

Initial Experiences of Weekly Isoniazid (INH) and Rifapentine (RPT) for Latent TB infection (LTBI): The Post-Marketing Project

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Treatment Choices for Latent Tuberculosis Infection (LTBI)

- 9 months of daily isoniazid
- 9 months of twice weekly isoniazid
- 6 months of daily isoniazid
- 4 months of daily rifampin
- 12 doses of weekly isoniazid and rifapentine
 - up to 900 mg Isoniazid
 - up to 900 mg Rifapentine
 - Known as 12-dose INH-RPT or 3HP
 - DOT only

Characteristics of Rifapentine (RPT)

Drug	Half Life (h)	MIC ₉₀ (µg/ml)	C _{max} /MIC ₉₀	AUC ₂₄ /MIC ₉₀
Rifampin (10 mg/kg)	2.46	0.25	58.44	471
Rifapentine (10 mg/kg)	15.9	0.12	98	2658

In contrast to Rifampin, Rifapentine -

- Stays in the body 7 times longer
- Kills TB organisms at a much lower concentration

J. Grosset '08 IUATLD Keystone

3 Clinical Trials With INH-RPT

- ❑ **Brazil (Jan 01 — July 03)** Schecter et al, AJRCCM 2006
 - 399 Household contacts; INH-RPT vs. 2RZ
 - Excess hepatotoxicity in 2RZ (20 vs. 2 for INH-RPT)
- ❑ **South Africa (Sep 02 — Jun 05)** Martinson et al, NEJM 2011
 - 1148 HIV-infected persons ; 4 arms (INH-RPT, 3HR, 6H, cont. H)
 - Serious adverse events more common in continuous H
 - No significant difference in development of TB among 4 arms
- ❑ **Prevent TB study (TBTC Study 26) multi-site (Jun 01 — Feb 08)** Sterling et al, NEJM 2011
 - 7731 high risk persons in 2 arms; DOT INH-RPT vs. SAT 9H
 - INH-RPT by DOT as effective as 9H in preventing TB; higher completion rate; less hepatotoxicity; more “hypersensitivity”
 - Long term safety monitoring important

CDC Recommendations: 12-dose INH-RPT by DOT

- ❑ 12 once weekly DOT doses of INH-RPT is equivalent to 9 months of daily self-supervised INH for treating LTBI
- ❑ Use in otherwise healthy patients aged ≥12 years with a greater risk of developing TB
 - Contacts
 - Convertors
 - Those with radiographic findings of healed TB
 - HIV-infected patients who are otherwise healthy and not taking anti-retroviral medications
 - For children aged 2-11 INH-RPT can be considered on a case-by-case basis

MMWR Dec 9, 2011

LTBI Treatment and a History of Adverse Events

- ❑ **National Surveillance for Severe Adverse Events (NSSAE)**
 - Approach: Passive surveillance system
 - Challenge: lack of denominator data to estimate incidence and risk ratios
- ❑ **AE monitoring for INH-RPT use in the field needed**
 - INH-RPT well tolerated in treatment trials
 - For both INH and RIF-PZA, fatal liver injuries came to attention only after regimens widely adopted

Post-marketing INH-RPT Project Objectives

- **Monitor for adverse events with 3 month INH-RPT in non-research settings**
 - Track number of patients started on regimen
 - Note if certain populations, risk factors or settings are associated with adverse effects (AE) more often
- **Assess compliance and treatment completion**
- **Assess impact of INH-RPT on programs**
 - Staffing
 - Costs
- **Match patients with TB registry at 2 years**
 - Observational measurement of effectiveness
 - Surveillance for drug-resistant TB after LTBI treatment

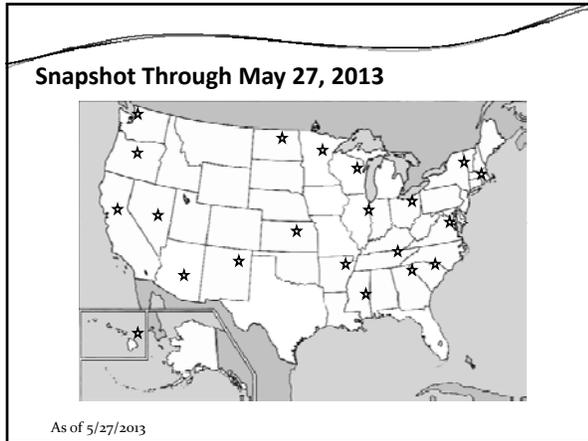
Post-Marketing Surveillance Project Sites

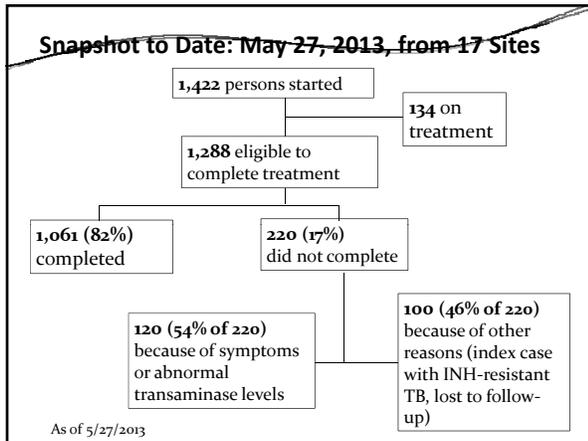
- 18 sites using the regimen, 22 sites contributed to project design and forms
- DOT used for all sites
- Project period: January 2012 through December 2013
- Original target: 4000 patients
- Fewer patients started on INH-RPT due to —staff shortages, drug-resistant TB outbreaks, drug shortages, unable to get state approval of regimen, and waiting to get local IRB approval



(dated 5/24/2013)

**Findings to Date
Preliminary Results**





Severe Adverse Events

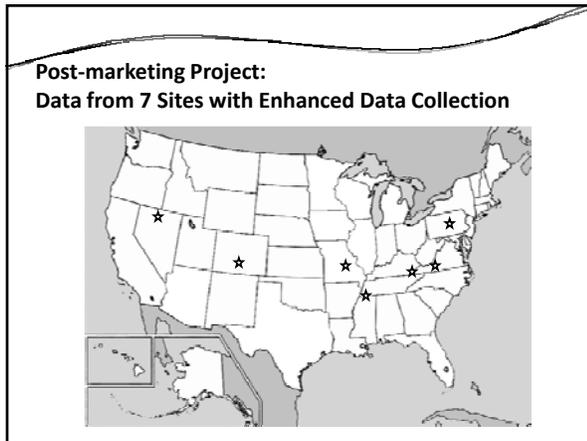
- Severe AE: any patient who was hospitalized or died while on LTBI therapy (NSSAE definition)
- 14 reports of hospitalizations
 - 6 on-site CDC investigations complete
 - 4 investigations in progress
 - 4 have not been initiated
 - No deaths
 - No serious or permanent medical sequelae
- Coordination with national NSSAE project under Krista Powell and Lilia Manangan

Preliminary Comparison Between TBTC Prevent TB Study and Post-marketing Project for Treatment Discontinuation Rates by Reason, 16 Sites

Reason for Discontinuation	Prevent TB, Study 26	%	Post-marketing Project	%
Discontinued due to adverse event	196/3986	4.9 [†]	120/1288	9.3 [†]
Hepatotoxicity *	18/4040	0.4	8/1288	0.6
Rash only	31/4040	0.8	14/1288	1.1
Hospitalizations	56/3986	1.4	14/1422	1.0
Death	4/3986	0.1	0	

*Defined as ALT 3xULN for symptomatic persons and 5xULN for asymptomatic persons
[†]These rates from Prevent TB Study 26 and Post-marketing Project are not directly comparable due to differences in definition

As of 5/27/2013

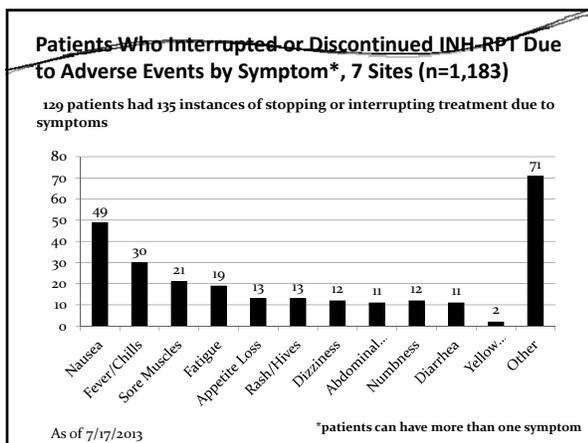


**Patient Demographics Profile
Post-Marketing Project, 7 sites (n=1,183)**

Patients	Number	%	Race*	Number	%
Male	608	51.4	White	457	38.6
Female	569	48.1	Black	538	45.5
Missing Gender	6	0.5	Native American	8	0.7
Hispanic	171	14.5	Asian	147	12.4
Non-Hispanic	993	83.9	Pacific Islander	10	0.9
Missing Ethnicity	19	1.6	Unknown Race	5	0.4
			Other	11	0.9
			Missing Race	7	0.6

* Includes Hispanic and non-Hispanic

As of 5/27/2013



"Other" Reasons Reported for Patients Who Interrupted or Discontinued INH-RPT, 7 Sites (n=1,183)

71 "other" reasons among 135 instances of stopping or interrupting treatment because of symptoms*

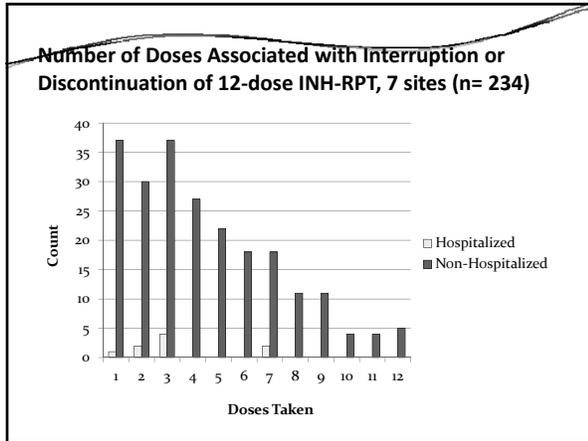
- > 15 instances of headache
- > 19 instances of elevation in liver transaminase levels
- > 3 pregnancies
- > The following reasons were reported in ≤ 2 events:
 - Swollen lips
 - Swollen tongue
 - Difficulty breathing
 - Menstrual irregularities
 - Blurred vision
 - Dry mouth
 - Platelet drop from 212 to 85
 - Gastrointestinal bleeding
 - Hip pain
 - Change in taste sensation
 - Body ache NOS
 - Muscle tightness
 - Low blood pressure
 - Blood pressure NOS
 - Swollen lymph nodes
 - Eye Pain
 - Weakness
 - Itching
 - Chest pain
 - Confusion

As of 7/17/2013 *patients can have more than one reason

Characteristics of AEs Associated with Interruption or Discontinuation of 12-dose INH-RPT, 7 sites (n=234)

	Non-severe (n=225)	%	Severe (n=9)	%
Symptom onset <2 hrs.	61	27	0	0
2-48 hrs.	104	46	5	56
>48 hrs.	27	12	1	11
Unknown onset	33	15	3	33
Duration <24 hrs.	58	26	5	56
Duration >24 hrs.	107	48	1	11
Unknown duration	60	27	3	33

As of 5/27/2013



Location Specific Findings

Homeless Contacts Receiving 12-Dose INH-RPT for LTBI Treatment, Two Post-marketing Project Sites

- Mississippi - 48 homeless contacts
 - 39 (81%) completed treatment
 - 9 (18%) did not complete INH-RPT > 1 (2%) because of an adverse event
- Kane County - 35 homeless contacts
 - 11 (31%) still in treatment
 - 24 completed (of 24 eligible to complete)
 - None stopped or lost to follow-up

As of 5/27/2013

Foreign-born Students Receiving 12-Dose INH-RPT for LTBI Treatment, Four Post-marketing Project Sites

- Kansas – 37 students
 - 35 (95%) completed
 - 2 (5%) discontinued INH-RPT because of adverse events
- Minnesota – 12 students
 - 11 (92%) completed
 - 1 (8%) discontinued INH-RPT because of an adverse event
- UC San Diego – 23 students
 - 6 in treatment
 - 15/17 (88%) completed
 - 2/17 (12%) because of adverse events
- Arkansas – 26 students
 - 25 (95%) completed
 - 1 (4%) discontinued because of an adverse event

As of 5/27/2013

Virginia’s Experience During the Post-marketing Project

- Information available for 68 persons
 - SEND IN THE COMPLETED DOT LOG SHEETS!
- 56 of the 68 completed– 82% completion rate!
- 12 stopped for various reasons
 - 6 for adverse reactions
 - 5 lost to follow-up
 - 2 “other” reasons
- **Very important**
 - No deaths
 - No hospitalizations

**Virginia’s Experience During the Post-marketing Project
Adverse Event Reports**

- Adverse event reports submitted on 11 clients
 - 3 HP discontinued on 6
 - 1 changed to INH to finish treatment for TBI
 - 4 discontinued treatment altogether
 - Symptom onset
 - < 2 hours – 2 (18%)
 - 2-48 hours – 4 (36%)
 - > 48 hours – 4 (36%)
 - Symptom duration
 - < 1 day – 3 (27%)
 - ≥ 1 day – 6 (54%)
 - 5 continued 3 HP regimen after evaluation

Virginia's Experience During the Post-marketing Project Symptoms for Which Treatment Stopped

- Six patients stopped treatment due to adverse events
- Reported symptoms for stoppage included:
 - Rash/hives – 4 patients
 - Nausea/vomiting – 3 patients
 - Appetite loss – 1 patient
 - Diarrhea - 1 patient
 - Abdominal pain - 1 patient
 - Sore muscles - 1 patient

*patients can have more than one symptom

Summary

- Initial field experience is similar to treatment trial experiences
- High completions rates, notably in difficult populations
- Rashes and nausea most common reasons for stopping
- No deaths or severe organ damage detected nationally
 - No deaths or hospitalizations in Virginia

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