3HP

MICHIGAN WORLD TB DAY CONFERENCE APRIL 8, 2016

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WHAT IS 3HP?

- **12 weekly doses of INH & Rifapentine (RPT) given by directly observed therapy to prevent TB in individuals with latent *Mycobacterium tuberculosis* infection**
- **For a person ≥ 50 kg. dose is 900 mg. INH & 900 mg. RPT**
- **3 300 mg. INH tablets per dose – 36 total tablets**
- **6 150 mg. RPT tablets per dose – 72 total tablets**

Sterling TR, et al. N Engl J Med 2011
(PREVENT TB Trial
1 of 3 studies done then

3HP

3 per dose / 36 total*

6 per dose / 72 total*

*For person ≥ 50 kg.

PREVENT TB TRIAL

The NEW ENGLAND JOURNAL of MEDICINE

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

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

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PREVENT TB TRIAL

- **Done in Brazil, Canada, Spain, USA**
- **Open label, randomized, prospective**
- **Subjects with high risk of progression from latent *M TB* infection to TB**
- **Enrollment June 2001-February 2008**
  - Followed for 33 months after enrollment
- **Compared 3 HP by DOT to 9 months of INH self supervised**
- **Subjects ≥ 2 years old; 7,731 individuals included in analysis**
  - 161 HIV infected, not on antiretroviral therapy (ART)
- **Was designed as noninferiority trial**
  - Outcome variable TB
  - Was 3HP at least as good as 9 months INH?

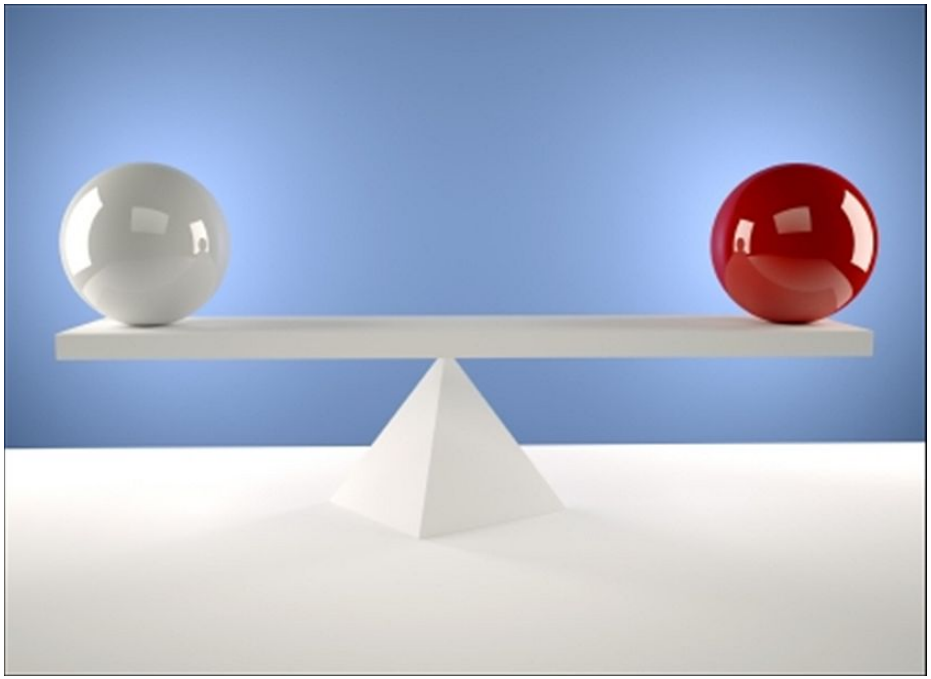
OUTCOME 3HP VS INH

*Permanent discontinuation
** No deaths attributable to study drugs

OUTCOME	3HP	INH	Hazard Ratio / P value
Tuberculosis	7	15	HR 0.38, CI=.15-.99 (adjusted for TB risk factors)
Completion of Regimen	82%	69%	P<0.01
Discontinuation*	18%	31%	P<0.01
Grade 3, 4 adverse effects	1.6%	3.0%	P<0.01
Discontinuation* for adverse effects	4.9%	3.7%	P<0.01
Discontinuation* for possible hypersensitivity	2.9% 6/152 had hypotension	0.4%	P<0.01
Discontinuation* for hepatotoxicity	0.3%	2.0%	P<0.01

WHAT DID PREVENT TB FIND?

- **3HP was noninferior to 9 months self-supervised INH for end point of cases of TB**
- **3HP had a higher completion rate (tolerability)**



CDC RECOMMENDATIONS FOR 3HP*

- **“Healthy” individuals ≥ 12 years old with LTBI**
  - Insufficient data from PREVENT TB & 2 other studies for diseases like diabetes, younger children
  - HIV ok unless on ART
- **3HP NOT recommended for**
  - Children <2 years old because safety & pharmacology of Rifapentine not established
  - HIV-infected individuals on ART because pharmacology unclear and potential drug drug interactions

* Recommendations for 3 HP MMWR Dec 9, 2011

ADD ON TRIALS YOUNG CHILDREN, HIV

- **More pharmacologic data on Rifapentine in children <12 years old became available in 2005**
- **Add-on trial took place after February 16, 2008 for young children & those infected with HIV**
  - Enrollment through December, 2010
  - Follow-up to September, 2013
- **Hong Kong additional site for children**
- **Hong Kong and Peru additional sites for HIV**

RECENT UPDATES CHILDREN ≥ 2 YEARS OLD

- **2005 – data on pharmacokinetics of Rifapentine in children aged 2-11 became known**
  - Enrollment in PREVENT TB was modified to include children
- **This study reported on all children aged 2-17 years enrolled in PREVENT TB & add-on trial– nested cohort**
  - 1,058 participants enrolled June 2001 – December 2010 with follow-up to September, 2013
  - 905 analyzed for efficacy, 1032 for safety

Villarino ME, et al. JAMA Pediatr 2015*

OUTCOME 3HP VS INH IN CHILDREN 2-17 YEARS OLD

OUTCOME	3HP	INH	Hazard Ratio / P value
Tuberculosis	0	3	
Completion of Regimen	88%	80.9%	P=0.003
Grade 3 adverse effects	3 subjects	1 subject	
Discontinuation* for adverse effects	4.9%	3.7%	P<0.01
Grade 4 adverse effect or death	0	0	
Hepatotoxicity	0	0	

RECENT UPDATES HIV-COINFECTED INDIVIDUALS

- **399 HIV-infected individuals with + TB skin tests or who were close contacts of case were analyzed**
- **Median CD4+ ~ 500 cells/mm3**
- **Enrollment required subjects to not start ART within 90 days of enrollment**
  - => Slow enrollment and study ended early
  - Underpowered

Sterling TR, et al. AIDS March, 2016

HIV

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.

RECENT UPDATES HIV

*Permanent discontinuation

OUTCOME	3HP	INH	Hazard Ratio / P value
Tuberculosis Modified Intention to Treat analysis	2 of 206	6 of 193	
Completion of Regimen	89%	64%	P<0.001
Discontinuation* for adverse effects	3.0%	4.0%	NS
Flu-like systemic drug reaction	1.0%	0%	NS
Discontinuation* for hepatotoxicity	1.0%	4.0%	P=0.05

UPDATE: DRUG INTERACTIONS RIFAPENTINE / ART

- Rifapentine, given either once-weekly or daily, has minimal interaction with daily **efavirenz**
- Rifapentine given once-weekly may be given with the integrase strand transfer inhibitor **raltegravir**

REFERENCES FOR INTERACTIONS BETWEEN RIFAPENTINE & ART

15. Farenc C, Doroumian S, Cantalloube C, Perrin L, Esposito V, Cieren-Puiseux I*, et al.* Rifapentine once-weekly dosing effect on efavirenz, emtricitibine and tenofovir PKs. *Conference on Retroviruses and Opportunistic Infections* 2014; **Boston, MA**:Abstract 493.

16. Podany AT, Bao Y, Swindells S, Chaisson RE, Andersen JW, Mwelase T*, et al.* Efavirenz Pharmacokinetics and Pharmacodynamics in HIV-Infected Persons Receiving Rifapentine and Isoniazid for Tuberculosis Prevention. *Clin Infect Dis* 2015; **61(8)**:1322-1327.

17. Weiner M, Egelund EF, Engle M, Kiser M, Prihoda TJ, Gelfond JA*, et al.* Pharmacokinetic interaction of rifapentine and raltegravir in healthy volunteers. *J Antimicrob Chemother* 2014; **69(4)**:1079-1085.

NEW CONCLUSIONS

- **3HP can be safe and effective for children ages 2-17**
- **3HP can be safe and effective for HIV-coinfected individuals with hig CD4+ counts (~ 500 cells/mm3)**
- **We may be moving to being able to use 3HP for HIV-coinfected individuals taking efavirenz or raltegravir**
- **Studies are still needed for effectiveness with efavirenz & raltegravir and HIV-coinfected individuals with lower CD4+ counts**
- **3HP is better tolerated (completion rate is higher) and has less hepatotoxicity in children 2-17 years old and HIV-coinfected individuals not on ART and with good CD4+ counts**

WSUPG TB PROGRAM 3HP DATA 2014, 2015

Program started in mid-2013

53 patients began 3HP in2014

- 44 (83.02%) completed treatment
- 21 (25%) had DOT at home, remainder came to clinic

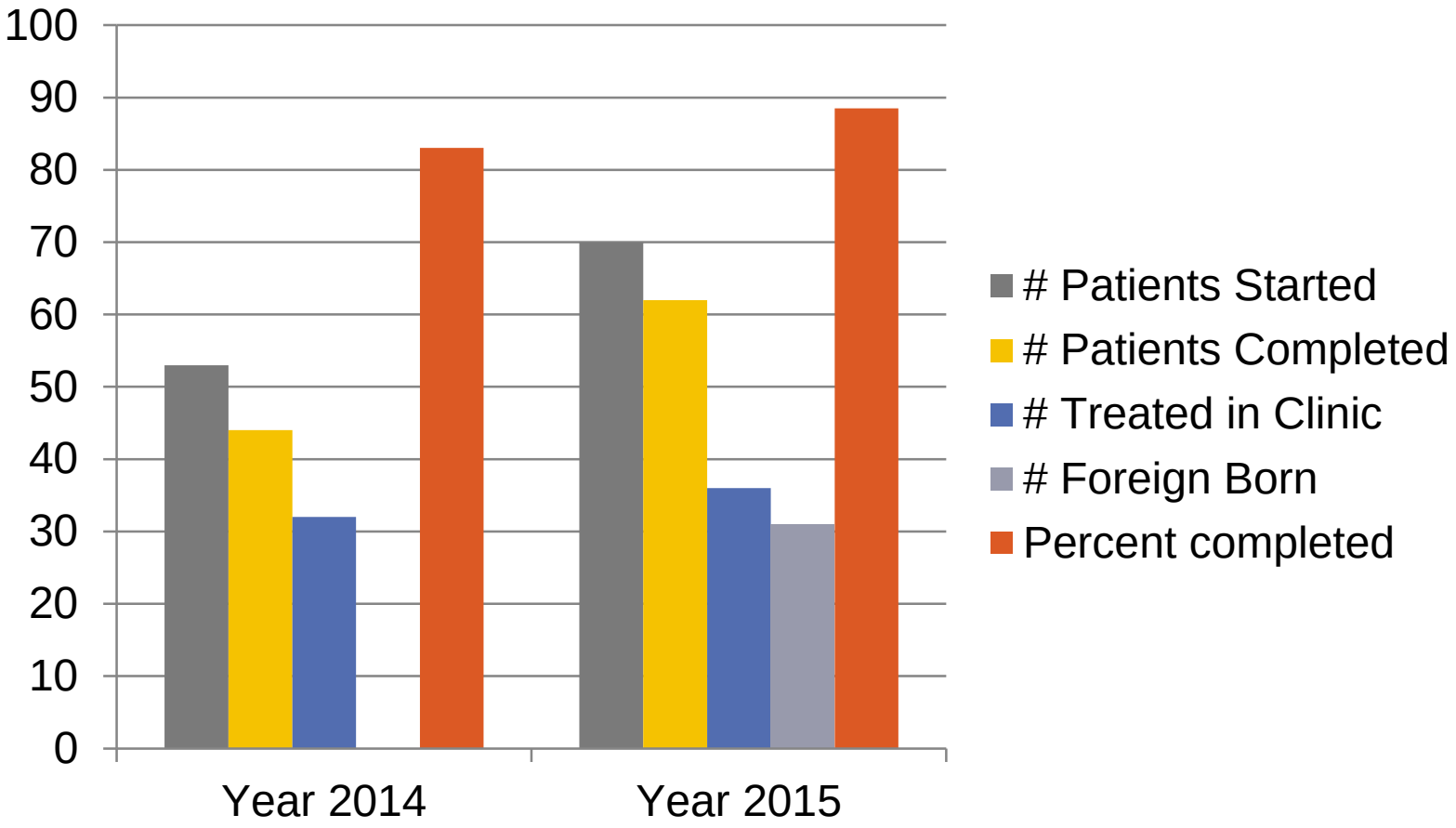
70 patients began 3HP in 2015

- 62 (89.5%) completed treatment
- 36 (51%) had DOT at home, remainder came to clinic

Barriers

- Biggest barrier – lack of access to Rifapentine
  - Manufacturing halted, pharmacy didn't supply it
- Cost is an issue – sometimes can use patient insurance
- More complicated than simply writing prescription

WSUPG TB GROUP
3HP EXPERIENCE 2014 & 2015



PRACTICAL ISSUES WITH 3HP

- **Skipped doses**
  - PREVENT TB definition of completion
    - At least 11 or 12 doses within 16 weeks
    - Doses separated by >72 hours to be counted
    - For children 2-17 at least 11 doses om 10-16 weeks
- **Start – Up**
  - Calendar to record doses, side effects
  - Plan for handling adverse effects
  - Packaging / handling of doses
- **Monitoring**
  - Labs for use only for symptoms, unusual patient issues
  - Careful patient education, symptom monitoring
- **Have a complete medication list**
  - Drug drug interactions a major problem (Rifapentine)

REASONS FOR STOPPING 3HP IN 2015

- **1 developed other serious illness => gap in Rx.**
  - Immunosuppression
  - Restarting Rx
- **1 was found dead at home, likely unrelated**
- **1 stopped, later took Rifampin for 4 months**
- **1 arrested, lost to follow-up**
- **2 lost to follow-up after leaving drug rehab program**
- **2 side effects (1 vague, 1 ongoing nausea)**

- **No hypersensitivity reactions;**
  1 in 2014 severe hives, likely due to INH