to uptake of medication and diagnostic services, our qualitative investigation into TB found that social cultural issues play a huge role. Stigma is still a big issue for example. Is there room for all**

aspects presented today to include language that specifically acknowledges social cultural issues and activities that could be implemented to address such issues?
Yes! See answer to above question. Section 2.5.4. of the PEPFAR COP19 guidance notes that "to control the epidemic, it is imperative that we identify and understand the often complex dynamics driving stigma, discrimination, and violence, and implement innovative, evidence-based, community-led approaches to address the specific types of stigma…at all points in the service-delivery cascade" (COP19 guidance, p. 117). Please refer to this section and a number of tools, activities, and mandates outlined by PEPFAR in planning your specific interventions related to stigma reduction.

PEPFAR COPs Process Questions

18 **Thanks for this very important session. Is there any strategy for supporting country level CSOs to advocate to support the PEPFAR COP process?**
Yes—Health Gap has created a comprehensive *Guide to Influencing and Monitoring PEPFAR Country Programs* that advocates can use to plan their strategies.

19 **What can you do if you have not been invited to the Strategic Retreat?**
Read Health Gap's guide to PEPFAR COPs advocacy—there are lots of suggestions for ways to get involved even if you haven't been invited to the strategic retreat.