LTBI Treatment and Cases

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October 2019

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Disclosures

- Unpaid occasional consultant to International SOS
- Ran TB surveillance program at UCLA for 4 hospitals, 200 clinics, campus researchers with live MTB aerosols and animal NHP work, international travel and field research; 7 years voting IBC member there
- CEO of a health consulting LLC
- Have been reimbursed and paid for work in Kenya and elsewhere by CDC and US DoS; TB surveillance and BBP
- No other disclosures

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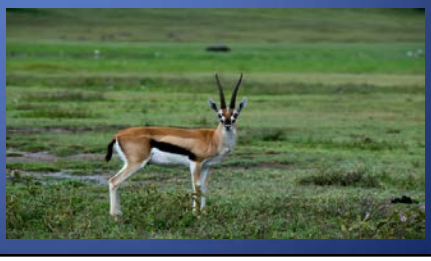
Outline

- What our focus should be on now
  - LTBI activation stories
  - TREAT LTBI
  - Have a process to STRONGLY encourage LTBI treatment
  - LTBI Treatment
- Companion paper to MMWR
- Q & A/Discussion



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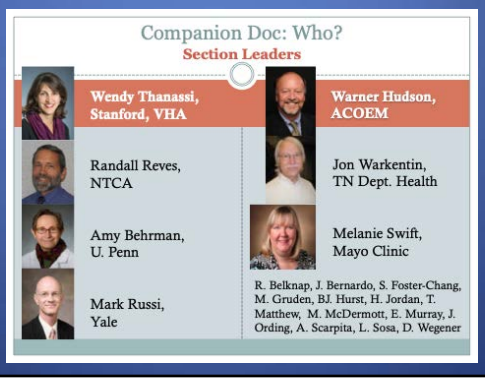
Companion paper to MMWR 2019 Update

- Companion paper adds operating details to the MMWR: Do read it
- Expected out in JOEM within 1-2 months
- Large collaboration between ACOEM and NTCA and others



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LTBI Activation Example 1

CASE

- Nurse hired 2007 with LTBI at onboarding, OH documented LTBI Rx declination
- Yearly OH Oct. TB screening; no symptoms until activates between screenings in spring 2014
- TB sxs for months, many primary/urgent care visits before active TB dx by Pulmonary MD
- Exposed 264 transplant pts. + >142 employees at one hospital; & worked other hospitals
- Huge challenge to manage for both OH and Infection Control and risk to patients and employees

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LTBI Activation Example 1

LESSONS

- While LTBI Rx decline documentation kept OH and institution out of trouble; far better to work really hard to treat the LTBI in the first place!
- Need to be sure the LTBI individual HCP knows and takes urgent appropriate steps if active TB sxs occur
- Annual screening missed this activation…yet this has been our focus
- Focus needs to be at onboarding and treating LTBI: don't miss this opportunity!

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Healthcare Personnel Treatment: Untreated LTBI

- Treatment offered to HCP and strongly encouraged to complete
- HCP less likely to accept LTBI treatment than others not in healthcare
- Newer regimens are shorter, safer and cost effective
  - INH + Rifapentine weekly for 3 months, that's 12 doses total, most likely to complete regimen
  - Not as widely known, recognized, discussed or utilized

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LTBI Treatment Options

- INH and rifapentine weekly for 3 months (DOT/SAT); that's a total of 12 doses and most likely to complete
- Rifampin daily for 4 months
- INH daily (or twice weekly DOT) for 9 months
- INH daily (or twice weekly DOT) for 6 months – less effective than 9 months

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CDC Detailed LTBI Rx Regimens

https://www.cdc.gov/tb/topic/treatment/ltbi.htm

INH 100 & 300 mg tabs

RPT 150 mg tabs

Latent TB Infection Treatment Regimens

Drug(s)	Duration	Dose	Frequency	Total Doses
Isoniazid (INH)* and Rifapentine (RPT)†	3 months	Adults and Children aged 12 years and older: 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 Children aged 2–11 years: INH*: 25 mg/kg; 900 mg maximum RPT†: as above	Once weekly§	12
Rifampin (RIF)¶	4 months	Adult: 10 mg/kgChildren: 15–20 mg/kg# Maximum dose: 600 mg	Daily	120
Isoniazid (INH)	9 months	Adult: 5 mg/kg Children: 10–20 mg/kg** Maximum dose: 300 mg	Daily	270
		Adult:15 mg/kgChildren: 20–40 mg/kg** Maximum dose: 900 mg	Twice weekly§	76
	6 months	Adult: 5 mg/kgChildren: Not recommended Maximum dose: 300 mg	Daily	180
		Adult: 15 mg/kgChildren: Not recommended Maximum dose: 900 mg	Twice weekly§	52

CDC MMWR updated 3HP SAT recs 2018:

https://www.cdc.gov/mmwr/volumes/67/wr/mm6725a5.htm?s_cid=mm6725a5_w

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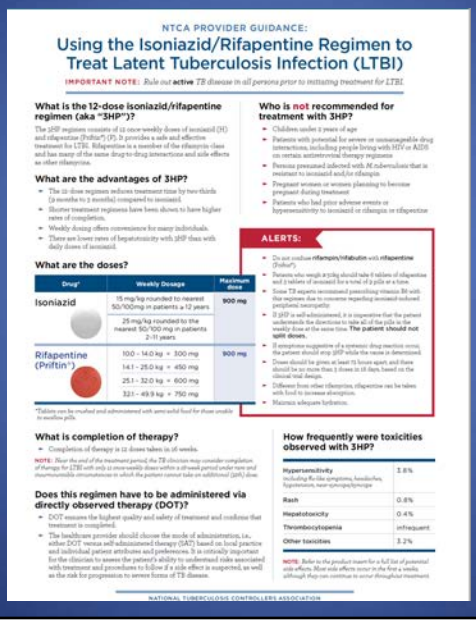
NTCA INH/Rifapentine



NTCA PROVIDER GUIDANCE:

Using the Isoniazid/Rifapentine Regimen to Treat Latent Tuberculosis Infection (LTBI)

IMPORTANT NOTE: *Rule out* **active** *TB disease in all persons prior to initiating treatment for LTBI.*

What is the 12-dose isoniazid/rifapentine regimen (aka "3HP")?

The 3HP regimen consists of 12 once-weekly doses of isoniazid (H) and rifapentine (Priftin®) (P). It provides a safe and effective treatment for LTBI. Rifapentine is a member of the rifamycin class and has many of the same drug-to-drug interactions and side effects as other rifamycins.

What are the advantages of 3HP?

- The 12-dose regimen reduces treatment time by two-thirds (3 months to 3 months) compared to isoniazid.
- Shorter treatment regimens have been shown to have higher rates of completion.
- Weekly dosing offers convenience for many individuals.
- There are lower rates of hepatotoxicity with 3HP than with daily doses of isoniazid.

What are the doses?

Drug*	Weekly Dosage	Maximum dose
Isoniazid	15 mg/kg rounded to nearest 50/100mg in patients ≥ 12 years 25 mg/kg rounded to the nearest 50/100 mg in patients 2-11 years	900 mg
Rifapentine (Priftin®)	10.0 - 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	900 mg

*Tablets can be crushed and administered with semi-solid food for those unable to swallow pills.

Who is not recommended for treatment with 3HP?

- Children under 2 years of age
- Patients with potential for severe or unmanageable drug interactions, including people living with HIV or AIDS on certain antiretroviral therapy regimens
- Persons presumed infected with *M. tuberculosis* that is resistant to isoniazid and/or rifampin
- Pregnant women or women planning to become pregnant during treatment
- Patients who had prior adverse events or hypersensitivity to isoniazid or rifampin or rifapentine

ALERTS:

- Do not coadminister rifampin/rifabutin with rifapentine (Priftin®).
- Patients who weigh 25 kg should take 4 tablets of rifapentine and 2 tablets of isoniazid for a total of 6 pills at a time.
- Some TB experts recommend prescribing vitamin B6 with the regimen due to concerns regarding isoniazid-induced peripheral neuropathy.
- If 3HP is self-administered, it is imperative that the patient understands the directions to take all of the pills in the weekly dose at the same time. **The patient should not split doses.**
- If symptoms suggestive of a systemic drug reaction occur, the patient should stop 3HP while the cause is determined.
- Doses should be given at least 72 hours apart, and there should be no more than 3 doses in 10 days, based on the clinical trial design.
- Different from other rifamycins, rifapentine can be taken with food to increase absorption.
- Maintain adequate hydration.

What is completion of therapy?

- Completion of therapy is 12 doses taken in 16 weeks.

NOTE: *Near the end of the treatment period, the TB clinician may consider completion of therapy for LTBI with only 11 once-weekly doses within a 20-week period under rare and insurmountable circumstances in which the patient cannot take an additional (12th) dose.*

Does this regimen have to be administered via directly observed therapy (DOT)?

- DOT ensures the highest quality and safety of treatment and confirms that treatment is completed.
- The healthcare provider should choose the mode of administration, i.e., either DOT versus self-administered therapy (SAT) based on local practice and individual patient attributes and preferences. It is critically important for the clinician to assess the patient's ability to understand risks associated with treatment and procedures to follow if a side effect is suspected, as well as the risk for progression to severe forms of TB disease.

How frequently were toxicities observed with 3HP?

Hypersensitivity including flu-like symptoms, headaches, hypotension, nausea/vomiting/syncope	3.6%
Rash	0.8%
Hepatotoxicity	0.4%
Thrombocytopenia	infrequent
Other toxicities	3.2%

NOTE: *Refer to the product insert for a full list of potential side effects. Most side effects occur in the first 4 weeks, although they can continue to occur throughout treatment.*

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NTCA INH/Rifapentine

What can an adverse event include and how should I respond?

	Adverse Event		Response
Moderate to Severe	Hypersensitivity Hypotension Dizziness or nausea/vomiting (these can be prodrome to syncope) Syncope/fainting Hospitalization Life-threatening event Flu-like syndrome (e.g., fever, chills, headaches, dizziness, muscle/skeletal pain) Thrombocytopenia	Shortness of breath Wheezing Acute bronchospasm Urticaria Petechiae Purpura Conjunctivitis Angioedema Shock	Discontinue treatment Conduct prompt clinical assessment with appropriate lab monitoring
Mild to Moderate	Rash Fever Pruritus		Continue to monitor the patient closely with a low threshold for discontinuing treatment

How do I report an adverse event regarding 3HP?

- Report all adverse events to FDA MedWatch at www.fda.gov/Safety/MedWatch/default.htm, 1-888-INFO-FDA (1-888-463-6332)
- Report adverse events leading to death or hospitalization to your health department. Health departments should report these adverse events to the Centers for Disease Control and Prevention at 1-800-232-4636 or LTBIsurvents@cdc.gov

Are there drug-drug interactions?

Yes, there are common interactions for isoniazid and rifapentine.

- **Isoniazid** increases blood levels of phenytoin and diazepam.
- **Rifapentine** decreases blood levels of oral or implanted hormonal contraceptives, warfarin, mifepristone, methadone, steroids, some cardiac medications, and certain antiretroviral therapy regimens may have serious drug interactions.

NOTE: Use a drug interactions checker and/or refer to the product insert for a full list of drug-drug interactions.

Whom do I contact with questions or concerns?

- Contact your local or state health department.
- NTCA has an online directory of TB programs at http://www.tbcontrollers.org/community/statecityterritory/

What type of monitoring do I need to do?

- Evaluate the patient at a monthly visit to identify adverse events and to assess treatment adherence.
- Some experts recommend baseline complete blood count (CBC) due to a possible adverse reaction decreasing the white blood cell count and platelet counts and comprehensive metabolic panel (CMP). Hepatitis panel may also be obtained.
- Baseline hepatic chemistry is recommended for patients with these specific conditions:
  - HIV infection
  - Liver disorders
  - In the postpartum period (≤ 3 months after delivery)
  - Regular alcohol or injection drug use

  In addition, consider baseline hepatic chemistry for older persons and for persons taking medications for chronic medical conditions.
- If baseline hepatic chemistry testing is abnormal, determine the risk vs. benefit of treatment. If a decision is made to treat, continue with subsequent hepatic chemistry testing until the patient is determined to be stable.
- If baseline hepatic chemistry is within normal limits and the treatment is self-administered, some experts recommend additional laboratory monitoring monthly to ensure that the patient does not develop hepatotoxicity.
- When or after the final dose is taken, conduct a final visit with the patient to monitor for any adverse events.

NTCA PROVIDER GUIDANCE:
USING THE ISONIAZID/RIFAPENTINE REGIMEN TO TREAT LATENT TUBERCULOSIS INFECTION (LTBI)

NOVEMBER 2018, REVISED, APRIL 2019

For references, go to http://www.tbcontrollers.org/resources/3hp

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What Could Go Wrong

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Healthcare Personel Treatment: Untreated LTBI

- Contraindications:
  - People with HIV/AIDS who are taking antiretroviral medications with clinically significant or unknown drug interactions with RPT*
  - People presumed to be infected with INH or rifampin (RIF)-resistant *M. tuberculosis*
  - Pregnant women, or women expecting to become pregnant during the 12-week regimen
  - Patients who had prior adverse evets or hypersensituvuty to INH or rifapentine

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Monitoring Treatment

- Monthly visits to assess safety, adherence and adverse events
- Monthly prescriptions with refill approved after monitoring visit
- Organizational support of visits and drug costs preferred
  - Some institutions partner with local health departments
- Appropriate laboratory monitoring monthly

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HCP Treatment: Untreated LTBI

STRATEGIES FOR COMPLIANCE

- 12 dose (3 month, weekly dosing) course
- Use Organization's Occupational Medicine or EH departments
- Escalation from NP based clinic to Occ. Med MD to specialty departments like ID
- Referral from PCPs to ID if Occ Med or EH resources are not available
- Readdress and encourage compliance for those who decline on an annual basis
- Organization pays for the LTBI treatment course ideally

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Should organization pay for LTBI Rx?

- Typically pay for HCP conversions ->LTBI but not new hires with LTBI
  - Risk management/WC/administrative decision
  - Now underlies many LTBI activations
- Ideally organization pays for LTBI Rx
  - Benchmark hospitals that do this like Penn
  - Talk of risk reduction to patients, employees and reputation as well as lawsuits
  - Use redirecting annual screening savings

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Healthcare Personel Treatment: Untreated LTBI

- If HCP does not complete therapy
  - Annual symptom evaluation
  - Reevaluate treatment options risks/benefits for LTBI Rx
  - Ongoing education between screening visits of TB signs and symptoms of infection and need for immediate eval. if these occur
  - Continue to offer treatment to those who initially decline, they may change their minds with the shorter regimen options

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Special Situations

- MDR TB LTBI
  - Follow for minimum 2 years regardless of treatment or no treatment
  - Rx regimens not well researched for efficacy
  - Longer treatment times; 6-12 months
  - Need to know what drugs the MDR TB is resistant to
  - Use resource like UCSF Curry Center https://www.currytbcenter.ucsf.edu/sites/default/files/tb_sg3_chap10_contacts.pdf#ltbitxoptions
  - Definitely need a consult with MDR TB expert
- HCPs involved in research
  - Non Human Primates (NHP)
    - Screen workers/researchers Q 6 or 12 months as whole NHP colony can die from TB from a worker
  - MTB research
    - Screen every 6 or 12 months if aerosolizing MTB
- MTB from field work, zoos, animal parks
  - Elephants, rhinos, marine mammals can get and transmit MTB to humans
- M bovis
  - Cattle and many other animals can get and transmit to humans who work around them, vets, dairy workers, hunters
  - Screening tests and LTBI treatment are as for MTB
  - https://www.cdc.gov/tb/publications/factsheets/general/mbovis.pdf

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LTBI Activation Example 2

- Clinic nurse 53, born Philippines, + IGRA 2012 = LTBI not Rx'd
- 2016 vague sxs fatigue; is perimenopausal
- PMD takes months to eval. & realize IGRA had been + since 2012
- After 3-4 months of sxs PMD gets lung CT -> dx active TB
- 180 contacts; 40 staff & 140 patients
- 1st contact conversion: heart transplant pt. in for first post - transplant bx from another state immune suppressed; how to treat
- Next a nurse with RA on immune suppressing meds who had been IGRA negative before exposure now has active TB
- 4 other patients convert

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LTBI Example 3

- Employee notifies supervisor of TB diagnosis (from LTBI activation)
- Hospital contacts 1,727 patients and employees who might have had contact with employee between June 2015 and end October 2015 and told to be tested
- Untold time, effort and dollars expended
- No conversions identified!
- **This all could have been avoided had the LTBI been treated**

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The End
Q & A and Discussion

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