3HP: Enough 'Horse Power' to drive the national TB Infection agenda?

Background, Rationale, Advantages of Once-Weekly 12-dose (3 mo.) Rifapentine-Isoniazid Regimen (3HP)

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Heartland National TB Center and
Southeastern National TB Center's Webinar on 3HP

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TBTC
TB Trials Consortium

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of Tuberculosis Elimination

CDC

Disclosures

- Statements in this presentation are individual opinion/s of the presenter/s, not official statements, views, or position of the CDC. Please visit www.cdc.gov for official recommendations and documents.

Disclosures

- Rifapentine (PRIFTIN) is approved by the FDA for the treatment of LTBI caused by *M. tuberculosis* in combination with isoniazid in patients 2 years of age and older at high risk of progression to TB disease. However, the label has the following statement:

"…2.2 Dosage in Latent Tuberculosis Infection PRIFTIN should be administered once weekly in combination with isoniazid for 12 weeks as directly observed therapy*.."

- Part of this presentation includes discussion of CDC-recommended use of 3HP as self-administered treatment (SAT)

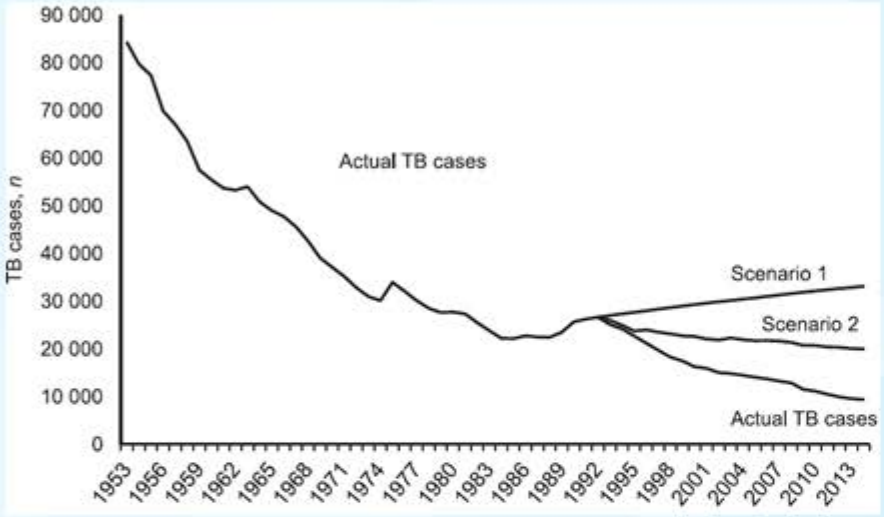
- ** FDA-approved prescribing information for PRIFTIN. http://products.sanofi.us/priftin/Priftin.pdf*

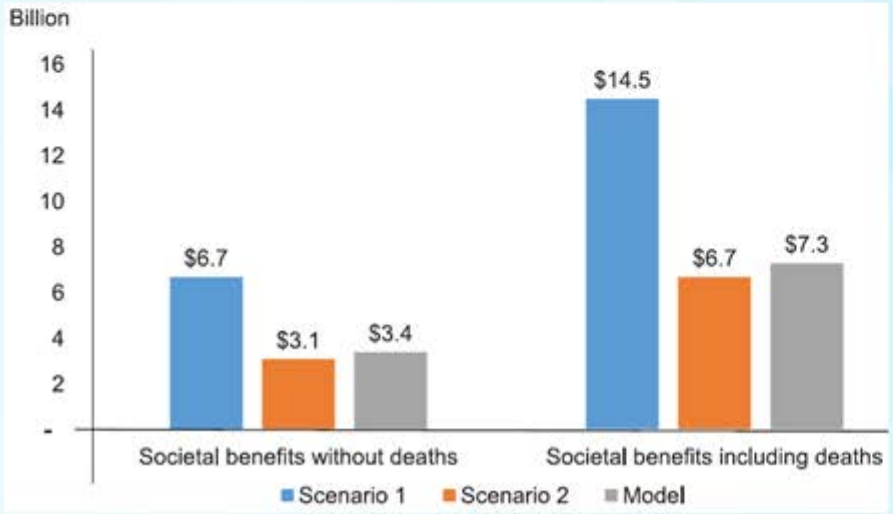
Specific Questions

- **Background, rationale, advantages of "3HP" regimen**
  - Where does LTBI therapy fit in the overall scheme of TB control in the US?
  - What is the rationale behind the 3HP regimen?
  - What do we hope to achieve by using this regimen?
  - What are the advantages of 3HP over alternative LTBI therapies?

Where does LTBI therapy fit in the overall scheme of TB control in the US?

Background





1950s - 1980s: Steady decline of TB cases

1989: Advisory Committee on Elimination of Tuberculosis (ACET) recommended CDC take specific actions to eliminate TB (<1 case per million) in the US by 2010

1985 – 1992: The number of reported TB cases increased 20%

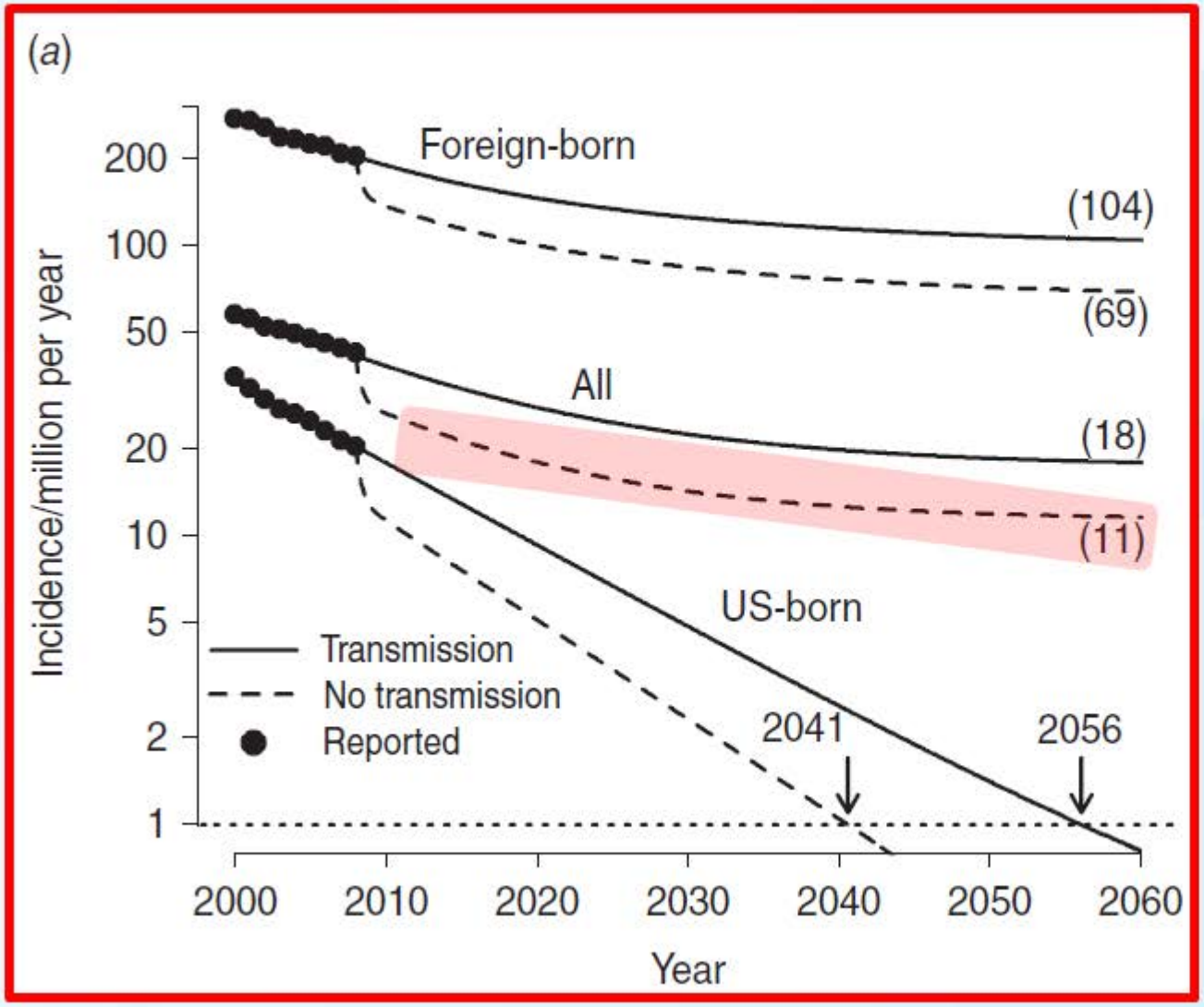
1992 – present: Tremendous efforts to reduce TB led to the prevention of new TB cases, saving human lives and reducing suffering, saving billions of US dollars.

Recent years: despite all efforts the case rate remains almost 30-times the elimination threshold (U.S. TB incidence was ~28 per million in 2017)

Graphs and data: Castro KG et al. Estimating tuberculosis cases and their economic costs averted in the United States over the past two decades. Int J Tuberc Lung 2016 Dis 20(7):926–933; Stewart, RJ et al. Tuberculosis — United States, 2017. CDC MMWR 2018 / 67(11);317–323

Where does LTBI therapy fit in the overall scheme of TB control in the US?

TB Incidence Projections to 2060

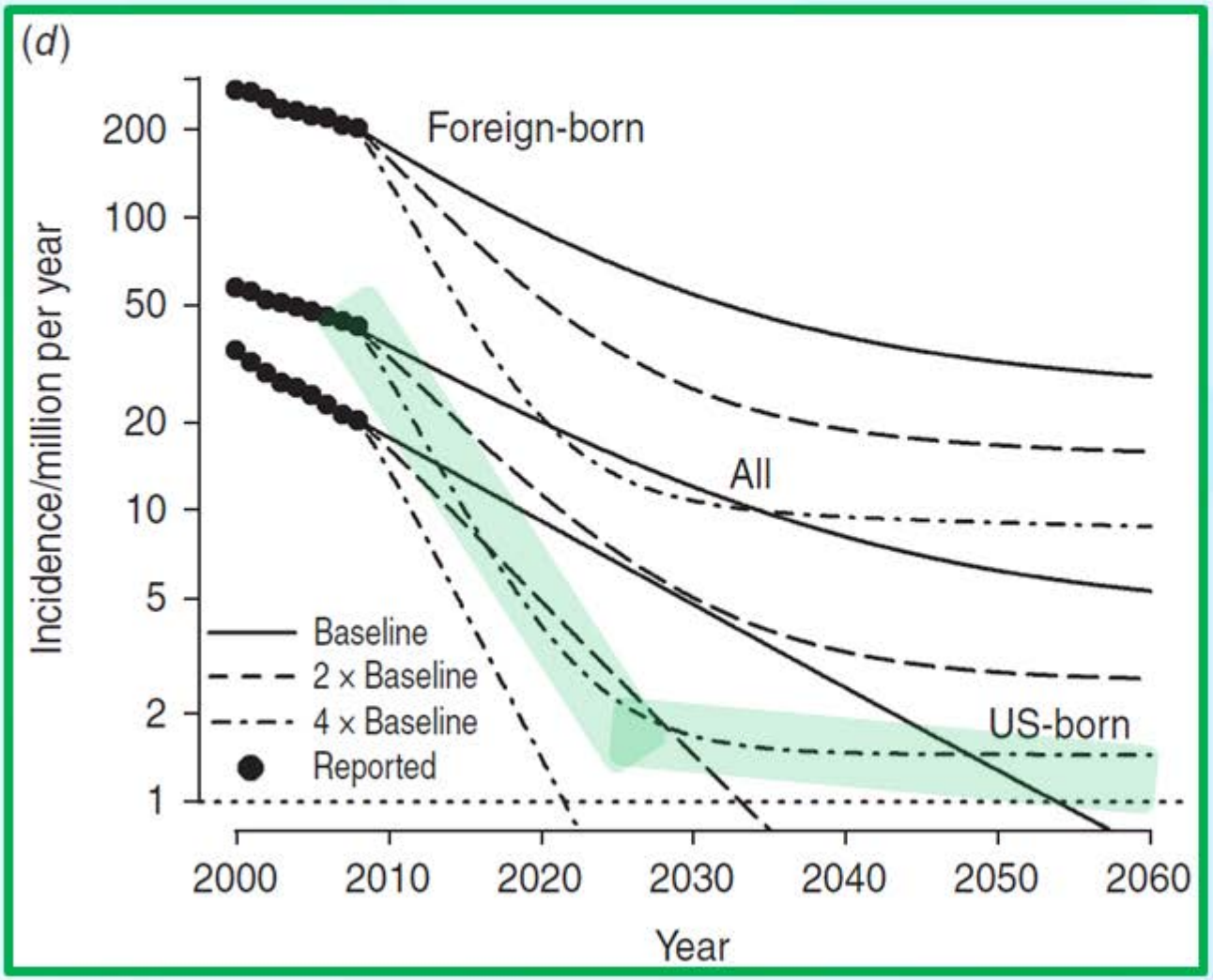


TB incidence projections to 2060 assuming TB transmission is cut

Graphs: Hill A. et al. Modelling tuberculosis trends in the USA. Epidemiol Infect. 2012 Oct;140(10):1862-72.

Where does LTBI therapy fit in the overall scheme of TB control in the US?

TB Incidence Projections to 2060 (LTBI)



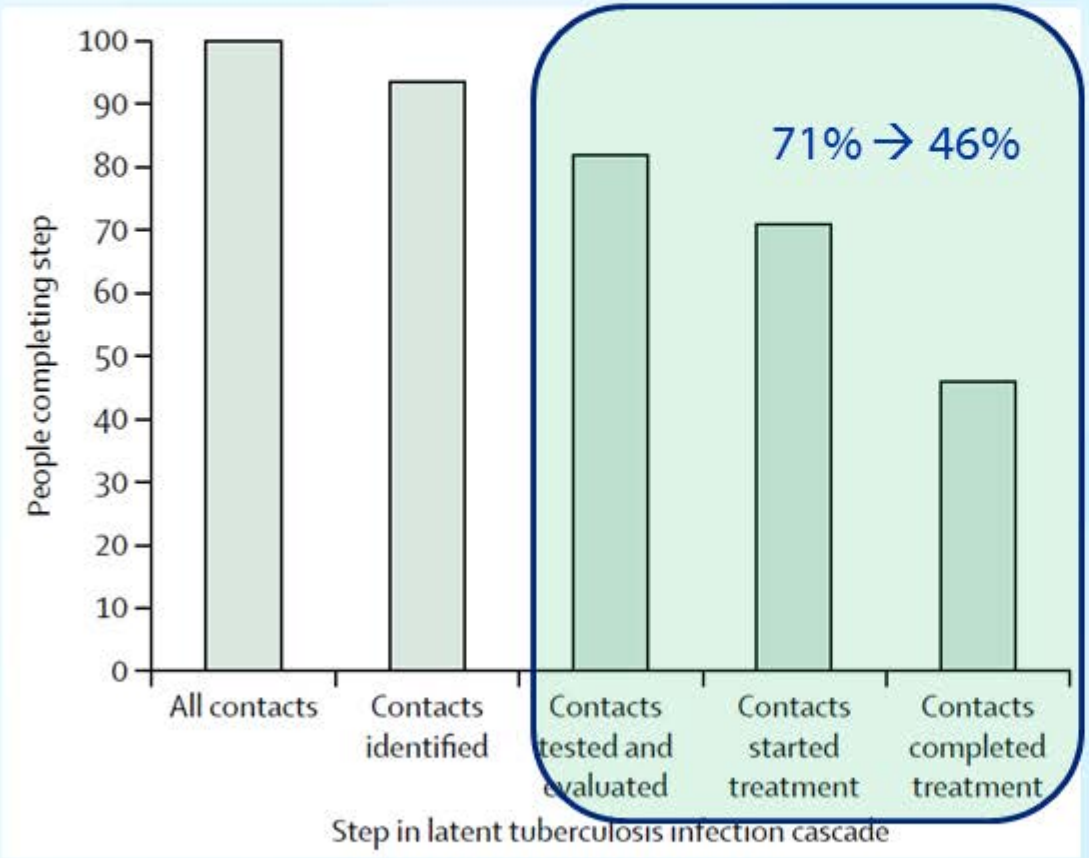
TB incidence projections to 2060 assuming

a) proportion of foreign-born arrivals with LTBI is reduced to 25% of the baseline AND
b) treatment rate of chronic LTBI is doubled or **quadrupled**

Graph: Hill A. et al. Modelling tuberculosis trends in the USA. Epidemiol Infect. 2012 Oct;140(10):1862-72.

What is the rationale behind the 3HP regimen?

LTBI prevention cascade using the example of contact investigation



People can fail to complete any of the steps

The impact is multiplicative
(0.71 X 0.46 = ~ 0.33)

Only 33% of contacts with LTBI complete LTBI treatment in the scenario

Graph: LoBue PA. Latent tuberculosis infection: the final frontier of tuberculosis elimination in the USA. Lancet Infect Dis. 2017 Oct;17(10)

Define the "3HP" Regimen

Latent TB Infection Treatment Regimens

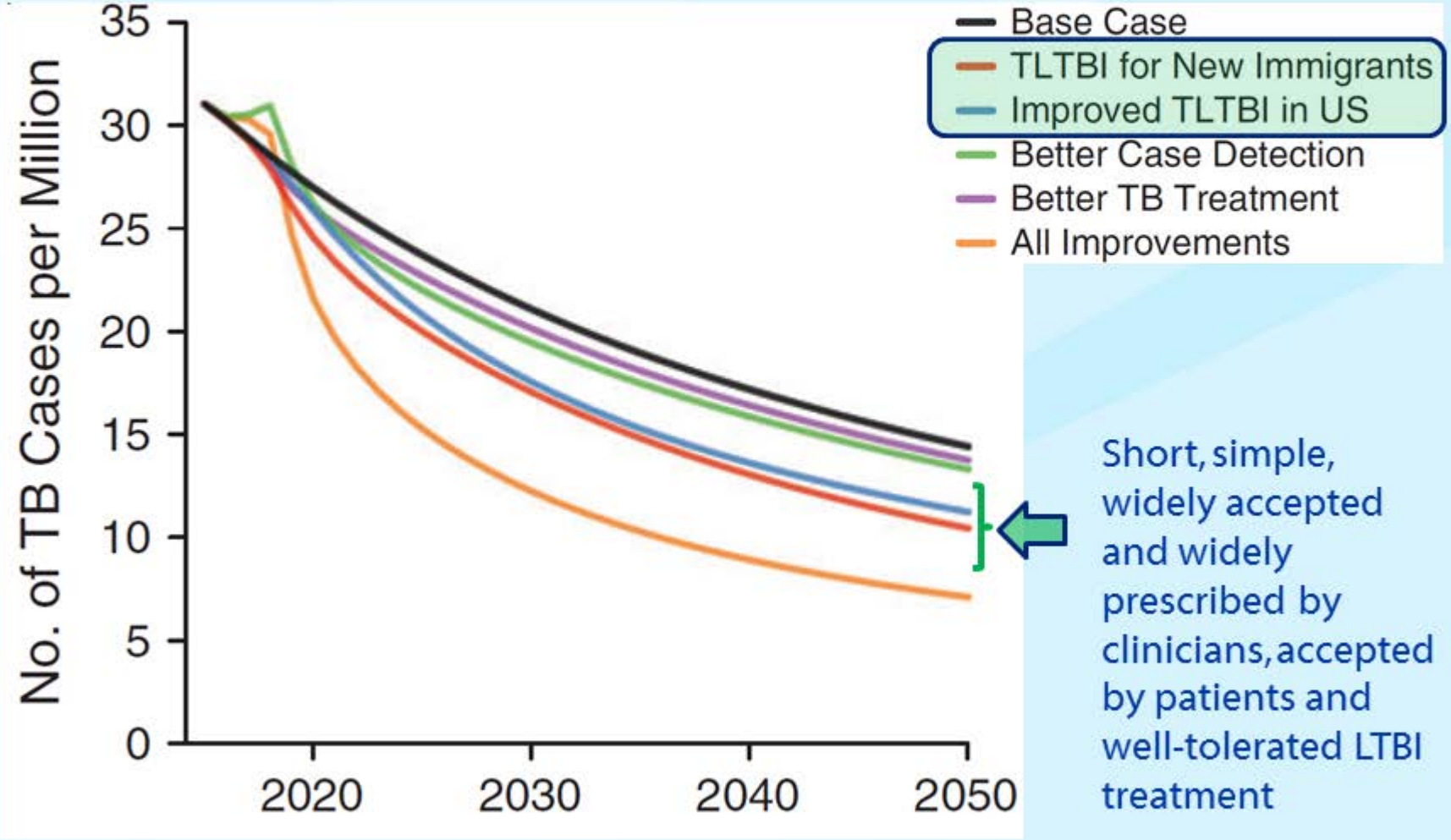
Drug(s)	Duration	Dose	Frequency	Total Doses	
Isoniazid (INH)* and Rifapentine (RPT)†	3 months	<u>Adults and Children aged 12 years and older:</u> INH: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum RPT: 10–14.0 kg 300 mg 14.1–25.0 kg 450 mg 25.1–32.0 kg 600 mg 32.1–49.9 kg 750 mg ≥50.0 kg 900 mg maximum <u>Children aged 2–11 years:</u> INH*: 25 mg/kg; 900 mg maximum RPT†: as above		Once weekly‡	12

What are the advantages of 3HP over alternative TBI therapies?

- Approved by the FDA for treatment of LTBI
- Recommended by the CDC
- Safer (lower rates of hepatotoxicity compared to 9H)
- Flexibility of administration: DOT or SAT
- Simpler and shorter (2 doses vs. 120 (4R) or 270 (9H))
- Higher acceptance by patients (compared to longer regimens)
- Better adherence (compared to longer regimens)
- Potential for use in immigrant prior to arrival to the US *(CDC research study in progress)*

What do we hope to achieve by using this regimen?

New simulation model allowing for changes in TB transmission, immigration, and other TB risk determinants developed in 2018



Short, simple, widely accepted and widely prescribed by clinicians, accepted by patients and well-tolerated LTBI treatment

Graph:. Menzies NA et al. Prospects for TB Elimination in the US Results of a Transmission Dynamic Model. Am J Epidemiol. 2018 Sep 1;187(9):2011-2020.

Summary

- *"LTBI: the final frontier of TB elimination in the USA"*
- 3HP: safe, effective, high acceptance and adherence
- Increased uptake of 3HP *(and in the future even shorter and simpler LTBI therapies)* is an essential component of interventions which have the most significant impact on TB elimination in the USA

3HP: Enough 'Horse Power' to drive the national TB Infection agenda?

Update of Recommendations for Use of Once-Weekly Isoniazid-Rifapentine Regimen to treat LTBI

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2001 CDC's Recommendations on Use of 3HP

- In 2011, CDC recommended 3HP by directly observed therapy (DOT) for LTBI treatment in the U.S.
- Recommendations for 3HP use in children under 12 years old and in persons living with HIV/AIDS were limited.
- Recommendations did not allow 3HP administration by self-administered therapy (SAT).

CDC Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent Mycobacterium tuberculosis infection. MMWR Morb Mortal Wkly Rep. 2011 Dec 9;60(48):1650-3.

New studies have been published since 2011

Key data sources for new 3HP guidelines

- CDC TBESC "FDA Postmarketing" 3HP Implementation Study
- CDC TBTC Study 26/ACTG 5259 (PREVENT TB) RCT Ped. Cohort
- CDC TBTC Study 26/ACTG 5259 (PREVENT TB) RCT HIV Cohort
- CDC TBTC Study 33 (IAdhere) RCT 3HP SAT Safety and Adherence
- *and many more….*

Sandul AL et al. High Rate of Treatment Completion in Program Settings with 12-Dose Weekly Isoniazid and Rifapentine (3HP) for Latent Mycobacterium tuberculosis Infection. Clin Infect Dis. 2017 Oct 1; 65(7): 1085–1093.

Villarino ME et al. Treatment for preventing tuberculosis in children and adolescents: a randomized clinical trial of a 3-month, 12-dose regimen of a combination of rifapentine and isoniazid. JAMA Pediatr. 2015 Mar;169(3):247-55.

Sterling TR et al. Three Months of Weekly Rifapentine plus Isoniazid for Treatment of M. tuberculosis Infection in HIV Co-infected Persons AIDS. 2016 Jun 19;30(10):1607-15.

Belknap R, et al. Self-administered versus directly observed once-weekly isoniazid and Rifapentine treatment of LTBI. A randomized trial. Ann Intern Med. 2017 Nov 21;167(10):689-697.

Process for development of new 3HP guidelines

- In 2017 a CDC Work Group (WG) was convened to review and update the 2011 recommendations.
- WG identified need for expansion of recommendations in 3 major areas:
  - use of 3HP in HIV+ adults
  - use of 3HP in children
  - use of 3HP by SAT)
- **Systematic review and meta-analysis** using methods of Community Guide were conducted and published:

Njie GJ. Et al. Isoniazid-Rifapentine for Latent Tuberculosis Infection: A Systematic Review and Meta-analysis. Am J Prev Med. 2018 Aug;55(2):244-252.

Issues for the new 3HP guidelines

How effective is 3HP in preventing TB disease in

- …children between the ages of 2-11 years old with LTBI?
  - 3HP is safe and effective (non-inferior to other LTBI regimens) in children 2-11 years old and adolescents when treatment is administered by DOT
- …persons living with HIV/AIDS?
  - 3HP is safe and effective (non-inferior to other LTBI regimens) in preventing active TB in persons co-infected with HIV/AIDS and LTBI when treatment is administered by DOT
- …persons receiving once-weekly 3HP given by SAT instead of DOT?
  - Completion of 3HP treatment, when given by DOT (87%) or SAT(82%), is higher than completion of other LTBI regimens (66%) in adulst

Njie GJ. Et al. Isoniazid-Rifapentine for Latent Tuberculosis Infection: A Systematic Review and Meta-analysis. Am J Prev Med. 2018 Aug;55(2):244-252.

Process for development of new 3HP guidelines

- WG held an in-person consultation with nine subject matter experts (SMEs) with TB and LTBI expertise in diagnosis, treatment, prevention, epidemiology, clinical research, pediatrics, HIV/AIDS, public health programs, and patient advocacy:

David Ashkin	Andrea Cruz	Mike Holcombe
John Bernardo	Jenny Flood	Masa Narita
Robert Belknap	Mike Frick	Neil Schluger

- CDC presented draft recommendations to Advisory Council on Elimination of Tuberculosis (ACET) public meeting
  - Experts' request for recommendation to permit use of SAT, when combined with clinical monitoring, in children aged ≥2 years.
  - Some experts noted preference for DOT for treating LTBI in children aged 2–5 years, in whom risk for TB progression and severe disease is higher than in older children and adults
  - ACET formally recommended expansion of the option of parentally administered SAT to children.

Summary of the new 3HP guidelines
Updated Recommendations

- CDC continues to recommend use of 3HP for treatment of LTBI in adults.
- CDC now also recommends:
  - use of 3HP in persons aged 2–17 years;
  - use of 3HP in persons with LTBI who are living with HIV infection, including AIDS, and taking antiretroviral medications with acceptable drug-drug interactions with rifapentine*; *should be guided by experienced clinicians*
  - use of 3HP by DOT or SAT in persons aged ≥2 years; the provider should choose DOT versus SAT based on local practice, patient attributes and preferences, and other considerations, including risk of severe TB

** https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/367/ overview.*

Borisov AS, et al. Update of recommendations for use of once-weekly isoniazid-rifapentine regiment to treat Mycobacterium tuberculosis infection. MMWR. June 2018:67(25); 723-26.

Guidance to Providers on Monitoring

- Evaluate all patients for active tuberculosis disease both before and during treatment of LTBI
- Inform patient or parents/guardians about possible adverse effects (AEs)
- Conduct monthly evaluation to assess adherence and adverse effects, with repeated patient education regarding AEs at each visit www.cdc.gov/tb/publications/pamphlets/12-doseregimen.htm.
- Order baseline LFTs for patients with: HIV, liver disorders, postpartum period, regular alcohol use, injection drug use, or medications with possible drug interactions
- Continuation of 3HP under observation can be considered in the presence of mild to moderate events as determined by the provider

Guidance to Providers on Safety

- ~4% of patients using 3HP experience flu-like symptoms, or other systemic drug reaction (SDR; fever, headache, dizziness, nausea, muscle and bone pain, rash, itching, red eyes or other symptoms)
- ~5% of patients discontinue 3HP because of adverse events, including systemic drug reactions;
- SDRs typically occur after the first 3-4 doses, and begin ~ 4 hours after ingestion of medication
- Hypotension and syncope have been reported rarely (2 cases per 1,000 persons treated)
- If symptoms suggestive of a systemic drug reaction occur, patients should stop 3HP while the cause is determined
- Symptoms usually resolve without treatment in 24 hours
- Neutropenia and elevated LFTs occur uncommonly

Guidance to Providers on Interactions

- Monitoring of patients when 3HP is prescribed with interacting medications (e.g., methadone or warfarin)
- Rifapentine can reduce the effectiveness of hormonal contraceptives; therefore, women who rely on hormonal birth control should be advised to add, or switch to, a barrier method.
- Women should be advised to inform their provider if they decide to try to become pregnant or become pregnant during 3HP treatment *(of note, FDA pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; further research is needed)*

Guidance to Healthcare Providers – Reporting

- Any LTBI-treatment-associated AEs leading to hospital admission or death should be reported to local or state health departments for inclusion in the National Surveillance for Severe AEs Associated with Treatment for LTBI:

  LTBIdrugevents@cdc.gov

- Serious drug side effects, medication errors, product use errors, product quality problems, and therapeutic failures should be reported to the U.S. FDA MedWatch system, either online https://www.fda.gov/Safety/MedWatch

  or by telephone at 1-800-FDA-1088

Links to 3HP Guidelines

https://www.cdc.gov/tb/publications/guidelines/treatment.htm

or download PDF version of the at document at:

https://www.cdc.gov/mmwr/volumes/67/wr/pdfs/mm6725-h.pdf

Thank you!

Questions & Comments welcome!

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