GENERAL SCREENING GUIDELINES IN HIV/TB COINFECTION

- The CDC recommends routine and opt-out HIV testing for all individuals aged 13-64 in all healthcare settings.
- At the time of HIV diagnosis, all patients should be screened for TB with a risk assessment and a TB skin test (TST) or Interferon Gamma Release Assay (IGRA).
- TB screening guidelines in HIV positive individuals include:
  - CDC recommends testing in HIV-infected patients without previously positive TST.
  - TST should be repeated annually if initial test negative and the patient is at high risk for TB.
  - TST should be repeated upon immune reconstitution or when CD4 count reaches 200.
- All patients diagnosed with LTBI or TB disease should be tested for HIV.
- A TST with ≥5 mm induration is positive in an HIV-infected individual.
- A diagnosis of LTBI can be made with: Positive TST or IGRA, NO signs or symptoms of active TB disease, and a normal CXR.
- Active TB must be excluded prior to starting treatment for LTBI. If the CXR is abnormal or the patient is symptomatic, sputum smears and cultures should be obtained. Consult your local health department for assistance in sputum testing.

INTERFERON GAMMA RELEASE ASSAYS (IGRAS) AND HIV/TB COINFECTION

IGRA's function through a lymphocytic recognition of protein antigens specific to MTB, not other strains of mycobacterium or BCG. The recognition process involves the generation and secretion of interferon gamma, which can be quantified.

It is suspected that these assays in general may be less sensitive in HIV positive patients, but are as sensitive as or slightly better than a TST. A higher number of indeterminate or negative IGRA reactions are likely in those with lower CD4 cell just as the TST is less likely to be positive with declining CD4 counts. The IGRA tests are more specific for MTB.

Early studies suggest that the T-spot may be more sensitive than the TST or QuantIFeron Gold tests in detection of MTB in HIV positive patients.

STRATEGIES TO LIMIT TOXICITY

- Recognize the potential for hepatotoxicity specific to medications prescribed.
- Identify patient risk factors that might predispose the individual to develop hepatotoxicity.
- Identify drug-drug interactions and needed dose adjustments.
- Screen for viral hepatitis and HIV.
- Provide ongoing assessment for hepatotoxicity through patient report, physical exam findings, and laboratory results.
- Rapid response and evaluation in response to possible toxicity. Where applicable include:
  - Temporary or permanent discontinuation of medication
  - Laboratory evaluation
  - Clinical evaluation
  - Alteration in therapeutic regimen
- Comprehensive and ongoing patient education

PATIENT EDUCATION

Printed instructions should include:
- Clinic telephone numbers.
- Instructions for after-hours care.
- Appropriate language/translation.

Explicitly tell patients to immediately stop medications and call the clinic for further instruction if they experience:
- Nausea
- Vomiting
- Abdominal discomfort
- Unexplained fatigue
- Discuss the potential for hepatotoxicity with the use of concomitant alcohol and over-the-counter medications such as acetaminophen. All alternative and prescription medications should be reported to both primary and infectious disease providers.
- Document all patient education.

REPORTING OF SERIOUS ADVERSE EVENTS

Health care providers should report serious adverse effects, including hepatotoxicity, to the U.S. FDA's MedWatch program. Reporting may be by mail, telephone (1-800-FDA-1088), fax (1-800-FDA-0178), or the internet website (www.medwatch.gov).

Adverse effect of treating LTBI that are serious enough to entail hospital admission or death should be reported to the CDC through local public health authorities or by calling 404-639-8401.

These surveillance systems capture different data, and reporting to both is necessary.

FOR CASE CONSULTATION

Heartland National TB Center
1-800-839-5864
http://www.heartlandntbc.org/

National HIV/AIDS Clinicians’ Consultation Center (NCCC)
1-800-933-3413
http://www.nccc.ucsf.edu/

For Additional Information:

Heartland National TB Center
1-800-839-5864
http://www.heartlandntbc.org/

MATEC
1-312-996-1373
http://www.matec.info

Consultation with a physician with expertise in the management of both TB and HIV should be sought. HIV and TB providers should work closely together to ensure that all management decisions avoid serious drug-drug interactions, minimize toxicity, and provide good patient outcomes.
LATENT TUBERCULOSIS INFECTION (LTBI) IN THE CONTEXT OF HIV

The risk of developing active TB from LTBI is increased 100-fold in the setting of HIV infection. Patients with HIV and latent tuberculosis infection have a 7-10% risk per year of progressing from latent to active TB disease. This is in contrast to a 10% risk over a lifetime in a non-HIV infected individual. Active TB must be excluded prior to treatment of LTBI. This is especially important, however more difficult, in the context of HIV infection. Treatment of active TB with a single drug leads to drug resistance. If a rifampin-based LTBI treatment regimen is used in a person with active TB, rifampin resistance may develop, markedly compromising a good treatment outcome.

POTENTIAL FOR HEPATOXICITY IN THE SETTING OF ANTI-TB TREATMENT & HIV

The risk of developing hepatotoxicity depends on the individual treatment regimens for both TB and HIV. Common culprits in hepatotoxicity for antiretroviral medications include the classes NRTI’s, NNRTI’s, and PI’s. The HIV virus itself may increase the risk of developing drug induced hepatotoxicity in the setting of TB treatment. Additional overlapping risk factors such as Hepatitis B or C coinfection, presence of chronic liver disease, alcohol use, pregnancy, age, and concomitant use of fluconazole, acetylamidophen, or other offending OTC agents may further compound the risk.

TOXICITY MONITORING CONSIDERATIONS FOR THE HIV POSITIVE PATIENT TREATED FOR LTBI

Baseline: CBC with platelets (rifamycins), LFTs, total bilirubin, hepatitis panel for everyone.

Monthly (at minimum) or as appropriate: Toxicity assessment, clinical evaluation, and laboratory assessment with INH include liver enzymes; with Rifamycins include CBC, platelets, liver enzymes, total bilirubin.

At first sign of toxicity: Laboratory assessment and provider visit within 24 hours.

**Patient education on clinical signs and symptoms of hepatotoxicity should be documented at baseline and monthly.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Treatment Duration</th>
<th>Frequency of Hepatotoxicity</th>
<th>HIV-Specific Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid (INH)</td>
<td>300 mg daily</td>
<td>9 months</td>
<td>0.1-1.86% Mild transaminitis occurs initially in &gt;10%, most asymptomatic, resolves with continued therapy.</td>
<td>Can be administered to HIV-infected patients on HAART without risk of drug-drug interactions</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Dose base on ARV regimen</td>
<td>4 months</td>
<td>0.0-0.8% No data, generally felt to be less hepatotoxic than rifampin</td>
<td>Key interactions occur between rifamycin antibiotics and a wide variety of medications including 4 classes of HIV medications: Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, CCR5-Receptor Antagonists, and Integrase Inhibitors. A common source of rifamycin interaction is the Cytochrome P450 system. Rifampin interacts with many drugs used in HAART. Prior to prescribing a rifamycin-based regimen, drug interactions and dose adjustments should be checked: <a href="http://AIDSinfo.nih.gov">http://AIDSinfo.nih.gov</a></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Dose base on ARV regimen</td>
<td>4 months</td>
<td>No data, generally felt to be less hepatotoxic than rifampin</td>
<td>Key interactions occur between rifamycin antibiotics and a wide variety of medications including 4 classes of HIV medications: Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, CCR5-Receptor Antagonists, and Integrase Inhibitors. A common source of rifamycin interaction is the Cytochrome P450 system. Rifampin interacts with many drugs used in HAART. Prior to prescribing a rifamycin-based regimen, drug interactions and dose adjustments should be checked: <a href="http://AIDSinfo.nih.gov">http://AIDSinfo.nih.gov</a></td>
</tr>
</tbody>
</table>

RIFAMPIN/PZA SHOULD NOT BE USED IN THIS PATIENT POPULATION

**Evaluating a Rash:**

An early finding with hepatotoxicity can be a maculopapular rash. If the rash does not resolve within 24 hours or have another likely cause, liver enzymes should be evaluated, particularly if associated with fatigue or GI upset. The antiretroviral Abacavir (ABC)/Ziagen can be implicated in the development of a lifethreatening hypersensitivity reaction often manifested by a rash. Additional HIV medications may also result in the development of severe rash and/or hypersensitivity reactions. In the case of a rash, medications warrant a thorough and prompt evaluation.

Identification: Early symptoms of hepatotoxicity can be subtle and mimic nonspecific drug effects, indigestion, or other infectious process. When a new or different compliant develops, evaluate liver enzymes to exclude hepatotoxicity. Symptoms may include:

- Decreased energy
- Decreased appetite
- Fatigue
- Indigestion
- Abdominal discomfort
- Nausea
- Vomiting
- Myalgia
- Rash*

Late symptoms of hepatotoxicity include:

- Dark urine
- Light stool
- Jaundice
- Mental status change
- Abdominal swelling
- Ascites

**Identifying and Management of Hepatotoxicity in HIV/TB Coinfected Patients Being Treated for LTBI**

**Identification:**

**Risk Factors:**

- Active TB
- HIV infection
- Coinfection with other hepatitis virus
- Presence of chronic liver disease
- Alcohol use
- Use of rifamycin
- Concurrent use of other hepatotoxic medications
- Use of concomitant medications that can increase the risk of hepatotoxicity

**Symptoms:**

- Fatigue
- Anorexia
- Abdominal pain
- Jaundice
- Hepatomegaly

**Diagnosis:**

- Laboratory evaluation of liver function tests (LFTs)
- Serum hepatitis panel
- Liver biopsy (if suspicion remains high)

**Treatment:**

- Stop the suspected hepatotoxic medication
- Monitor liver enzymes and clinical symptoms
- Consider alternative medications
- Liver transplantation in severe cases

**Management:**

- Close monitoring of liver enzymes and clinical symptoms
- Regular follow-up appointments
- Consider alternative medications if possible
- Liver transplantation if necessary