



NJ TB Update 2023

Clinical Update on Treatment of TB Infection and Disease: How Short Can Our Regimens Go?

Henry Fraimow, MD
Division of Infectious Diseases
Cooper University Hospital and Cooper Medical School of Rowan
University
Camden, New Jersey



Disclosures

- I have no financial disclosures or other conflicts of interest to disclose related to this talk.

State of the Art TB Treatment 100 years ago



Source: <https://www.saranaclake.com/history>

Treatment of TB

Infection:

None

Treatment of TB

Disease:

Bed Rest

Fresh Mountain Air

Healthy Food

Duration: Often years,

Until “self cure” or death

Fast Forward to Recent Past: 2000

- Effective Treatments for TB Infection to prevent of TB Disease
 - Preferred Regimen: INH x 9 months
 - Alternatives: INH x 6 mos, RIF x 4 mos, RIF + PZA x 2 mos
- Effective Treatments for TB Disease
 - RIPE + DOT
 - 6- 9 mos, longer for some extrapulmonary forms
- Moderately Effective Treatments for MDR TB Disease
 - 5-7 drugs for 1.5-2 years

Fast Forward to Now: 2023

- Effective Treatments for TB Infection to prevent of TB Disease
 - Preferred Regimen: ~~INH x 9 months~~ ^{3HP}
 - Alternatives: INH x 6 mos, ~~RIF x 4 mos~~ ^{RIF + PZA x 2 mos}
- Effective Treatments for TB Disease
 - RIPE + DOT ^{INH + Mox + RPT + PZA x 4 mos}
 - 6- 9 mos, longer for some extrapulmonary forms
- ~~Moderately~~ Effective Treatments for MDR TB Disease
 - 5-7 drugs for 1.5-2 years

^{BPAL x 6 mos}

Objectives

- Review newer and shorter Regimens for Treating TB Infection
 - Current Preferred and Alternate Regimens
 - Options for HIV-co-infected
 - What about contacts of MDR Infection?
- Review 4 month regimens for Treating TB Disease (RPT-MOX)
 - INH + Rifapentine + Moxifloxacin * + PZA regimen (HPMZ)
 - Some other shorter Regimens under study
- Review 6 month regimens for MDR Disease
 - BPAL and BPAL + Moxifloxacin *
- Current Challenges in implementation of Shorter (and any) Regimens
 - Impact of Drug Shortages

*Will be discussing CDC and WHO approved regimens that include Moxifloxacin, but Moxifloxacin is not FDA approved for treatment of TB infection or Disease

TB Infection Treatment Options (Shortest to Longest)

Regimen	Priority	Duration	Total Doses
INH Plus Rifapentine (RPT) weekly	Preferred	12 Weeks (3HP)	12
INH Plus RIF Daily	Preferred	3 Months (3HR)	90
RIF Daily	Preferred	4 Months (4R)	120
INH			
Daily	Alternative	6 Months (6H)	180
2x/Week		6 Months	52
INH			
Daily	Alternative	9 Months (9H)	270
2x/Week		9 Months	76

<https://www.cdc.gov/tb/topic/treatment/tbi.htm>

Treating TB Infection: Navigating the Menu of Choices



Courtesy Jacqueline French MD

The Decision to Treat TB Infection: A Risk-Benefit Assessment

- There are benefits of treating TB infection for most infected individuals
 - Individual Benefit: Prevent TB Disease
 - Public Health Benefit: TB Elimination
- New preferred Treatment regimens are shorter, safer and lead to higher completion rates
- With these treatment regimens → **benefit** outweighs **risks** in most with TB Infection



Source: hfrainow

Comparison of Regimens:

• INH plus RPT x 12 weeks (3HP)

- Shortest Duration, fewest doses, Low rate of Hepatotoxicity in comparison to Daily INH x 6 or 9 months
- Easiest to implement for DOT (though no longer mandatory DOT) so ideal for Occupational Health, Student Health settings
- High pill burden all at once
 - Average Adult: 150 mg Rifapentine x 6, INH 300 x 3, B6 = 10 pills
 - RPT only available as 150 mg tabs
- Toxicities: Nausea, vomiting, dizziness, flushing
- Rifapentine Drug interactions
 - Fewer interactions than Rifampin
 - OK with some but not all Antiretroviral Rx for PWHIV

➤ **Drug shortages: Recent shortages of both INH and Rifapentine**

Comparison of Regimens:

- **INH Plus RIF x 3 mos (3HR)**

- Shortest Duration
- 3 pills per day plus B6
- Good Tolerability and High completion rates, as effective as 9H
- Less data for this regimen for LTBI, though extensive use for TB Disease
- But hepatotoxicity risks from INH and drug interaction issues from RIF
 - Primary use: when Rifapentine has been unavailable
 - Also impacted by INH shortages

Comparison of Regimens:

- **RIF x 4 months (4R)**

- Short Duration
- 2 pills per day
- Much Lower Hepatotoxicity than Daily INH Regimens
- Good Tolerability and High completion rates, lots of experience
- Some Toxicities: flu-like Sx, GI symptoms, HA, itching, rare hepatitis, other
 - Drug Interactions: Increases metabolism of many drugs, limits use in patients on multiple meds, interactions with many HIV Meds
 - Intermittent Rifampin shortages

Comparison of Regimens:

- **INH Monotherapy (6H, 9H)**
 - Many years of experience, most accumulated data on effectiveness
 - Few drug interactions, No nitrosamine concerns
 - Completion rates lower due to longer duration
 - 6H better than 9H
 - Toxicities: hepatotoxicity, also GI, peripheral neuropathy (give B6), others
 - May need more intensive lab monitoring due to Hepatitis risks
 - 6H preferred to 9H for most, either 6H or 9H for HIV positive

Treatment Options for PLWHIV

Regimen	Priority	Duration	Doses
INH Plus Rifapentine (RPT) weekly*	Preferred	12 Weeks (3HP)	12
INH Plus RIF Daily**	Preferred	3 Months (3HR)	90
RIF Daily**	Alternative	4 Months (4R)	120
INH			
Daily	Alternative	6 Months (6H)	180
Daily	Alternative	9 Months (9H)	270
INH Plus RPT Daily*	Alternative	1 month (1HP)	30

*Rifapentine can use with: Patients on efavirenz-, raltegravir-, or once-daily dolutegravir-based ARV regimen, but not on some other 1st line HIV regimens such as Biktarvy (BIC-TAF-FTC)

**Rifampin: Many ARV drugs either cannot be used or require dose adjustment

<https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/mycobacterium-0?view=full>

What about contacts of MDR TB Cases?

- **Get expert Help!**
- If index case known to be susceptible to Fluoroquinolones, option would be 6 months of a Fluoroquinolone unless FQ contraindicated
 - Expert opinion
 - Extensive Global experience
 - Ongoing formal clinical trials in adults and children

Why Would Someone with No Symptoms Agree to Take Treatment for TB infection?

Some Barriers to Initiating Treatment for TB Infection

- Medical Literacy
- Language Barrier
- Social Situations: Unstable Housing, Substance Use disorders, transient stay in your area, other
- Those with Highest risks for toxicity and need for more careful monitoring (for example advanced liver disease)
- Other reasons why some are reluctant to accept LTBI Rx
 - “I Don’t like to take medicines”
 - “But I’m not sick”
 - “The medicines might make me sick”
 - “I had a vaccine (BCG) so I can’t get TB”



Shorter Course Regimens for TB Disease



Recommendation for Use of the 4-month Rifapentine-Moxifloxacin Regimen

CDC recommends the 4-month RPT-MOX regimen for treating patients aged ≥12 years with body weight ≥40 kg with **pulmonary TB caused by organisms that are not known or suspected to be drug-resistant and who have no contraindications to this regimen**. The 4-month daily treatment regimen consists of an intensive phase composed of 8 weeks of daily treatment with RPT, MOX, INH, and PZA, followed by a continuation phase of 9 weeks of daily treatment with RPT, MOX, and INH (Table 1).

What are the Benefits and Concerns about Shorter Regimens for TB Disease?

- Less burden to Patients: finish their treatment sooner
- Less burden on TB Programs– less resources needed for DOT and monitoring for shorter treatment regimens
- Are they as effective (“non-inferior”) to standard regimens (RIPE)?
- Are they as safe as standard regimens?
- Are there any additional barriers for implementation?

Where does the Evidence come from?

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

S.E. Dorman, P. Nahid, E.V. Kurbatova, P.P.J. Phillips, K. Bryant, K.E. Dooley, M. Engle, S.V. Goldberg, H.T.T. Phan, J. Hakim, J.L. Johnson, M. Lourenco, N.A. Martinson, G. Muzanyi, K. Narunsky, S. Nerette, N.V. Nguyen, T.H. Pham, S. Pierre, A.E. Purfield, W. Samanek, R.M. Savic, I. Sanne, N.A. Scott, J. Shenje, E. Sizemore, A. Vernon, Z. Wajda, M. Weiner, S. Wundell, and R.E. Chaisson, for the AIDS Clinical Trials Group and the Tuberculosis Trials Consortium

- Multicenter trial 13 countries
- CDC Tuberculous Trials Consortium and ACTG
- 2343 Patients with drug susceptible pulmonary TB
- 3 regimens:
 - RIPE: RIPE x 8 wks and IR x 18 wks
 - IPE-RPT x 8 wks and I-RPT x 9 wks
 - IP-RPT-Moxi x 8 wks and I-RPT-Moxi x 9 wks
- Results:
 - A 4-month RPT based regimen containing Moxi was noninferior to standard 6-month RIPE regimen in treatment of tuberculosis.
 - Rates of Adverse effects of RIPE x 6 mos and RPT-Moxi regimen x 4 mos were similar

Who are and are not good Candidates?

Good Candidates:

- Pulmonary TB*
- No known or suspected Drug resistance
- No other medications that would interact with any of the drugs in the regimen and no other QTc prolonging medications
- Not pregnant or Breastfeeding
- Have not received > 5 doses of TB treatment or exposure to any of the drugs in the regimen over the past 6 months*
- Normal baseline liver (Transaminases < 3 x ULN, Bili < 2.5x ULN) and renal function (Serum Cr < 2 x ULN)*
- If HIV infected, CD4 > 100, on ART but with a regimen that does not interact (Efavirenz containing regimens)

Some additional potential Candidates:

Get Expert Guidance:

- Some forms of Extrapulmonary disease where organism burden is low and are generally treated with 6 months of Rx: Pleural, Lymph node disease
- On treatment with RIPE for less than a few weeks
- Elevated baseline liver or renal function
- Culture negative cases or cases where no culture was submitted where risk of resistance is felt to be low

NTCA PROVIDER GUIDANCE

A 4-Month Regimen to Treat Pulmonary Tuberculosis: Isoniazid, Rifapentine, Moxifloxacin, and Pyrazinamide (HPMZ)

What is the 4-month HPMZ Regimen for treatment of drug susceptible TB?

The HPWZ regimen consists of an 8-week intensive phase of isoniazid (H), rifampine (P), moxifloxacin (M), and pyrazinamide (Z) given daily, followed by a 9-week continuation phase of isoniazid, rifampine, and moxifloxacin given daily. The total duration of therapy is 17 weeks.

What is the medication dosage of the HPMZ

Medication	Body weight	Dose/day
Isoniazid (INH, H)	> 40 kg (88 pounds)	300 mg
Rifampine (RPT, P)	> 40 kg (88 pounds)	1200 mg
Moxifloxacin (MOX, H)	> 40 kg (88 pounds)	400 mg
Pyrazinamide (PZA, Z)	40–55 kg (88–121 pounds)	1000 mg
	>55–75 kg (121–165 pounds)	1500 mg
	> 75 kg (> 165 pounds)	2000 mg

The entire regimen should be administered once daily with food 7 days per week.

What are the advantages and disadvantages of the HPMZ Regimen?

Potential pros of the 4-month regimen

- A shorter duration of treatment for culture-positive pulmonary TB.
- Facilitates treatment completion in patients with barriers
 - planned geographic relocation, incarceration, or
 - residents in congregate or institutionalized settings
- Avoids potential for ocular toxicity with ethambutol (EMB)
- May reduce time to culture conversion

Potential cons of the 4-month regimen

- Higher pill burden
- Required to be taken with food to optimize drug absorption
- Avoiding drug interactions with comorbidities (e.g., *H. pylori*)
- Potentially higher program cost for HRP2 regimen
- Limited long-term outcome data (2 months post-treatment)
- Potential side effects of fluoroquinolones (e.g., QT prolongation, tendinitis, effects on gut microbes)
- Lack of data for treating extrapulmonary TB, including CNS disease and osteomyelitis

0.332 < (L/MR) < 0.354

Intensive Phase	8 weeks	Continuation Phase	16-26 weeks
	Isoniazid Rifampin Pyrazinamide Ethambutol Vitamin B6		Isoniazid Rifampin Vitamin B6

Photos courtesy of Georgia Lee, MD

Treatment interruption:

- The 56 doses of initiation phase should be administered completely within 70 days.
- The 63 doses of the continuation phase should be administered within 84 days.
- If these targets are not met, the patient should be considered to have interrupted therapy and should be managed with clinical judgment and in consultation as described in TB treatment guidelines.

Are there drug-drug interactions?

Are there drug-drug interactions?

Practical Aspects of the RPT-Moxi Regimen

Morbidity and Mortality Weekly Report

TABLE 1. Dosing recommendation for a 4-month rifapentine-moxifloxacin regimen for patients aged ≥12 years with pulmonary tuberculosis caused by drug-susceptible organisms — United States, 2022

Medication*	Body weight, kg	Dose	Intensive phase	Continuation phase	Total doses
			7 days/wk for 56 doses (8 wks)	7 days/wk for 63 doses (9 wks)	
Rifapentine	≥40	1,200 mg			
Moxifloxacin	≥40	400 mg			
Isoniazid†	≥40	300 mg			
Pyrazinamide	40–55	1,000 mg			
	≥55–75	1,500 mg			
	>75 kg	2,000 mg			
				NA	119

Abbreviation: NA = not applicable.

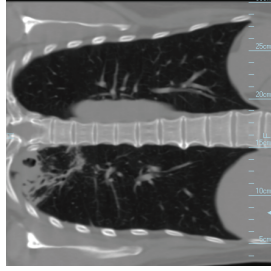
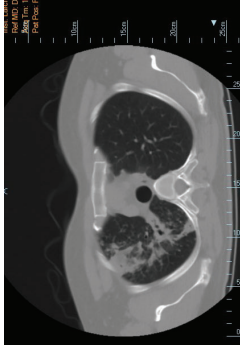
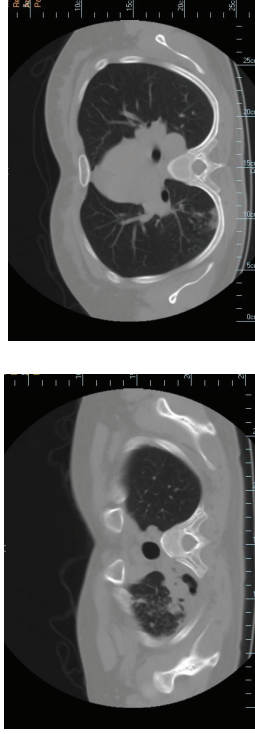
* Medications should be administered with food.

† Pyridoxine (vitamin B6), 25–50 mg/day, should be given with isoniazid to all patients.

For “Average” 60 kg Patient: 14 pills vs. 10 pills for RIPE

Shorter Regimens for MDR TB? A recent patient from our Regional Clinic

- 44-year old healthy Indonesian born woman
- In US for 11 years but goes back to Indonesia frequently
- Cough and sputum production starting 7/2020, no response to a course of antibiotics, symptoms partially improved but persistent cough throughout the fall. No constitutional symptoms
- A CXR shows Right upper lobe infiltrate and scarring
- Saw an Infectious Diseases Physician in December, sputum sent for AFB Smear and culture, Gene Xpert sent to LabCorp. The smear is reported as positive, the GeneXpert is pending
- She is started on RIPE



CT Scan 1/21/21

The Story Continues

- The GeneXpert is reported out as **MTB detected, RIFAMPIN resistance detected**
- She is referred to the Southern NJ Regional Clinic to deal with
- She looks and feels well, she has been on RIPE now for 2 weeks and doesn't feel any different- still with intermittent cough
- History is negative for known exposures to MDR TB
- She had been doing (pre-Pandemic) volunteer work in a legal office for Indonesian and Southeast Asian immigrants
- **What do we do now?**

Anti-TB Drug Resistance Among Counted Cases New Jersey, 2018–2022



Multidrug resistant TB (MDR TB) is defined as resistance to both isoniazid and rifampin

Slide Courtesy Frank Romano, MPH

Options for MDR Disease (2020)

- Standard MDR Regimen of at least 5 Drugs
 - Linezolid, FQ, Bedaquiline,
 - Clofazamine, Cycloserine?
- An injectable?
- Minimum duration of 18 mos

AMERICAN THORACIC SOCIETY DOCUMENTS

Treatment of Drug-Resistant Tuberculosis
An Official ATS/CDC/ERS/IDSA Clinical Practice Guideline: Executive Summary

8 Piyani Nalid, Sander B. Meier, Giovanni Battista Migliori, Giovanni Sotgiu, Graham H. Borhan, Jan L. Brink, Aditya Cattamanchi, J. Peter Goggin, Lisa Chen, Charles L. Daley, Tracy L. Dalton, Raquel Duarte, Frederica Fregonese, C. Robert Horsburgh, Jr., Fitz Ahmad Khan, Fayez Khoury, Zhiyi Lin, Alfred Landrabi, Michael Lazzaro, Joan M. Mangano, Ann Raftery, H. Simon Schaaf, Nisha S. Shah, Jeffrey R. Starke, John W. Wilson, Jonathan M. Workman, Tennessee Chao, and Barbara Sazawal on behalf of the American Thoracic Society, U.S. Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America

© American Thoracic Society 2019. All rights reserved. For personal use only. For more information, please visit <https://www.atsjournals.org>. This document is copyrighted by the American Thoracic Society or one of its allied publishers. This article is intended solely for the personal use of the individual user and is not to be disseminated broadly.



But What about that new 6 month regimen BPaL? Can we start her on that?



MARCH 5, 2020

VOLUME 382

PAGE 48

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Cordale, M.B., B.Ch., Andrea H. Dilson, M.D., Neelofar Nigam, M.B., B.Ch., Pauline Howell, M.B., B.Ch., David Everett, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Genevieve H. Willis, M.Sc., Anna Bateman, Ph.D., Robert Hunt, B.Sc., Christa Van Nieuwen, M.D., Mengchun Li, M.D., Moroufou Ougbo, M.D., and Kevin Spigleman, M.D., for the Nix-TB Trial Team*

ABSTRACT

BACKGROUND: Patients with highly drug-resistant forms of tuberculosis have limited treatment options and historically have had poor outcomes.

DESIGN: A randomized, double-blind, single-group study in which follow-up is ongoing at three South African sites. We investigated treatment with three oral drugs — bedaquiline, pretomanid, and linezolid — that have bactericidal activity against tuberculosis and are expected to have fewer side effects than standard therapy. We evaluated the safety and efficacy of this regimen in patients with multidrug-resistant tuberculosis that was not responsive to treatment or for which a second-line regimen had been discontinued because of toxicity. The primary end point was the proportion of patients who were culture-negative at 6 months after the end of treatment. Patients were classified as treatment failures (bacteriologic or clinical) or relapse during follow-up, which continued until 6 months after the end of treatment.

So what did we do?

- Decision (joint decision making with patient) made to start patient on BPaL (Bedaquiline, Pretomanid, Linezolid x 6 months)
- Drugs obtained with assistance of NJ DOH TB Program
- **Cough resolves in 2 weeks, sputum AFB cultures negative at 2 weeks**
- Successfully completed therapy
- Tolerated treatment without side effects except for some decrease in hemoglobin- linezolid levels adjusted
- Newer short course BPaL based regimens based on additional trials:
 - Ze-Nix and others Use of lower initial Linezolid doses (600 mg daily) and can go even lower with monitoring of levels
 - TB PRACTICAL: 6 mos of BPaL-M (BPaL plus Moxifloxacin) with even higher cure rates than BPaL



The Nix-TB Trial

109 Patients

Extensively DR or MDR and drug intolerant or nonresponsive

Regimen:

Bedaquiline

400 daily x 2 wk then 200 mg 3x/wk x 24 wks

Linezolid 1200 mg daily x 26 wk (adjust for toxicity)

Pretomanid 200 mg daily x 26 wk

Results:

90% favorable response

Linezolid toxicity common

Can we do even better with our Treatments?

- What is in trials now?
- Even shorter regimens for both TB Infection and TB Disease
- A “Universal” regimen for all TB Disease whether or not there is Drug resistance

Speedbumps on the Road to Implementing Shorter TB Regimens: Medication Shortages

- Current Medication Shortage: Isoniazid
 - Situation improving, impact uneven, some pharmacies able to get medication even when we can't
- Other Intermittent Shortages
 - Rifamycin shortages from a variety of issues: single manufacturer, Nitrosamine contamination, other
 - Rifampin
 - Rifapentine
 - Need to consider drug availability when starting any patient on medication
 - Workarounds for some shortages- alternative regimens

FDA Drug Shortages

[f](#) Share [t](#) Tweet [in](#) LinkedIn [e](#) Email [p](#) Print

From FDA Website 10/8/23

Isoniazid Tablet

Status: Currently in Shortage

» **Date first posted:** 05/17/2023

» **Therapeutic Categories:** Anti-Infective

- Rifampin Capsule (*Currently in Shortage*)
- Rifampin Capsule (*Discontinuation*)
- Rifampin Injection (*Currently in Shortage*)
- Rifapentine Tablet, Film Coated (*Currently in Shortage*)

INH-Alternate Regimens for TB Disease: Similar to regimens used for INH Mono-resistance

Options	Regimen	Duration	Notes
Option 1	RIF, EMB, PZA, and a FQN	Daily 6-9* months	• Moxifloxacin (MXF) is the preferred FQN • If the patient is intolerant to MFQ, levofloxacin (LFX) may be substituted • If PZA is not tolerated in the initial phase of treatment, extend to 9 months of RIF/EMB/FQN • Ensure vision monitoring, as EMB is used for duration • Do not use this regimen if there is evidence of rifampin resistance. If so, seek consultation
Option 2	RIF, EMB, PZA	Daily 6-9* months	• Seek consultation prior to using this regimen • Consider this option only if FQN intolerant • Ensure vision monitoring, as EMB is used for duration.

*Considerations to extend therapy to 9 months include: treating extensive disease (i.e., cavitation at two months, slow conversion of AFB smears, slow conversion of AFB cultures beyond two months), and/or when PZA cannot be used for the full initial phase in Option 1.

Source: NJ DOH

Regimens for LTBI without INH: No 3HP or 6H

Table 3. Tiered Regimens for LTBI, Window Prophylaxis During INH Shortage			
Tier 1		Tier 2	Tier 3
4 Months Rifampin (4R) • Rifampin duration is 4 months, 120 doses, for TB infection regimens		4 Months Rifabutin (R8T) • Duration/total doses: 4 months, 120 doses • Consider for patients with significant drug-drug interactions with rifampin, including protease inhibitors (PIs) and/or nonnucleoside reverse transcriptase inhibitors (NNRTIs) • <u>check for drug interactions of rifabutin prior to using R8T</u> ◦ are transplant recipients. ◦ are taking methadone; and/or ◦ have a sensitivity/intolerance to rifampin. • Review drug interactions and consider comorbidities impacting renal function prior to R8T; consider consultation if needed. Dosing: Pediatric dosing is 5mg/kg/day • < 30kg = Do not use without a consult • Children ≥ 30kg can take 150mg • Children ≥ 60kg can take 300mg Adult dosing • 300 mg daily	6 Months MFX or LFX • By consultation only

Some Take Home Points

- Regimens to treat LTBI, TB Disease and even MDR TB are getting shorter
- Shorter regimens for LTBI lead to higher completion rates; shorter regimens for TB disease increase patient satisfaction and decrease burdens on TB program staff
- A 4 month Rifapentine-Moxifloxacin based regimen (HPMZ) is an appropriate option for many with Pulmonary TB, with some caveats
- BPaL and newer versions of BPaL such as BPaL plus moxifloxacin x 6 months are new shorter options for treating MDR TB
- Drug shortages, such as the current INH shortage, pose continuing challenges to TB programs, but things are getting better