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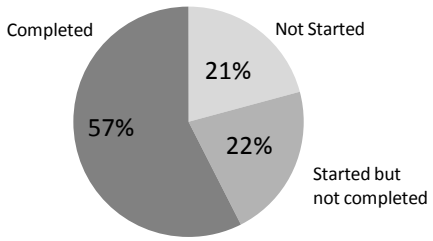
OREGON PUBLIC HEALTH DIVISION • OREGON HEALTH AUTHORITY

TREAT LATENT TB IN JUST 12 WEEKS!

The incidence of tuberculosis disease continues to fall in Oregon and in the United States. During 2011, a mere 74 cases of TB disease were reported in Oregon. Treating the remaining reservoir of latent tuberculosis infection (LTBI) in the community is an essential step towards keeping the incidence of TB disease low. LTBI is not reportable, so the number of infected Oregonians is unknown. However, the National Health and Nutrition Examination Survey indicates that approximately 4% of the U.S. population (4% of Oregon's population is approximately 150,000 people) have LTBI.[1]

The standard current treatment for LTBI is 9 long months of daily isoniazid (INH). The risk of developing active tuberculosis following exposure varies widely by age and underlying immune status. However, most cases occur within two years of exposure — about half of them within one year.[1] Local public health nurses try to administer tuberculin skin tests (TSTs) and to offer LTBI treatment to all newly infected contacts of active TB cases. Despite aggressive public health efforts, which included phone calls and home visits, only 57% of TST-positive persons with clear exposures to patients with active tuberculosis completed treatment during 2006–2011 (Figure 1). In medical settings where close follow-up and assistance with adherence are not feasible, the proportion of persons completing treatment for LTBI is probably even lower.

Figure 1. TB case contacts with LTBI, percentages starting and completing treatment, Oregon 2006–2011



THE NEW LTBI REGIMEN

On December 9, 2011, the Centers for Disease Control and Prevention (CDC) endorsed a new, shorter treatment regimen as an alternative to the standard 9-month course of INH for LTBI.[2] The regimen consists of just 12 weekly oral doses of INH plus rifapentine (INH-RPT) taken under the direct observation of a health worker or representative (i.e., directly observed therapy [DOT]).

Table 1. Dosing for once weekly isoniazid-rifapentine regimen

Drug	Dosage	Max. dose
INH	15 mg/kg rounded to nearest 50 or 100mg	900 mg
Rifapentine	10.0 – 14.0 kg = 300 mg	
	14.1 – 25.0 kg = 450 mg	
	25.1 – 32.0 kg = 600 mg	
	32.1 – 49.9 kg = 750 mg >50 k = 900 mg	

In a big* randomized trial, 82% of patients assigned to the 12-dose regimen (INH-RPT) and 69% of the INH group completed the regimen. The risk of active TB disease during 33 months of follow-up was 62% lower in the INH-RPT group.[3] Who says no free lunch? And, with dessert!: drug discontinuations were lower (18% vs. 31%) for the INH-RPT group; and just 0.3% of INH-RPT patients permanently discontinued their meds because of hepatotoxicity, compared to 2.0% of those taking the standard INH regimen.†

Before starting INH-RPT (or any other regimen) for LTBI, one should rule out active TB disease by asking the patient about symptoms and checking a chest X-ray. INH-RPT should *not* be used in the following:

- children <12 years of age
- persons with HIV infection who are taking antiretrovirals
- pregnant women
- persons who have had adverse reactions to either INH or rifampin
- persons who might have acquired their latent TB infection by exposure to someone with INH- or rifampin-resistant TB.

Don't forget that, like rifampin, rifapentine increases cytochrome P450-related metabolism of many medications, and can decrease effectiveness of other drugs taken concurrently.[2] For this reason, INH-RPT should not be used in patients taking other P450-metabolized medications that have narrow therapeutic ranges — such as methadone, phenytoin, or warfarin — except with careful monitoring. Women using hormonal birth control may enjoy renewed fertility unless they employ a barrier method. Patients with peripheral neuropathy or risk factors for same should take pyridoxine (Vitamin B6), 25–50 mg daily. See the fact sheet on our web site for all of the nitty-gritty details on baseline labs, monitoring patients, and potential drug interactions.‡ Key points for patient education include the need and rationale for DOT, possible side effects, and the risks of alcohol use during treatment. Also, save yourself panicky calls from patients by warning them that both rifapentine and rifampin will turn urine, saliva, tears and sweat orange, and stain contact lenses and dentures. Look for CDC's patient education materials on INH-RPT on their website.∫

DO YOU REALLY HAVE TO WATCH PATIENTS TAKE THEIR MEDICINE?

To ensure patient adherence, the INH-RPT trial employed DOT. We lack evidence to assert that completion rates or effectiveness of the shorter regimen would be comparable under self-administered, unobserved conditions. Accordingly, CDC currently recommends

* it was *way* big: 7,731 subjects

† Hepatotoxicity aside, however, more patients on the INH-RPT regimen discontinued permanently for other adverse effects.

‡ https://apps.state.or.us/cf1/DHSforms/Forms/Served/le8353.pdf.

∫ www.cdc.gov/tb/publications/pamphlets/12-doseregimen.htm

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DOT for all patients treated with INH-RPT. Research is underway to investigate the efficacy of INH-RPT when self-administered. For the time being, DOT should be the rule. Though DOT may seem daunting, it can be accomplished by a single weekly patient visit to a clinic or pharmacy. Any professional, including medical and office assistants, and pharmacy technicians, can be trained to provide DOT. DOT should include a review for any side effects — particularly those related to hepatoxicity; observation of the patient swallowing each pill; and documentation. Those providing DOT must be instructed to report any side effect immediately to the treating clinician. DOT training materials are available from Oregon's TB Control Program (www.healthoregon.org/tb) upon request. If the patient cannot visit a clinic or office weekly, modified DOT could be accomplished with technology such as Skype™, cell phone video or other telemedicine interfaces with the patient.

COSTS

Recently, Sanofi-aventis announced a decreased price of rifapentine for public health departments to $1.71 per 150-mg pill. Since the typical adult takes 900 mg each week on the INH-RPT regimen, and INH costs pennies a pill, medication costs for public health will now run about $123 per person for the whole course.¶ Though this remains higher than the cost of 9 months of INH, it begins to approach affordability for public health. When one takes into account all related health and economic costs and benefits, such as clinic visits, lost work, and cases of TB disease averted, INH-RPT looks to be cost effective compared to INH for 9 months.[4] Health economists we're not, but we did some back of the napkin calculations (Napkin). Over the 5 years from 2006 through 2010, had we been using the INH-RPT regimen for just infected contacts to cases of active TB disease, and completion rates were the same as reported during the trials, we would have prevented 24 additional cases of TB disease.

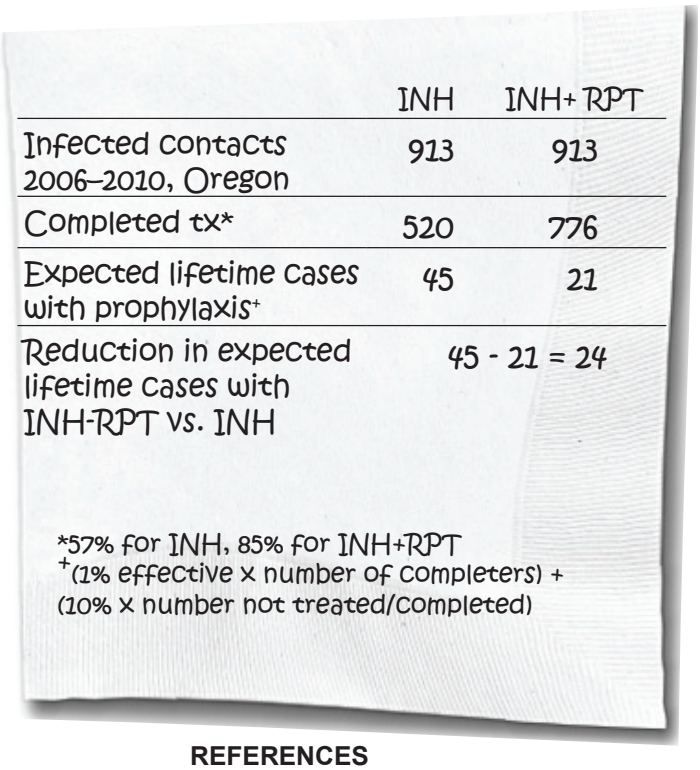
JUST CHOKE 'EM DOWN!

Most adults over 50 kg need to take six 150-mg rifapentine pills and two to three 300-mg INH pills per visit (Table 1, *verso*). The sheer number of pills (9) to ingest all at once might be a barrier for some. New formulations with larger dosage per tablet and fixed-dose INH-RPT combinations are in development.

SEVERE DRUG REACTIONS

Data collected within several large clinical trials suggest a safety profile similar to INH alone. However, such trials are not designed to identify rare events. As always with a new drug or new use of existing drugs, rare serious side effects could be discovered after this regimen is administered to larger numbers of patients. In the event that a patient experiences a serious reaction while on the INH-RPT regimen or even just INH alone, contact the OHA TB Program at 971-673-0169 so that we can report it to CDC. Also, report serious adverse events to FDA's Medwatch.**

Napkin. Estimated active TB cases prevented if INH-RPT replaced INH for infected contacts



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¶12 weeks x 6 pills/week x $1.71/pill

**www.fda.gov/Safety/MedWatch/HowToReport/default.htm