# LTBI Management for TB Nurses

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# LTBI Management For TB Nurses

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# Why do we treat LTBI?

# Latent Tuberculosis Infection

- LTBI can be persistent for many years and lead to TB disease if untreated
- 80% TB disease arises from prior infection
- Treatment is up to 90% effective
- Treating LTBI is less costly with less morbidity as compared to TB disease

# Percent Risk of Disease by Age

| Age at Infection | Risk of Active TB |
|---|---|
| Birth – 1 year* | 43% |
| 1 – 5 years* | 24% |
| 6 – 10 years* | 2% |
| 11 – 15 years* | 16% |
| Healthy Adults | 5-10% lifetime risk |
| HIV Infected Adults+ | 30-50% lifetime |

*Miller, Tuberculosis in Children Little Brown, Boston, 1963

+WHO, 2004

# LTBI Treatment Regimens

# Treatment Options for LTBI

| Drug | Duration | Number of Doses |
|---|---|---|
| INH + Rifapentine (3HP) | Once weekly x 12 weeks | 12 |
| Rifampin | Daily x 4 months | 120 |
| INH + Rifampin | Daily x 3-4 months | 90-120 |
| INH | Daily x 9 months | 270 |
| INH | Daily x 6 months | 180 |

The longer the duration/more doses, the less likely your patient is to complete treatment

Fewer than 60% complete 9 months of INH

# Isoniazid (INH) Therapy

Isoniazid monotherapy for 6-9 months has been used for decades and its efficacy in preventing TB disease is approximately 90%.

**But less than 60% complete -** Primarily due to long duration of treatment but also increased adverse effects

- Is the option when drug-drug interactions with rifamycins are significant and must be avoided
- The regimen is effective and is the preferred regimen for HIV infected people taking antiretroviral therapy with drug-drug interactions that do not allow a rifamycin

# Isoniazid (INH) Dosing

- Adults: 300 mg single daily dose or 900 mg twice weekly*
- Children: 10-15 mg/kg single daily dose (max dose 300 mg daily)
  - 20-30 mg/kg twice weekly*
- Duration of treatment for TB Infection: 6 - 9 months
  - 9 month regimen more effective
  - 9 month regimen is very difficult to complete
  - 6 months is considered adequate therapy by ATS/IDSA/CDC guidelines

*** twice weekly treatment must be given by directly observed therapy through health department**

# INH Side Effects


- Hepatotoxicity
- Migraine headaches
- Fatigue
- Gastrointestinal
  - Nausea, Diarrhea, Constipation
- Rash
- Peripheral Neuropathy
  - ➢Pyridoxine 50mg daily can help prevent this but is not fail-safe.

# INH Hepatotoxicity

- Asymptomatic elevation of aminotransferases: 20% of patients
  - Ok to continue IF enzymes remain < 5X ULN and NO SYMPTOMS
- Clinical hepatitis: 0.6% of patients
- Fulminant hepatitis (hepatic failure)
  - Approximately 4/100,000 persons completing therapy (continued INH with symptoms of hepatitis, prior INH hepatotoxicity, malnutrition).

# Severe INH Liver Injuries Among Persons Being Treated for LTBI, U.S., 2004-2008

MMWR 3/5/10/ 59(08); 224-229

"Medical providers should emphasize to patients that ***INH treatment should be stopped immediately upon the earliest onset of symptoms*** (e.g. excess fatigue, nausea, vomiting, abdominal pain, or jaundice), even before a clinical evaluation has been conducted, and that initial symptoms might be subtle and might not include jaundice."

# Rifampin (RIF) Regimens


RIF daily for 4 months has become the first choice in many practices.

- Compared to INH, RIF has similar efficacy, higher completion rates and lower hepatotoxicity rates

In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted. **Drug-drug interactions still need to be checked.

# 4 Months RIF vs 9 Months INH for Treatment of LTB Infection

- Menzies et al AJRCCM 2004, 170; 445
  - **Completion** of therapy **significantly better** with rifampin with fewer side effects than INH
- Lardizabal et al Chest 2006, 130; 1712
  - Patients receiving rifampin were **significantly more likely to complete** therapy than those receiving INH
- Menzies et al Ann Int Med 2008, 149; 689
  - **Significantly higher rate of treatment completion** with **fewer serious adverse events**

# Rifampin Dosing for TB Infection

- Adults
  - 600 mg daily x 4 months
- Children:
  - 10 – 20 mg/kg daily x 4 months
  - Capsules 150mg/300 mg round up - use higher range
  - Higher rifampin doses well tolerated

# Rifampin Treatment of TB Infection (versus INH)

- **Pros**:
  - Higher Completion Rates
  - Equally effective
  - Fewer Side Effects
  - Less Hepatotoxicity
  - Cost effective
  - Rifampin resistance uncommon
    - Globally 3%

- **Cons**:
  - Drug Interactions
    - Hormone Contraceptives
    - Warfarin
    - Prednisone
    - **HIV Antiretroviral agents**
    - And many more…
  - Other Potential Side Effects (rare):
    - Rash
    - Thrombocytopenia
    - Anemia
    - Leukopenia
    - Allergic Interstitial Nephritis

# 3 HP

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Prevent TB Study (TBTC 26)

## Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D.,

Active TB disease: 7/3986 in 3 HP arm; 15/3745 in 9H arm
Completion of treatment: **82.1% 3HP arm**; **69% 9 H arm**
Hepatotoxicity: 0.4% 3HP arm; 2.7% 9 H arm.

**Conclusion: Use of 3 HP x 3 months was as effective as 9 months of INH and had a higher treatment completion rate.**

# Tolerability and Effectiveness in Children

## TBTC S26 + IMPAACT

- Study 26 amended to enroll 352 additional children; 1,058 total There were 908 for efficacy evaluation
- Follow-up complete September 30, 2013
- No hepatotoxicity, grade 4 events, or deaths

| Endpoint | 3HP N=472 | 9H N=436 | P-value |
|---|---|---|---|
| Treatment completion | 88% | 81% | 0.003 |
| D/C—adverse drug reaction | 2% | 0.5% | 0.11 |
| Grade 3 toxicity | 0.6% | 0.2% | 0.49 |
| TB | 0 (0%) | 3 (0.78%) | Upper bound of difference: 0.44% |

JAMA Pediatr. 2015; 169(3): 1-9

**3 HP weekly for treatment of M. tuberculosis infection in HIV co-infected persons:**
TBTC Study 26 ACTG 5259;  AIDS Sterling et al. June 2016

Objective: Compare effectiveness, tolerability, and safety of 3 months of weekly 3 HP by DOT vs. 9 months of daily INH in HIV-infected persons.
Median baseline CD4+ counts were 495 and 538 in the 3HP and 9 INH arms (P = 0.09)

In the modified intention to treat analysis:

2 TB cases among 206 persons in the 3HP arm
6 TB cases among 193 persons in the 9H arm.

**Cumulative tuberculosis rates were: 1.01% vs. 3.50% in the 3HP and 9H arms**

**Treatment completion was higher with 3HP (89%) than 9H (64%)** (P < 0.001)
Drug discontinuation due to an adverse reaction was similar (3% vs. 4%); (P = 0.79)

Conclusions: Among HIV-infected persons with median CD4+ count of approximately 500 cells/mm3, **3HP was as effective and safe for treatment of latent M. tuberculosis infection as 9H, and better tolerated.**

# 12-DOSE REGIMEN (3HP)

## for Latent Tuberculosis Infection Treatment

CDC continues to recommend the use of the short-course combination regimen of once-weekly isoniazid-rifapentine for 12 weeks (3HP) for treatment of latent tuberculosis infection (LTBI) in adults.

CDC now also recommends use of 3HP:

- by directly observed therapy (DOT) **or self-administered therapy (SAT)***
- in persons aged **2–11 years**
- in persons with LTBI who are **living with HIV infection** including AIDS and taking antiretroviral medications with acceptable drug-drug interactions with rifapentine

Shorter treatment regimens, like 3HP, **have higher treatment completion rates** and **lower costs**.

* Healthcare providers should choose the mode of administration (DOT vs. SAT) based on local practice, individual patient attributes and preferences, and other considerations, including risk of progression to severe forms of tuberculosis disease.

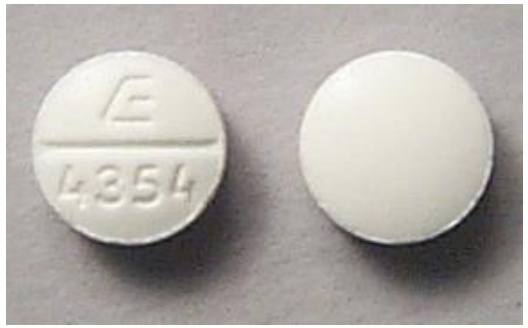
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CDC. June 2018.

# 3HP NOT Recommended

- Children < 2 years old
- Pregnancy, or likely to become pregnant during treatment
- Presumed INH or RIF resistance
- Prior adverse reaction with INH or rifamycin

# Dosing for 3 HP


**Adults and children > 45 kg**

- 900 mg INH once weekly
- 900 mg Rifapentine once weekly
- Vitamin B 6 50 mg once weekly

**Children 2 – 12 years**

- INH 15 mg/kg (round to nearest 50 or 100 mg tablet)
- Rifapentine
  - 10-14 kg: 300 mg
  - 14.1-25 kg: 450 mg
  - 25.1-32 kg: 600 mg
  - 32.1-49.9 kg: 750 mg
  - ≥ 50 kg: 900 mg

# Clinical Toxicity with 3 HP

- Approximately 4% a people treated with 3HP will experience a flu-like illness with fever, HA, dizziness, nausea and body aches.
- Hypotension has been reported rarely (2 cases/1,000 people treated).
- Side effects are reported more commonly when taking other medications.
- Drug-drug interactions are important to consider.
- Hepatotoxicity is less common but still important. ALT should be monitored as you would with INH monotherapy.
- Monthly, in-person toxicity monitoring is recommended.

# Choice of Treatment, in Summary

- 3HP (INH + Rifapentine weekly x 12 weeks)
- 4R (RIF daily x 4 months)
- 9H (INH daily x 6-9 months) if on essential medications with unacceptable interaction with rifamycins

# LTBI Treatment

Special considerations

# Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

With daily isoniazid alone for 6 or 9 months, any ARV regimen can be used **(AIII)**.

With once-weekly isoniazid plus rifapentine for 3 months:
Efavirenz (EFV) 600 mg once daily or raltegravir 400 mg twice daily (in combination with either abacavir/lamivudine [ABC/3TC] or tenofovir disoproxil fumarate/emtricitabine [TDF/FTC]) can be used **(AII)**.

http://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/tuberculosishiv-coinfection
(last reviewed and updated June 3, 2021.

# LTBI in Transplant Candidates and Patients receiving TNF-α Inhibitors

Transplant candidates should receive one of the recommended LTBI regimens, ideally prior to transplantation.

- LTBI medications are metabolized in the liver and can safely be given to patients with renal disease

Patients receiving TNF-α inhibitors should be tested and treated for LTBI.

- The American College of Rheumatology recommends completing at least one month of LTBI treatment prior to starting or resuming TNF-α inhibitors

**Humira** **Enbrel** **Remicade**

# Should Pregnant Women Be Treated for LTB Infection during Pregnancy?

- Increased risk of serious, even fatal hepatotoxicity with INH during pregnancy and the immediate post-partum period ( 3 months following delivery)
- Treatment usually only given to those with recent contact to a person with active TB disease, HIV positive women or those with other immunosuppressive conditions
- Monitoring should be very close
  - Blood work for any symptoms and hold medication if taking
  - Monitor liver enzymes and patient at every monthly visit.

However for many women, the only time they have access to care or willingly seek care is during pregnancy or immediate post-partum period.
The next time you see them they may be pregnant again and still without treatment for TB infection.

PLOS | ONE

RESEARCH ARTICLE

# Latent Tuberculosis in Pregnancy: A Systematic Review

**Isabelle Malhamé[1,2,3], Maxime Cormier[1,2,3], Jordan Sugarman[2,3], Kevin Schwartzman[1,2,3]***

1 Department of Medicine, McGill University, Montreal, Quebec, Canada, 2 Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, Montreal, Quebec, Canada, 3 McGill International Tuberculosis Centre, Montreal, Quebec, Canada

May 5, 2016

## Findings:

- One study suggested increased risk of active TB in 180 days postpartum
- In USA prevalence of LTBI ranged from 14-18% of women tested
- Excellent adherence with CXR and TST/IGRA evaluation during pregnancy (> 95%)
- Poor adherence with post partum evaluations and treatment
- Only 14 – 69% attended follow-up visits; only 5 – 42% of these women completed at least 6 months of INH

# Should Pregnant Women Be Treated for LTB Infection during Pregnancy?

- Current CDC guidelines recommend CONSIDERING LTBI treatment in pregnant women who are HIV + or have recent TB contacts.
- In pregnant women who are not at high risk for progression to TB, LTBI treatment can be delayed until 2-3 months post-partum.
- Both INH and RIF are considered category C drugs during pregnancy.
- Decision to treat LTBI during pregnancy should be a shared decision with each individual patient.

# Drug-Resistant TB Contacts

The choice of LTBI regimen should be informed by the susceptibilities of the source patient.

- For mono-resistance, this is simple – use something other than the resistant drug.
- For MDR contacts, the choice can be very difficult and should be done by experts in the field.

# Monitoring Patients on LTBI Treatment

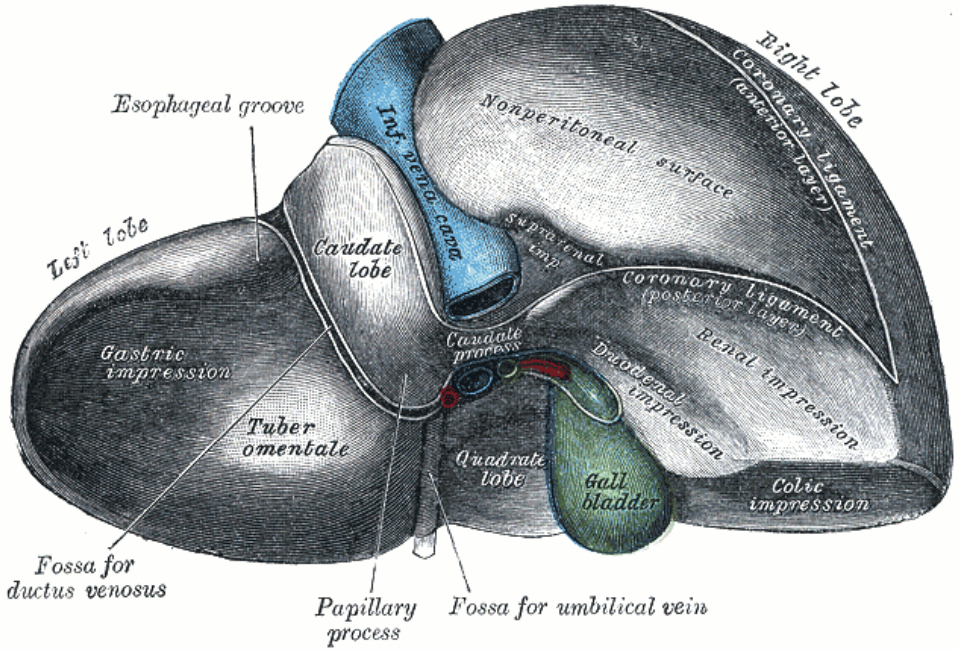
# Monthly Monitoring During LTBI Treatment

- Reinforce patient's understanding of LTBI and its treatment
- Evaluate for signs and symptoms of active TB and drug reactions
- Monitor adherence to prescribed regimen
- Educate patient about signs and symptoms of hepatotoxicity
- Review all medications and assess for potential drug interactions

# Monthly Monitoring During LTBI Treatment

Check liver function tests for:

- Patients with abnormal baseline
- Persons with HIV infection
- Pregnant and post-partum women
- History/risk of liver disease
  - Heavy alcohol ingestion
  - Chronic hepatitis
  - History of injection drug use
  - On two or more meds



# LTBI Treatment Adverse Effects

<u>Isoniazid</u>

- Asymptomatic LFT elevation in 10-20% on INH
  - Usually return to normal even if medication continued
- Clinical hepatitis – 0.1% on INH
  - Can increase depending on other risk factors and medications
  - Severe/fatal very rare but have been reported
- Peripheral neuropathy <0.2%

<u>Rifamycin</u>

- Asymptomatic hyperbilirubinemia 0.6%
- Clinical hepatitis increases when INH + RIF
- Cutaneous – up to 6% of people, usually self limited
- Hypersensitivity reactions - rare

# Back to Our Family

37 y.o. male from Eritrea. Entered U.S. 10/15/2016

05/13/2019 Tspot (+)

32-year-old wife/mother

No prior TB test

05/02/2019 TSpot (+)

17 mo. old Male

No prior TB test (U.S. Born)

05/04/19 TST (+) 14 mm

3 –year- old Male

06/11/2018 Tspot (-)

05/04/2019 TST (+)15 mm

4 –year- old Female

06/11/2018 Tspot (-)

05/04/2019 TST (+) 18mm

13 –year- old Female

05/08/2018 TSpot (-)

05/02/2019 TSpot (+)

15 –year- old Male

05/02/2018 Tspot (+)

No current testing

# 3 year old male

- 3 year old child born in Ethiopia,  received BCG, and  is identified as a contact to his father who was recently diagnosed with smear positive Pulmonary TB. Child entered U.S. from Ethiopia 09/22/2016
- 05/04/2019 TST read as 15mm induration, but 05/07/2019 is significantly >10 mm and ulcerated. Mom noted blistering and then loss of skin. Lesion is clean and healing with granulation tissue visible.
- Child has a known TST positive 02/24/2018 with 20 mm of induration, but negative TSPOT on  06/11/2018. No treatment was given. Evidence of TB infection with ulcerated TST,  believe this represents a true positive.
- Child had a cough which developed over past month, but its was associated with a runny nose. Both cough and URI symptoms now improved, though he has some residual intermittent cough.
- Mother (via language line) notes child well and she has no concerns. He is playful and happy. Plays with siblings. No fever, no difficulty sleeping, good appetite.
- Weight 33 pounds (50%).
- Note dated 05/10/2019 – CXR normal

Diagnosis -> LTBI

Rx -> 3HP

# 3 year old male

- Child started 3HP and had no reported complications with therapy.
- On 06/14/2019 therapy changed to Rifampin 300 mg daily. Father MTB with high level INH resistance.
- He completed 4 months of Rifampin 300mg daily without any interruptions.

Congratulations!

# Thank you

Heartland National TB Center