Mississippi State Department of Health

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Twelve Doses for Tuberculosis Prevention – Review of a New Evidenced Based Regimen

Introduction: Prevention of active Tuberculosis (TB) by treating latent TB infections (LTBI) has long been a key component in the strategy to eliminate TB in both the U.S. and Mississippi. Traditionally the treatment of LTBI has been a difficult and lengthy process extending over nine months; frequently impacted by patient non-adherence. A new *directly observed treatment regimen for LTBI* was presented at the American Thoracic Society International Conference in May 2011 and then published in the New England Journal of Medicine in December 2011. The new regimen consists of 12 weeks of once weekly directly observed doses of rifapentine (RPT) and isoniazid (INH), and is recommended as an equal alternative to the standard nine month INH regimen, but with potentially improved treatment completion rates.

In the summer of 2011 the Mississippi State Department of Health (MSDH) began utilizing the new combined regimen in two pilot sites in the state and expanded its availability to all local Health Department clinics for use in appropriate candidates in April 2012. The combined twelve week INH-RPT regimen is more costly than the usual nine month INH regimen with increased costs in both nursing time and effort, and laboratory tests. However, it is projected that the initial costs will be offset by increased completion rates, decreased morbidity and a reduction in future transmission of TB. The standard nine month regimen of INH will still be available and will remain a mainstay for LTBI treatment, but for those patients who qualify, the new regimen promises to be efficient and convenient.

What follows is excerpted from the recently published study that compares the new combined regimen to nine months of INH. Additionally a brief summary of the use of INH-RPT in Mississippi is provided.

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

The current standard regimen for the treatment of latent *Mycobacterium tuberculosis (M. tuberculosis)* infection is 9 months of daily isoniazid. The efficacy for isoniazid was found to be 69 to 93% in a study that was published in 1982 (before the era of widespread infection with the human immunodeficiency virus [HIV]). However, the effectiveness of isoniazid is limited by treatment completion rates of 30 to 64%, owing in part to the long duration of the regimen. Isoniazid induced hepatotoxicity is also a concern. Rifapentine, a rifamycin derivative with a long half-life and greater potency against *M. tuberculosis* than rifampin, has shown promise for treating latent tuberculosis in animal models. Since weekly rifapentine and isoniazid are effective in the continuation phase of tuberculosis treatment in patients with a low bacillary burden, it was reasoned that a 3-month course of these agents would be effective for treating latent *M. tuberculosis*. A shortened course of intermittent treatment would also be more convenient for both patients and public-health programs responsible for ensuring treatment completion

The study was an open-label, randomized noninferiority trial comparing 3 months (12 weeks) of directly observed once-weekly therapy with rifapentine 900 mg plus isoniazid 900 mg, with isoniazid 300 mg daily self administered for nine months. Multiple sites enrolled patients from 2001 to 2008. Patients were at high risk for progression from LTBI to active disease. All subjects were required to be at least 12 years of age and have had close contact to a patient with culture confirmed tuberculosis (within 2 years before enrollment) regardless of tuberculin skin test results, or have other situations that would put them at higher risk for progression to active TB such as a recent positive tuberculin skin test, or a positive tuberculin skin test with HIV infection or with fibrotic changes on chest radiography consistent with previously untreated tuberculosis. In 2005 children aged 2-4 were also enrolled in the study. The number of children in this age range who have received INH-RPT is insufficient for assessing tolerability and efficacy.

Patients were followed for 33 months with the primary study endpoint of culture-confirmed TB in subjects 18 years of age or older, and culture-confirmed or clinical TB in children under the age of 18 years. Active TB developed in 7 of 3986 (cumulative rate 0.19%) patients in the RPT/INH group and in 15 of 3745 (cumulative rate of 0.43%) patients in the nine month INH group. Treatment completion in the INH-RPT group was 82.1% but only 69% in the INH group ($P<0.001$).

While the rates of permanent drug discontinuation due to an adverse event were higher in the INH-RPT group (4.9%) compared to the INH alone group (3.7%), drug related hepatotoxicity was less than the INH alone group (0.4% vs 2.7%, respectively, P<0.0001). Hypersensitivity reactions were more common among the INH-RPT group. Six of the 152 hypersensitivity reactions included hypotension. No deaths were attributed to any study drugs.

The study showed that directly observed, once weekly therapy with rifapentine plus isoniazid for 3 months was as effective as self-administered daily isoniazid for 9 months, with the rate of tuberculosis in the combination-therapy group approximately half that in the isoniazid-only group. The combination-therapy group had higher treatment completion rates and a toxicity profile similar to that of the isoniazid-only group, with lower rates of adverse events, severe adverse events, and hepatotoxicity attributable to the study drug. This simple, effective new regimen has a potential public-health benefit.

As with any patient, active disease must be ruled out prior to initiating treatment for LTBI. This is particularly important in patients when considering this new combination therapy since receiving this combination while a patient has active disease will easily lead to resistance to both isoniazid and rifampin.

The Centers for Disease Control and Prevention (CDC) recommendations were released in April 2012, and state that the new combination therapy should **ONLY be given under direct observation.**

Use of INH-RPT in Mississippi

In summer 2011, MSDH began a pilot project implementing the use of INH-RPT at two sites, Hinds County and Public Health District VIII (Hattiesburg area). In November the project was expanded to include Public Health Districts II (Tupelo area) and IX (Gulf Coast). MSDH expanded the availability of the combined regimen statewide in April 2012.

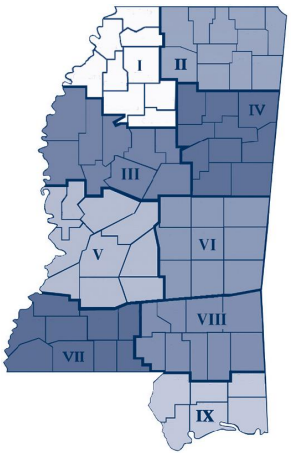
The 12–dose regimen of INH and RPT does not replace other recommended LTBI treatment regimens; it is another effective regimen option for *otherwise healthy* patients aged ≥12 years who have a predictive factor for greater likelihood of active TB developing. These factors include recent exposure to contagious TB, conversion from negative to positive on an indirect test for infection (i.e. interferon-γ release assay or tuberculin test), and radiographic findings of healed pulmonary TB. It should be noted that while the regimen is once weekly it consists of nine tablets.

In Mississippi this regimen is not recommended for

- Children younger than 2 years old, INH is the recommended regimen for children aged 2-11 years,
- People with HIV/AIDS who are taking antiretroviral treatment,
- People presumed to be infected with INH or RIF-resistant *M. tuberculosis*,
- Pregnant or nursing women or women expecting to become pregnant within the 12–week regimen
- History of intolerance to INH or rifampin
- Individuals receiving other medications that interact with rifapentine (RPT) and levels of RPT or the interacting drug cannot be regulated.

The patients undergo weekly assessments and at least monthly laboratory tests to monitor for potential adverse reactions including hepatotoxicity. Close observation for drug hypersensitivity reactions, particularly hypotension or thrombocytopenia is done. If hypotension requiring intravenous fluid support develops, then INH-RPT should be discontinued. Patients with dizziness can be treated with rest or oral fluids with the option for continuing treatment under observation.

As of May 2012, a total of 191 LTBI patients have been started on the combined therapy and 111 of these should have completed therapy. Seventy-three percent (79 of 111) of patients have completed therapy. Of the 32 patients no longer on INH-RPT, 26 had an adverse reaction or a perceived adverse reaction. Six had elevated liver tests but three were associated with alcohol. Abdominal complaints were the most common complaints. Other reasons for not completing the regimen included moving out of state, lost to follow up or patient refusal.



Mississippi
Provisional Reportable Disease Statistics
May 2012

		Public Health District									State Totals*			
		I	II	III	IV	V	VI	VII	VIII	IX	May 2012	May 2011	YTD 2012	YTD 2011
Sexually Transmitted Diseases	**Primary & Secondary Syphilis**	0	0	0	1	6	1	0	0	1	**9**	17	71	56
	Early Latent Syphilis	3	2	2	2	11	2	0	2	3	**27**	36	113	136
	Gonorrhea	69	41	73	37	154	35	17	53	51	**530**	494	2,812	2,276
	Chlamydia	261	187	245	129	465	164	89	173	202	**1,915**	1,758	10,454	8,731
	HIV Disease	7	3	7	1	24	2	4	2	7	**57**	57	250	281
Myco-bacterial Diseases	**Pulmonary Tuberculosis (TB)**	0	0	2	0	2	0	1	1	1	**7**	5	30	33
	Extrapulmonary TB	0	1	0	0	0	0	0	0	0	**1**	1	6	4
	Mycobacteria Other Than TB	2	3	1	1	4	5	1	0	1	**18**	33	113	156
Vaccine Preventable Diseases	**Diphtheria**	0	0	0	0	0	0	0	0	0	**0**	0	0	0
	Pertussis	0	0	1	0	0	0	0	0	1	**2**	1	33	9
	Tetanus	0	0	0	0	0	0	0	0	0	**0**	0	1	0
	Poliomyelitis	0	0	0	0	0	0	0	0	0	**0**	0	0	0
	Measles	0	0	0	0	0	0	0	0	0	**0**	0	0	0
	Mumps	0	0	0	0	0	0	0	0	0	**0**	0	1	2
	Hepatitis B (acute)	0	0	0	2	0	0	0	1	3	**6**	5	27	19
	Invasive *H. influenzae* disease	0	0	0	0	0	1	0	0	1	**2**	6	10	12
	Invasive Meningococcal disease	0	0	0	0	0	0	0	0	0	**0**	0	3	2
Enteric Diseases	**Hepatitis A (acute)**	1	0	0	0	0	0	0	0	0	**1**	1	2	3
	Salmonellosis	9	18	2	12	14	8	4	5	15	**87**	83	239	211
	Shigellosis	1	2	0	0	6	0	0	1	5	**15**	17	111	53
	Campylobacteriosis	1	1	0	0	1	1	0	1	1	**6**	6	29	30
	***E. coli* O157:H7/shiga toxin-producing *E. coli* (STEC)/HUS**	0	0	0	0	0	0	0	0	0	**0**	2	7	8
Zoonotic Diseases	**Animal Rabies (bats)**	0	0	0	0	0	0	0	0	0	**0**	0	1	1
	Lyme disease	0	0	0	0	0	0	0	0	0	**0**	0	0	0
	Rocky Mountain spotted fever	0	1	0	0	1	0	0	0	0	**2**	2	3	6
	West Nile virus	0	0	0	0	0	0	0	0	0	**0**	0	0	1

*Totals include reports from Department of Corrections and those not reported from a specific District.

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Nine months of INH will continue to be offered to LTBI candidates. In 2010, 2058 individuals started treatment for LTBI and of those 1557 (76%) completed therapy. In 2011 more than 1500 patients started therapy; final completion rates are not yet available due to the prolonged treatment requirements with INH. In Mississippi the goal is that at least 85% of patients starting therapy for LTBI will complete treatment.

Mississippi continues to work to eliminate TB. Prevention of active disease is a priority among LTBI patients with recent exposure to active TB cases (within past two years) or patients with other conditions that place them at higher risk for the development of active TB. The new 12 week regimen has the potential to increase the numbers who complete treatment for LTBI. MSDH is working with CDC and other sites to closely follow implementation of this regimen.

All patients with positive tuberculin skin tests or positive interferon-gamma release assays (IGRAs) may be referred to MSDH for evaluation and treatment. Please feel free to contact the MSDH Office of Tuberculosis and Refugee Health with questions at 601-576-7700 or the Office of Epidemiology at 601-576-7725.

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References:

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- CDC. Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. MMWR 2011; 60:1650-53.