INDIAN HEALTH SERVICE

PHARMACY LATENT TUBERCULOSIS THERAPEUTIC MONITORING CLINIC PROTOCOL

Latent Tuberculosis Clinic Consulting Physician:
Chief of Pharmacy:
Pharmacy Clinic Director:

Purpose/Statement of Need:

Treatment of latent tuberculosis infection (LTBI) is essential to controlling and eliminating tuberculosis (TB) in the United States. More than 80% of cases of tuberculosis in the United States are the result of reactivated latent infection.[1] Treatment of LTBI with pharmacotherapy substantially reduces the risk of LTBI's progression to active pulmonary disease. In 2015, the rate of TB among American Indian/Alaskan Natives (Al/AN) Is reported to be 4 cases per 100,000 population.[2] In the state of Arizona in 2017, there were 188 cases of active tuberculosis reported with Native Americans accounting for 7.1% of all cases In the state.[1] Certain groups are at very high risk of developing TB disease once infected, and every effort should be made to begin appropriate treatment and to ensure those persons complete the entire course of treatment for LTBI. The utilization of clinical pharmacists as physician extenders to enhance adherence to treatment regimens and improve treatment outcome is on the rise in health care organizations.[1]A pharmacist acting as a physician extender can assist clinicians in optimizing tuberculosis therapy to achieve success for particular regimens and minimize toxicity.[4]

Goals:

1. Maximize the benefits of pharmacologic treatments for latent tuberculosis.
2. Educate patients regarding indications, risks, and complications of anti-tuberculosis pharmacotherapy.
3. Identify patients who are at high risk for adverse outcomes of specific tuberculosis pharmacotherapy.

Policy:

1. Patient must be officially diagnosed, referred, and have a treatment plan ordered by an Indian Health Service medical provider with diagnosis of latent tuberculosis.
2. Pharmacy will perform physical assessment and order and interpret laboratory tests as needed per protocol.
3. Patient will be referred back to their primary care physician for follow up if serious complications arise during the monitoring period.
4. A designated physician will retain responsibility for oversight of the Pharmacy Latent Tuberculosis Therapeutic Monitoring Clinic.
5. Pharmacy will discharge patient from clinic upon completion of treatment or non-adherence (DNKA policy) to treatment plan.
6. Exclusions: HIV+, pediatric, and active tuberculosis patients.

Guidelines:

1. Pharmacy will collaborate with the Public Health Nursing Department to provide LTBI treatment for the patient population. Public Health Nursing will help with the tracking and the contacting of patients. The County Health Department may be a resource for local trends in medication management as they relate to drug sensitivities to LTBI treatment plans.

2. Pharmacy Appointments:
   A LTBI clinic pharmacist will schedule the first clinic appointment after the initial physician assessment, diagnosis, and referral. The Pharmacy Latent Tuberculosis Therapeutic Monitoring Clinic will not be responsible for diagnosis of patients. After the initial appointment, patients will

be followed at least monthly until the completion of the recommended course of pharmacotherapy.

3. Initial Pharmacy Evaluations and Management:

The pharmacist will interview and assess all patients in order to:

- Determine the appropriateness of pharmacotherapy
- Perform medication reconciliation (including herbal, nutraceutical and dietary supplements)
- Provide therapeutic monitoring through physical assessment and laboratory monitoring
- Provide patient specific education on pharmacotherapy
- Provide appropriate medication(s), with quantity sufficient until the next appointment date, not to exceed a 42 days' supply of medication (pending clinic availability).
- Follow-up visits will be at least monthly and no more than 42 days of medications will be given at any time. There will be no automatic refills or courtesy fills, and the patient must be evaluated before any medication will be reordered.
- Patients may be asked to bring medication bottles to clinic appointment for evaluation of adherence to medication.

It is important to know why the patient is on LTBI therapy. If they are a close contact to active TB patients, then they should be treated differently from other at-risk patients. (See Candidates for the Treatment of LTBI below.)

4. Subsequent visits:

- The pharmacist will interview and assess patients for any adverse effects and adherence, and evaluate and follow up on any pertinent laboratory results.
- Telephone triages may be performed in place of physical clinic visit if appropriate and - necessary, in extenuating circumstances to assure continuation of therapy.
- Medication reconciliation will be performed at every visit.

5. Case management:

The pharmacist will be responsible for the monitoring of the patient's pharmacotherapy. This includes reviewing and following up on any related laboratory results. The Public Health Nursing (PHN) Department will be responsible for keeping an updated log of patients tracked, and report to appropriate channels as per requirement. PHNs are licensed, professional nursing staff available to provide services via home visits, such as patient education, medication management, and direct observation therapy of medication which are effective interventions for performance impact. The PHN expertise in communicable disease assessment, outreach, investigation, and surveillance helps to manage and prevent the spread of communicable disease. A Referral will be sent to the PHN program for contact investigation.

6. DNKA policy:

- The pharmacist will attempt to contact the patient to reschedule or perform telephone triage.
- If the pharmacist is unable to contact the patient. Public Health Nursing Department will attempt to contact the patient.
- If a patient fails to follow up with the LTBI clinic and does not reschedule, the PHN will be informed and will track this and report patient status updates.
- If the patient fails to keep two consecutive clinic appointments, the primary care physician or referring medical provider will then be informed and the patient may then be discharged from the clinic.

7. Documentation:

Documentation of each visit must include:

- Assessment of any medication related side effects
- Patient's progress and therapy goals
- Education provided:
    - Medications that can affect hepatic function and LTBI therapy
    - Effects of concurrent alcohol use
    - INH and the occurrence of paresthesia (reason for pyridoxine)
    - INH and food Interactions
    - Rifampin and rifapentine decreases efficacy of birth control pills in women of child- bearing age
    - Decreased efficacy of methadone and other opioids due to rifampin and rifapentine
    - Red body fluids with rifampin and rifapentine

8. Length of pharmacy monitored treatment of Latent TB:
    - 3HP (INH/RPT) isoniazid-rifapentine: weekly therapy for 12 weeks with monthly follow up is the preferred treatment regimen. (**PREFERRED**)
    - 4 months of daily rifampin (RIF) or
    - 9 months of daily isoniazid (INH /pyridoxine (vitamin B6) or other therapy determined as appropriate by infectious disease specialists.

9. Pharmacotherapy Completion

    LTBI pharmacist(s) will be responsible for:

    1. Providing patient with a letter of Completion that states diagnosis, medication and duration taken, and treatment completion certification letter.
    2. Electronic Health Record (E.H.R) will be updated with:
        - Diagnosis: Latent Tuberculosis, S/P-INH, Rifampin (RIF), or INH-RPT with date of completion
        - Electronic Health Record (EHR) note of completion will be co-signed by referring or primary medical provider if available and medical director of LTBI clinic
    3. Exit counseling will be provided to patient by clinical pharmacist

10. Pharmacist Certification

    Pharmacists certified to provide patient care in the LTBI clinic will complete the pharmacy certification exam (including knowledge with current ATS/CDC guidelines for LTBI treatment) and perform ten visits under the observation of a certified LTBI pharmacist.

11. Clinic Outcome Evaluation:
    - Evaluation of clinic outcomes will be reported annually.
    - Evaluations shall include: geographical location of patient, indication for treatment, medication regimens, patient adherence (including if they are lost to follow-up), adverse outcomes, and completion dates.
    - Reports will be submitted to the Chief Pharmacist and Clinic Consulting Physician (and other responsible entities on a PRN basis).

Candidates for the Treatment of LTBI

Persons in the following high-risk groups should be given treatment for LTBI if their reaction to the Mantoux tuberculin skin test is 25 mm or greater:

- HIV-infected persons
- Recent contacts of an active TB case
- Persons with fibrotic changes on chest radiograph consistent with old TB
- Patients with organ transplants
- Persons who are immunosuppressed for other reasons (e.g., taking the equivalent of >15

mg/day of prednisone for 1 month or longer, taking TNF-alpha antagonists)

In addition, persons in the following high-risk groups should be considered for treatment of LTBI if their reaction to the Mantoux tuberculin skin test is >10 mm:

- Recent arrivals (< 5 years) from high-prevalence countries
- Intravenous drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that make them high-risk
- Children under 4 years of age, or children and adolescents exposed to adults in high-risk categories

Persons with no known risk factors for TB may be considered for treatment of LTBI if their reaction to the tuberculin test is between 2 - 15 mm. However, targeted skin testing programs should only be conducted among high-risk groups. All testing activities should be accompanied by a plan for follow-up care by a medical provider for persons with TB infection or disease.

Persons with positive results from Interferon Gamma Release Assays (IGRA) such as Quantiferon Gold or T-Spot that also meet the CDC recommended Latent TB treatment criteria should also be treated.

Regimens

For persons suspected of having LTBI, treatment should not begin until active TB disease has been excluded. Persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease until the diagnosis is confirmed or ruled out. (This population will not be followed in the LTBI clinic.

Although regimens are broadly applicable, there are modifications that should be considered under special circumstances (i.e. HIV infection, suspected drug resistance, pregnancy, or treatment of children).

Due to the reports of severe liver injury and deaths, CDC now recommends that the combination of rifampin (RIF) and pyrazinamide (PZA) should generally not be offered for the treatment of LTBI. If the potential benefits significantly outweigh the demonstrated risk of severe liver injury and death associated with this regimen and the patient has no contraindications, a TB/LTBI expert should be consulted prior to the use of this regimen.

	Adults	Notes/Comments
Preferred LBTI Regimen	***Isoniazid + Rifapentine "3HP" (INH-RPT)** **(Total of 12 doses within 16 weeks)** **Isoniazid:** 15mg/kg rounded up to the nearest 50 or 100mg; Max dose = 900ng **Rifapentine:** 10.0 - 14.0 kg 300mg 14.1 - 25.0 kg 450mg 25.1 - 32.0 kg 600mg 32.1 - 49.9 kg 750mg ≥50.0 kg 900mg maximum **Pyridoxine:** 50mg weekly	*12 weeks DOT/SAT (Direct-Observed Therapy/Self-Administered Therapy) is equivalent to 9 months of INH therapy.* The choice between daily and weekly dosing depends on feasibility of DOT/SAT, resources for drug procurement, program operations including patient monitoring, expectance of treatment non-completion as foreseen from medical and social circumstances of the patient, and the prescribing physician
Alternative Regimen	**Isoniazid (INH):** 300mg PO daily for 9 months (or total of 270 doses within 12 months) **Pyridoxine:** 50mg daily **Rifampin (RIF):** 600mg PO daily for 4 months (or minimum 120 doses within 6 months)	
Adjunctive Therapy	Ondansetron (Zofran): 4 to 8mg ODT by mouth 1 hour before weekly therapy, and every 4 hours as needed for nausea if other preventative therapies not working (Max 30 tables per prescription)	

Therapeutic Monitoring

Routine laboratory monitoring during treatment of LTBI is indicated only for those whose baseline tests suggest a liver disorder and for other persons with a risk of hepatic disease. Laboratory testing should be performed to evaluate possible adverse reactions that occur during the treatment regimen. (See Figure 1 for algorithm.)

Interruption of Treatment / Changes in Therapy

The pharmacist can restart patient's medication if there are acceptable breaks in therapy, depending on regimen. However, if the patient is non-adherent to treatment (i.e. 2 missed clinic appointments or did not pick up medication}, the patient may be referred to the prescribing provider to decide if continuation of treatment is needed, and may be discharged from the LTBI therapeutic monitoring clinic.

If there is a gap greater than 3 months in INH daily regimen, 1 month in RIF daily regimen, it may be necessary to restart treatment. Patient may be referred to the physician / prescriber in this case. (See Figure 2 for algorithm of interruptions of therapy.)

3HP (INH/RPT) weekly treatment: If there is a gap greater than 4 weeks (28 days), restart will be necessary. (Completion criteria for 3HP is 11 or 12 doses within 16 weeks, and doses must be separated by minimal 72 hours).

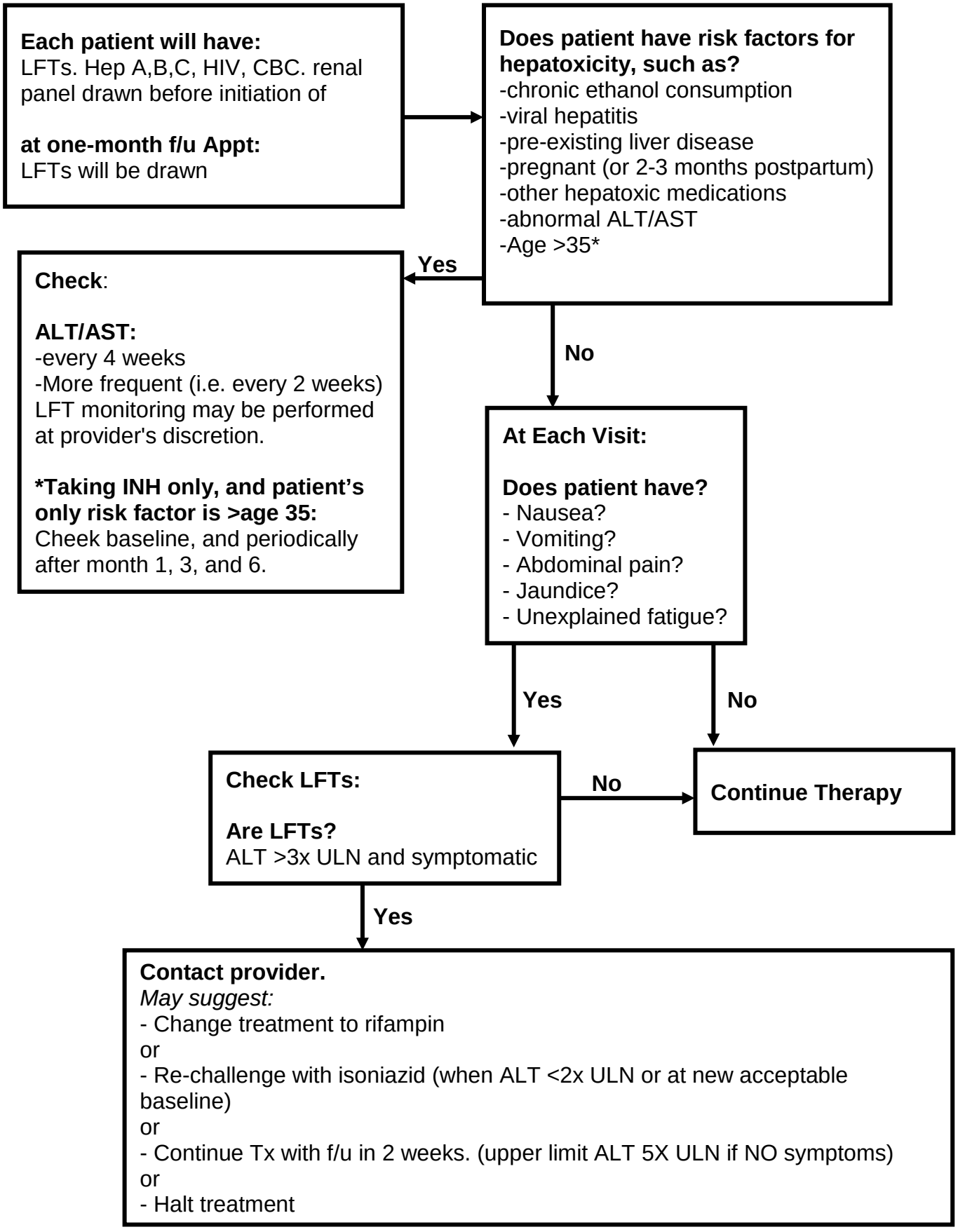
If intolerance or other clinical problems necessitates changes in treatment, patient may complete alternate treatment with percent completed subtracted: i.e., 3 doses of 3HP (25%) will require 7 more months (210 doses) of INH daily treatment, or 3 more months (90 doses) of RIF daily treatment.

Baseline and routine laboratory monitoring during treatment of LTBI are indicated only when there is a history of liver disease, HIV infection, pregnancy (or within 3 months post-delivery), or regular alcohol use. Baseline hepatic measurements of serum AST, ALT, and bilirubin are used in the situations mentioned above and to evaluate symptoms of hepatotoxicity. Laboratory testing should be performed to evaluate possible adverse reactions that occur during the treatment regimen.

REFERENCES:

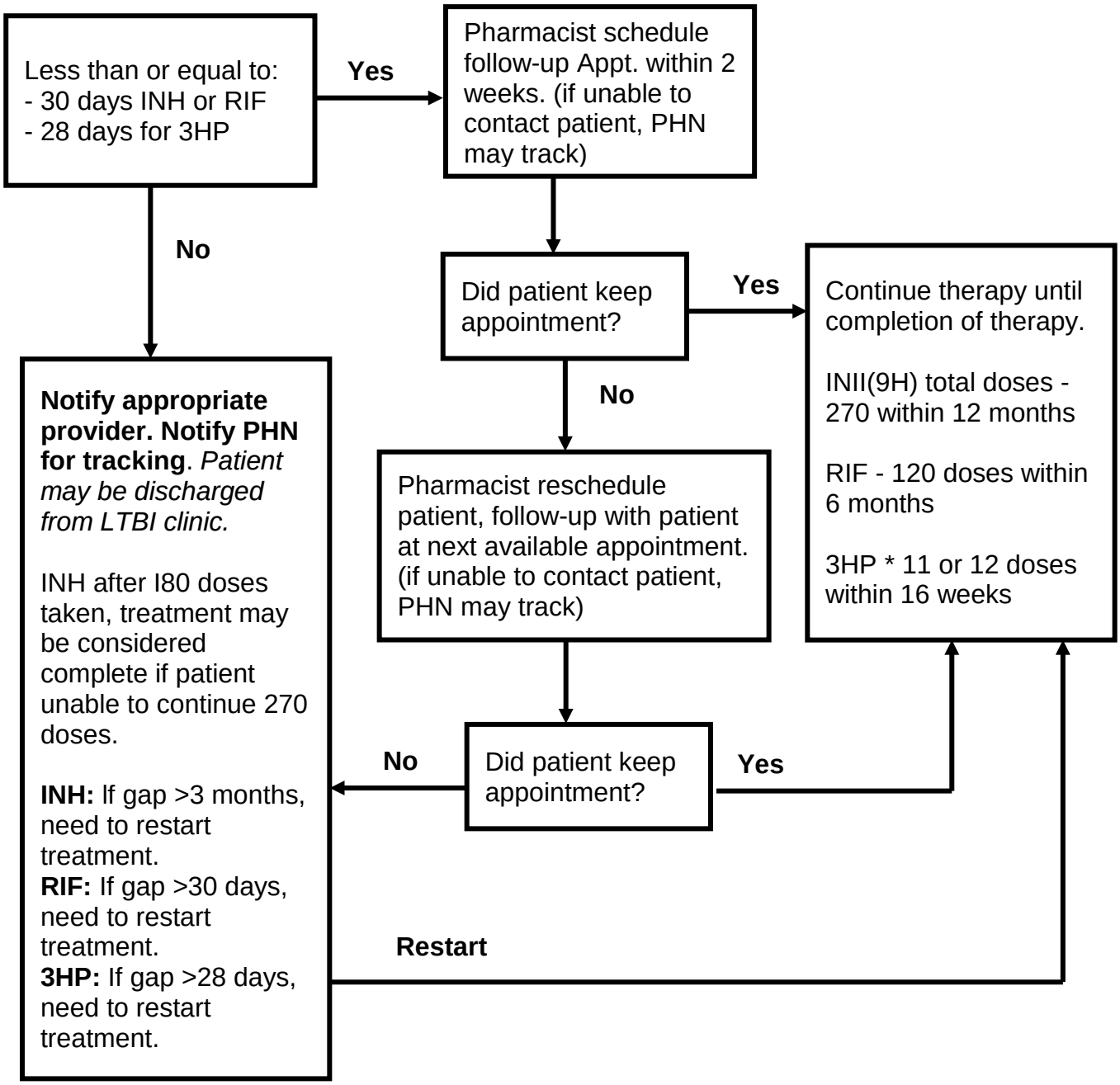
1. American Thoracic Society. Targeted tuberculin testing and treatment of latent tuberculosis infection. Am J Respir Crit Care Med 2000; 161:S221-S247.
2. Trends in Tuberculosis https:/5
3. AZDOH Tuberculosis Surveillance report. https://www.azdhs.gov/documents/preparedness/epidemiology-disease-control/disease-integrated-services/tb-conirol/reports/2015-tb-survelllance-report.pdf
4. Yew WW. Therapeutic drug monitoring in anti-tuberculosis chemotherapy. *Therapeutic drug monitoring.* 1998;20:469-72.
5. Fact Sheet. Treatment Options for latent Tuberculosis infection https://www.cdc.gov/tb/publications/factsheets/treatment/ltbitreatmentoptions.htm

Figure 1: Monitoring for Hepatotoxicity during INH and 3HP Treatment for Latent Tuberculosis Infection



Adapted from American Thoracic Society Hepatoxicity Statement.
Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, ULN=upper limit of normal

Figure 2: Interruptions in LTBI Pharmacotherapy: INH, RIF, and 3HP Therapies



If intolerance or other clinical problems necessitates changes in treatment, patient may complete alternate treatment with percent completed subtracted: i.e., 3 doses of 3HP (25%) will require 7 more months (210 doses) of INH daily treatment, or 3 more months (90 doses) of RIF daily treatment.

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