

**USE OF RIFAPENTINE FOR THE TREATMENT OF PULMONARY TUBERCULOSIS IN THE CHEST CENTERS**

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**EFFECTIVE DATE:            JANUARY 1, 2003 (Revised 2/18/03) (Figure revised 12/11/03)****POLICY:**

1. Rifapentine (Priftin®), a long-acting cyclopentyl-substituted rifamycin approved by the FDA for the treatment of tuberculosis, will be used in the DOHMH chest centers from January 1, 2003.
2. Rifapentine 600 mg plus isoniazid 900 mg should be given once a week only under directly observed therapy (DOT) in the *continuation phase* of treatment of drug susceptible pulmonary tuberculosis in patients who (1) are HIV-negative; (2) do not have cavitation on their *initial* chest radiograph; and (3) have a negative sputum smear at the end of 2 months of intensive phase of treatment.
3. If there is no sputum culture conversion at the end of the two-month intensive phase of treatment, the continuation phase of treatment should be extended to seven months (i.e., a total of nine months of therapy).
4. Rifapentine should not be used in HIV-infected patients because of the increased risk of acquired rifamycin resistance. Therefore, a negative HIV test must be documented before a patient is placed on rifapentine.
5. Rifapentine should not be used in pregnant women or children under the age of 12.

**BACKGROUND:**

Rifapentine (Priftin®-Aventis) is a cyclopentyl-substituted rifamycin that was first synthesized in 1965 by the same company that produced rifampin. Rifapentine, like other rifamycins, works by inhibiting bacterial DNA-dependant RNA polymerase. It also has in vitro activity against *M. avium* and *Toxoplasma gondii*. Tuberculosis strains resistant to rifampin are also resistant to rifapentine [1].

Rifapentine is well absorbed from the gastrointestinal tract, reaching peak concentrations in serum 5 to 6 hours after ingestion. When taken with food, peak concentrations and the area under the curve are increased by 43% over fasting values. Therefore, rifapentine should be given with food to enhance absorption. The drug is excreted partly in urine and mostly in feces (70%). It is metabolized to 25-desacetyl rifapentine, which is microbiologically active, contributing 38% of the drug's overall activity. Both the drug and the active metabolite have an elimination half-life of about 13 hours (compared to 2 hours for rifampin). Rifapentine is 98% bound to plasma proteins. Because of the high protein binding hemodialysis is not expected to enhance elimination of the drug. The drug is metabolized mostly by the liver. Pharmacokinetics of rifapentine in renally impaired patients has not been evaluated [2, 3, 4].

*Clinical Trials:*

Phase I and II trials conducted in China had shown that rifapentine was safe in humans. The Hong Kong Tuberculosis Service conducted a trial comparing thrice weekly rifampin/isoniazid (HR<sub>3</sub>) with once weekly rifapentine/isoniazid (HP<sub>1</sub>) or 2 of 3 wk (HP<sub>1,2/3</sub>) (no medications given one week out of every three weeks to simulate non-adherence) in the continuation phase of a six (6) month regimen. All patients received an initial 2 months of 4 drug therapy (HRZS<sub>3</sub>). Relapse rates were higher in the HP<sub>1</sub> (8.9%, p=0.04) and in the HP<sub>1,2/3</sub> (10.4%, p=0.01) regimens compared to the HR<sub>3</sub> (3.7%) regimen. The drug used in this trial was known to have a low bioavailability [5,6,7].

From 1995 to 1998, Aventis, then known as Hoescht Marion Roussel, conducted an open-label, randomized multicenter study with 722 HIV-negative patients with pulmonary tuberculosis (Protocol 008). The trial compared a rifapentine-based regimen with a rifampin-based treatment. During the intensive phase, one group received rifapentine dosed twice weekly (plus HZE daily), and the other received rifampin daily (plus HZE daily). The trial used an improved formulation of rifapentine manufactured in the US. In the continuation phase, the rifapentine plus isoniazid group was dosed once weekly while the rifampin plus isoniazid group was dosed twice weekly. Six months after completion of treatment, 25 of 249 patients (10%) in the rifapentine arm had relapsed vs. 11 of 229 patients (5%) in the rifampin arm. Relapse in the rifapentine arm was not associated with development of rifampin resistance [2].

The US Public Health Service began a study of rifapentine (called Study 22) in 1995 through the CDC-funded TB Trials Consortium (TBTC) comparing once-weekly rifapentine plus isoniazid (HP<sub>1</sub>) with twice-weekly rifampin plus isoniazid (HR<sub>2</sub>) for the continuation phase in patients who had completed a course of induction therapy with four standard drugs. The HIV (+) arm of the study was stopped in March 1997 because 4 of 36 patients enrolled in the once weekly INH/Rifapentine arm had relapsed with rifampin mono-resistant TB [8]. The final findings of the trial were recently published [9] and the recommendations in this protocol are based mostly on those findings. The recently published TB treatment guidelines also recommend the use of once weekly rifapentine for selected HIV negative patients [10].

The table below summarizes these three clinical trials.

**Table 1: Summary of treatment regimens in 3 Trials of Once-Weekly Rifapentine**

<i>Phase of Therapy</i>	Hong Kong Chest Service	HMR South Africa (Protocol 008)	USPHS/TBTC Study 22
Induction Phase	2 months of HRZS gives three times a week.	2 months of EITHER: Daily HRZE, or Daily HZE plus twice weekly Rifapentine (RPT)	2 Months of daily, twice weekly or thrice weekly HRZE or HRZS)
Continuation Phase	Either Thrice weekly HR (HR <sub>3</sub> ) or Once weekly INH plus RPT (HP <sub>1</sub> ); a third group omitted every 3 <sup>rd</sup> dose to simulate poor compliance (HP <sub>1,2/3</sub> )	Either Twice weekly HR (HR <sub>2</sub> ) or Once Weekly INH plus rifapentine (HP <sub>1</sub> )	Either Twice weekly HR (HR <sub>2</sub> ) or Once weekly INH plus rifapentine (HP <sub>1</sub> )
Outcomes	Relapse/failure rates: 3.7% for HR <sub>3</sub> 8.9% for HP <sub>1</sub> 10.4% for HP <sub>1,2/3</sub>	Relapse rates (all patients): 5% for HR <sub>2</sub> group 10% for HP <sub>1</sub> group	Relapse/failure rates (HIV negative, no cavitation on CXR): 2.9% for HP <sub>1</sub> group 2.5% for HR <sub>2</sub> group
Comments	Randomized <i>after</i> induction. A formulation of rifapentine with poor bioavailability was used.	Randomized <i>before</i> induction. All patients were HIV negative. High rate of poor adherence during intensive phase was noted.	Randomized <i>after</i> induction. All patients were HIV negative in final analysis; HIV+ arm of study was stopped because of acquired rifamycin monoresistance

H=Isoniazid; R=Rifampin; P= Rifapentine; Z=Pyrazinamide; E=Ethambutol.  
USPHS/TCTC-United States Public Health Services, TB Trials Consortium.

## ELEMENTS OF THE PROTOCOL

**1.0 Procedure:** (see Figure 1)

- 1.1 Patient selection--Rifapentine should only be used in carefully selected patients in order to avoid relapse or the development of acquired rifamycin resistance.
  - 1.1.1 Once a week rifapentine 600 mg together with INH 900 mg should only be used in the *continuation phase* of the treatment of pulmonary tuberculosis.
  - 1.1.2 Only HIV-negative patients may receive rifapentine. Therefore, a negative HIV test must be documented before initiating this therapy.
  - 1.1.3 Patients with any form of extrapulmonary tuberculosis are not candidates for this regimen; mediastinal and hilar lymphadenopathy accompanying an infiltrate is not extrapulmonary TB.
  - 1.1.4 Patients with a cavitary lesion on chest radiographs are at increased risk of relapsing if treated with rifapentine and INH; these patients should therefore not be given this regimen.
  - 1.1.5 Clinically confirmed cases of pulmonary TB ,which requires treatment with four drugs throughout the entire six months, and children under the age of twelve are not candidates for once a week rifapentine plus INH.
- 1.2 Potential candidates for rifapentine/INH must be educated about the availability of this option early in their therapy and educational brochures about this treatment should be given to them before hand.
  - 1.2.1 One to two weeks prior to the end of the two month intensive phase of therapy, sputum must be obtained to demonstrate that sputum smears are negative before the RPT/INH regimen is initiated.
  - 1.2.2 Offering a once weekly regimen to patients also provides an opportunity to re-introduce DOT if a patient is not already on DOT.
- 1.3 Treatment length--Treatment length for drug sensitive pulmonary tuberculosis is generally six (6) months.
  - 1.3.1 A patient will be considered to have taken an adequate regimen if he/she takes at least eighteen (18) doses of INH/RPT during the continuation phase of TB treatment.
  - 1.3.2 If an appropriate candidate is started on RPT/INH and is later found to have positive cultures on sputums obtained at the end of or after the intensive phase of therapy, the total length of therapy should be NINE months, with at least twenty eight (28) doses of INH/RPT in the continuation phase.
- 1.4 Dosing:
  - 1.4.1 The recommended dosage of rifapentine is 600 mg weekly, always in combination with other anti-tuberculosis drugs. The drug is available as 150 mg tablets.
  - 1.4.2 Dosing rifapentine with food improves absorption of the drug, so the drug should be administered with food, or patients should be encouraged to eat before a dose is given.

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- 1.4.3 If a patient misses a dose of medication the dose can be given on another day during the week as long as the subsequent dose is separated from last dose by at least 72 hours.
  - 1.4.4 Patients who are delinquent for two consecutive weeks or more should be switched back to a rifampin based regimen.
  - 1.4.5 Some patients receiving INH 900mg may require supplementation with pyridoxine (vitamin B<sub>6</sub>) 25 mg *daily* that can be self administered. This includes patients with diabetes, cancer, chronic renal disease, chronic liver disease, alcoholism, pre-existing peripheral neuropathy, malnourished individuals ( $\geq 10\%$  below ideal body weight) or individuals with any wasting syndrome, and pregnant women.
- 1.5 Monitoring patients on rifapentine:
- 1.5.1 Patients should have a baseline liver function test and a complete blood count (CBC) at the beginning of TB therapy. Additional blood tests at the start of rifapentine are not necessary.
  - 1.5.2 Monthly follow-up blood testing is not necessary if the baseline is normal unless a patient develops symptoms consistent with adverse drug reaction (see below).
  - 1.5.3 Therapeutic levels of rifampin have been known to interfere with assays for vitamin B12 and folate; similar interactions should be considered for rifapentine.
  - 1.5.4 Clinical monitoring will be the same as for all other Class III patients in the Chest Centers.
- 2.0 Adverse effects:**
- 2.1 Rifapentine, like other rifamycins, may produce a predominantly orange-red discolorations of body fluids and tissues (skin, teeth, tongue, tear, sputum, saliva, feces, CSF). Contact lenses may also become permanently stained..
  - 2.2 Hepatic adverse effects
    - 2.2.1 A patient who develops symptoms consistent with hepatitis (anorexia, nausea, vomiting, abdominal pain, jaundice) while taking rifapentine/INH should be instructed to discontinue all medications promptly. (In clinical trials with isoniazid, rates of adverse reactions were similar with rifampin and rifapentine, with increased aminotransferase activity seen in about 5% of all patients).
    - 2.2.2 The patient should be examined promptly by a physician and have blood drawn to measure liver function tests (LFTs).
    - 2.2.3 If LFTs are normal, drug-induced hepatitis is unlikely. Another cause for the symptoms should be suspected; depending upon the nature, duration, and severity of symptoms, a decision should be made regarding further diagnostic investigation and possible referral.
    - 2.2.4 Patients with mildly elevated LFTs can continue to take anti-TB medications with close monitoring.
      - 2.2.4.1 If AST or ALT is  $>3$  times the upper limit of normal and the patient is symptomatic, anti-TB drugs should be discontinued. The patient should be examined and have LFTs repeated at least weekly.
      - 2.2.4.2 If symptoms persist for more than 2 weeks without anti-TB medication(s), or if LFTs continue to worsen, the physician should

suspect progressive drug-related hepatitis or an unrelated cause of hepatitis and evaluate appropriately.

- 2.2.5 Depending on the severity of the hepatitis, as indicated by clinical findings and LFTs, hospitalization may be necessary for closer observation, evaluation and therapy.
- 2.2.6 If AST or ALT is >5 times the upper limit of normal, anti-TB medication(s) should be discontinued even if the patient is asymptomatic.
- 2.2.7 Resumptions of drugs after adverse events should follow TBTC guidelines as outlined in the 1999 Clinic Manual.
- 2.2.8 As soon as hepatitis is identified, a viral hepatitis profile should be requested.

### **3.0 Use in pregnancy and lactating mothers:**

- 3.1 Rifapentine has been shown to be teratogenic in rats and rabbits given anywhere from 0.3 to 1.3 times the human dose of rifapentine.
- 3.2 There are no adequate data in pregnant women. The effect on the human fetus is unknown. (In protocol 008, six patients randomized to rifapentine become pregnant while taking rifapentine; two had normal deliveries, two had first trimester abortions, one had an elective abortion, and one was lost to follow up [2]).
- 3.4 As a precaution, rifapentine should not be used in pregnant women.
- 3.5 It is not known whether rifapentine is excreted in human milk. Rifapentine is therefore not recommended in lactating mothers.

### **4.0 Use in children:**

- 4.1 The safety and efficacy of rifapentine in children under the age of 12 have not been established.
- 4.2 Rifapentine should not be used in individuals under 12 years of age.

### **5.0 Drug interactions:**

- 5.1 Like other rifamycins, rifapentine induces the cytochrome P450 system of enzymes, specifically the CYP3A4, CYP2C8 and CYP2C9 isozymes.
  - 5.1.1 It increases metabolism and markedly lowers serum concentrations of drugs that are metabolized by these enzymes [8, 11].
  - 5.1.2 Rifapentine's ability to induce CYP3A4 is less than that of rifampin but greater than that of rifabutin. CYP3A4 is important in the metabolism of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). The clinical implications of rifapentine's interactions with the P450 systems is not clear; moreover, rifapentine should not be used in HIV infected persons because of the risk of developing rifamycin resistance.
  - 5.1.3 The maximal induction of these enzymes occurs within 4 days after first dose and returns to baseline within 14 days after rifapentine is discontinued.
  - 5.1.4 Degree of enzyme induction is dependent on rifapentine dose and frequency.
- 5.2 Drugs (or classes of drugs) known to be affected by rifapentine:
  - 5.2.1 Anticonvulsants (phenytoin)
  - 5.2.2 Antiarrhythmics
  - 5.2.3 Antibiotics ( fluoroquinolones such as cipro, moxi, levo; tetracyclines, clarithromycin, dapsone, chloramphenicol)

- 5.2.4 Azole antifungals (fluconazole, ketoconazole etc.)
- 5.2.5 Barbiturates (phenobarbital)
- 5.2.6 Beta blockers (propranolol, atenolol etc.)
- 5.2.7 Calcium channel blockers (diltiazem, verapamil, nifedipine etc.)
- 5.2.8 Digitalis derivatives (digoxin, digitoxin)
- 5.2.9 Oral anticoagulants (warfarin derivatives)
- 5.2.10 Oral or other systemic hormonal contraceptives including progestins
- 5.2.11 Immunosuppressives (cyclosporine, tacrolimus ( FK506))
- 5.2.12 Thyroxine
- 5.2.13 Narcotic analgesics (methadone, morphine etc.)
- 5.2.14 Antiretroviral drugs (NNRTIs and PIs)
- 5.2.15 Sildenafil (Viagra®)
- 5.2.16 Tricyclic antidepressants (imipramine, nortryptiline etc.)

5.3 Any drug that is known to have an interaction with rifampin should be considered to have similar interactions with rifapentine as well, unless proven otherwise through clinical trials. Drug information manuals and package inserts should be consulted for latest information.

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<b>Revised:</b>	Date: (mm-yy)	0 2 - 0 3			
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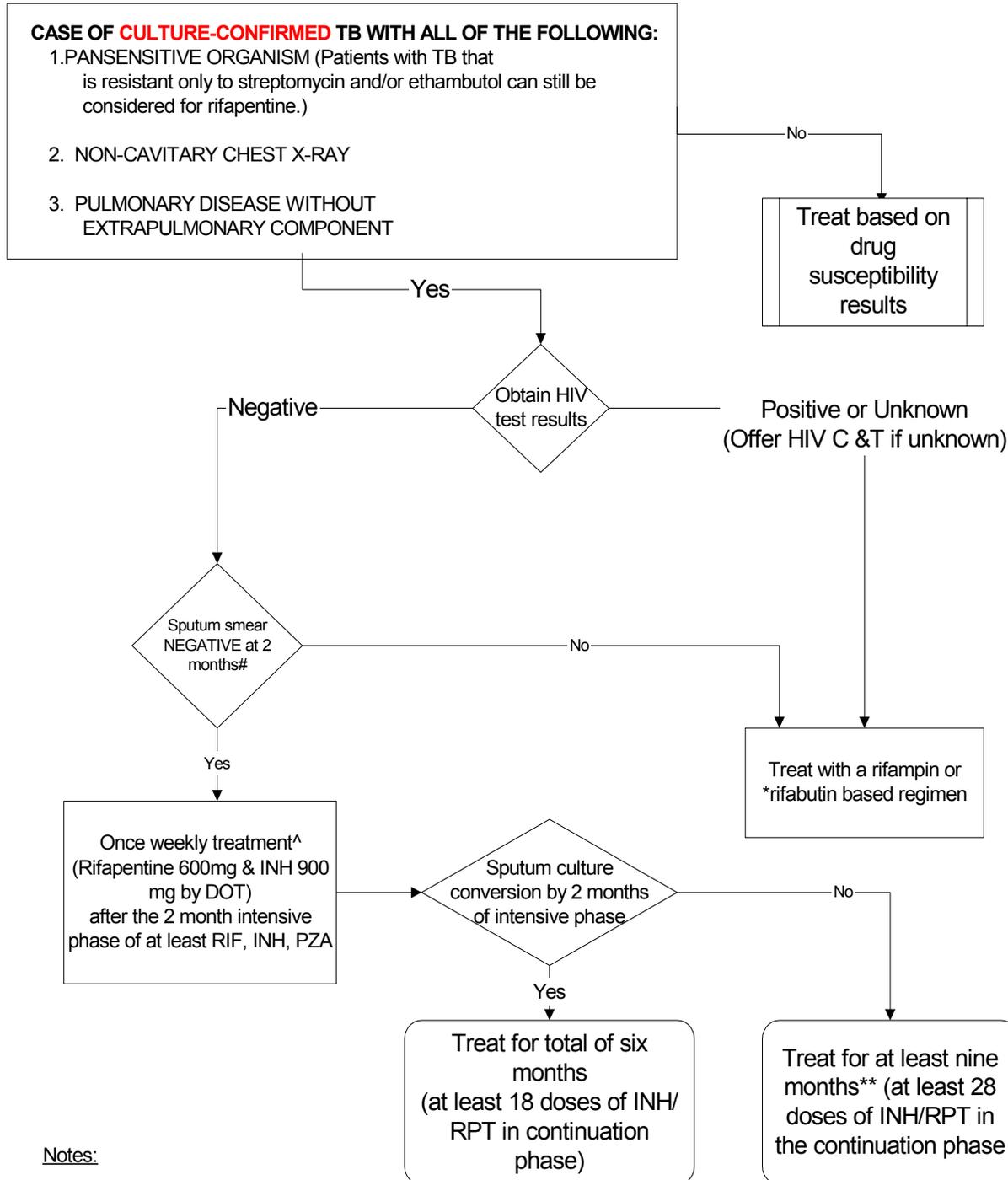
## DISEASE: DRUG TREATMENT

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FIGURE 2: Treatment of tuberculosis with rifapentine



Notes:

\*Rifabutin should not be given biweekly in HIV infected patients with CD4 counts <100; it should be given either 3x week or daily

^Intermittent therapy should only be given under DOT

\*\*This is a change of policy that will be formally adopted soon for all culture positive patients

#A sputum smear should be done 1 to 2 weeks prior to the end of the two-month intensive phase