

Implementation of Isoniazid/Rifapentine for Latent TB Infection in Virginia



Characteristics of Rifapentine

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 2001 —July 2003)
 - 399 Household contacts
 - DOT 3 months of INH-RPT vs. 2 months of RIF-PZA
 - Enrollment stopped due to hepatotoxicity from RIF-PZA
 - 3 TB cases for INH-RPT vs. 1 for RIF-PZA
- ▶ South Africa (Sep 2002 —Jun 2005)
 - 1148 HIV-infected persons not on HAART
 - 3 months of weekly INH-RPT vs. 3 months of twice-weekly INH-RIF vs. 6 months of daily INH vs. daily INH indefinitely
 - No difference in 4 arms
- ▶ United States, Canada, Brazil, Spain (Jun 2001 — Feb 2008)

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Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

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ABSTRACT

BACKGROUND
Treatment of latent Mycobacterium tuberculosis infection is an essential component of tuberculosis control and elimination. The current standard regimen of isoniazid for

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Comparison by Treatment Regimen

	INH-RPT	INH only	P-value
Total =7731			
N (person-years observed)	3986 (10327)	3745 (9619)	
Developed TB (%)*	7 (0.19%)	15 (0.43%)	
Treatment Completion	82%	69%	<0.001
Drug discontinuation from adverse event	4.9%	3.7%	0.009
Drug related hepatotoxicity	0.4%	2.7%	<0.001
Possible hypersensitivity reaction	2.9%	0.4%	<0.001

*non-inferior

- Virginia Specific Guidelines**
- ▶ VDH specific guidelines on TB control web www.vdh.virginia.gov/tb
 - DOT mandatory for this regimen
 - Completion defined as 11 or 12 doses within 16 weeks
 - “Weekly” doses must be separated by > 72 hours to be countable

Monitoring

- ▶ Weekly monitoring for side effects at each DOT visit
- ▶ Monthly clinical assessment including brief physical examination for jaundice, tenderness of liver, or rashes
- ▶ Baseline LFTs for the following clients:
 - HIV-infected clients
 - Clients with liver disorders
 - Clients in the immediate postpartum i.e. < 3 months after delivery
 - Clients with regular alcohol usage
 - Testing clients on other hepatotoxic medications should be considered on a case by case basis.
- ▶ Monthly monitoring of LFTs is not necessary unless baseline testing is abnormal or the client is at risk for liver disease.

Early Usage in Virginia

- ▶ Contact Investigation in Correctional Facility
 - Reported adverse events
 - Reaction likely to tyramine containing foods
 - Likely due to INH
 - Thrombocytopenia
- ▶ A Metro Health District
 - > 25 started
 - Reported adverse events/side effects
 - Headache
 - Abdominal pain
 - Rash
 - One stopped for flu-like symptoms

A surprise windfall

- ▶ Large supply available late June 2012
 - Treatment for ~385 persons+
- ▶ Available first come, first served statewide through state pharmacy
 - For individuals without other insurance options

Current Usage in Virginia

- ▶ Almost 70 persons started 3HP through end of September
- ▶ 1 reported client with adverse events to date
 - Sore throat after 2 doses of med
 - Lasted 1 day each week
 - Medication continued
 - Numbness and tingling in extremities
 - B6 added
 - Medication continued
- ▶ Exponential increase each month in usage

LTBI Treatment and a History of Adverse Events (AE)

“Those who do not remember the past are condemned to repeat it.....”

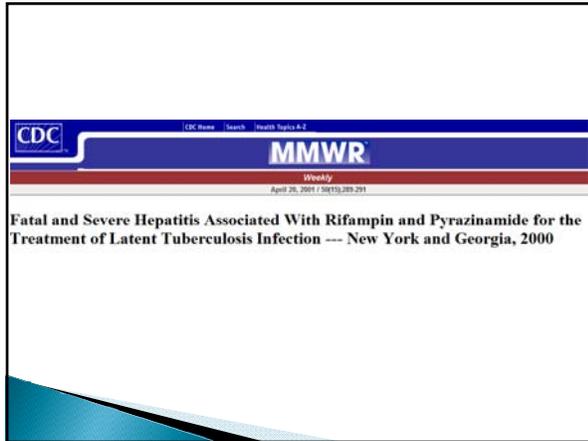
◦ Santayana

INH Mono-therapy for LTBI

- ▶ 1972 report among 2321 persons treated; 19 (0.8%) developed INH-associated hepatitis, 2 died
- ▶ Large USPHS study with 13,838 persons from 21 cities. 0.1% rate of INH-associated hepatitis, 8 deaths occurred, 7 occurred in 1 city
- ▶ 1975-1991 6 studies published with varying results. CDC recommends INH for <35 years old
- ▶ 1989-1995 Seattle prospective study follows 11,000 on INH – 11 (0.1%) had reversible hepatitis, no deaths
- ▶ 2000 CDC recommends INH for LTBI treatment irrespective of age

2 Months of RIF-PZA (RZ) for LTBI Treatment

- ▶ Multi-site study (U.S., Mexico, Haiti, Brazil) 1992-1997
 - 6 INH vs. 2 RZ daily; 1583 HIV-infected patients
 - AE-related stopped treatment : 6% INH vs.10% RZ
 - Treatment completion 69% INH vs. 80% RZ
 - More nausea/vomiting RZ; more hepatitis INH
- ▶ Zambia 1992-1996:
 - 6 INH vs. 3 RZ biw; 1053 HIV-infected patients
 - TB and hepatitis rates no different
- ▶ Haiti 1990-1994: 6 INH vs. 2 RZ biw; 750 HIV-infected
 - More abdominal pain and diarrhea INH
- ▶ Florida study (n=135) INH vs. RZ biw
 - Treatment completion 61% INH vs. 93% RZ no hepatitis

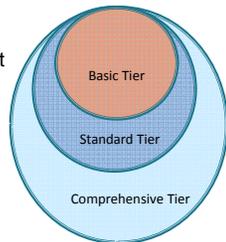


Post-marketing Project Objectives

- ▶ Assess the use of 3HP in non-research settings for adverse effects
 - Collect 'denominator data' prospectively
 - Note if certain populations, risk factors or settings are more often associated with adverse effects
- ▶ Assess adherence and treatment completion
- ▶ Assess impact of 3HP on programs
 - Staffing
 - Costs
- ▶ Match patients with TB registry at 2 years

Information To Be Collected by Programs

- ▶ Essential data – core set of information
 - Number of patients started and completed
 - Weekly screening for adverse effects
 - Demographics
 - Notification of adverse events
- ▶ Full complement – ideal assessment
 - Epidemiological risk factors
 - Medical risk factors
 - Medications



Project Sites



- Arkansas
- Arizona – Pima
- Bureau of Prisons
- California
- Georgia
- Hawaii
- Illinois – Kane
- Kansas
- Mississippi
- Minnesota
- New Mexico
- Nevada
- New York
- North Dakota
- Ohio – Columbus
- Oregon
- South Carolina
- Seattle WA
- Tennessee
- Virginia
- Wisconsin

An Opportunity to Make a Difference

- ▶ Participating in CDC Post marketing Surveillance Project
- ▶ VDH IRB for participation approved
- ▶ Data collection forms modified to use as chart forms
- ▶ Monthly list of persons starting 3HP
- ▶ Fax completed 3HP DOT sheet to 804-371-0248

If adverse reactions occur:

- ▶ Call TB Control
 - **Immediately if hospitalization or death!**
- ▶ TB Control – 804-864-7906
 - Jane Moore – 804-864-7920
 - Debbie Staley – 804-864-7972
 - Denise Dodge – 804-864-7968
- ▶ Complete Adverse reaction form
 - Fax to 804-371-0248

Other Activities

- ▶ Planning analysis of LTBI completion rates
 - Two cohorts
 - persons starting on "windfall" supply
 - infected contacts from 2010 and 2011

2010 & 2011 Contacts

For 2010

- ▶ 3409 contacts identified
- ▶ 3054 were evaluated
- ▶ 270 of those found to have LTBI
 - 142 started treatment
 - 106 completed treatment
- ▶ Only 39% of infected contacts completed treatment!

For 2011

- ▶ 1887 contacts identified
- ▶ 1693 were evaluated
- ▶ 301 of those found to have LTBI
 - 155 started treatment
 - 46 completed treatment to date
- ▶ Only 15% of infected contacts completed treatment!

**3HP – a GAME
CHANGER?**



Anecdotal success reported in hard to reach populations such as homeless and substance abusers
