Tuberculosis Drug Toxicities & Approaches to Management

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Need to acknowledge for patients

TB therapy *can be difficult*

- Prolonged treatment program
- Many pills in treatment program
- Common drug intolerances

- *But treatment is effective!*
Tools for Managing Adverse Drug Reactions

- Consider a non-TB drug or condition
- Treat symptoms and continue the medication
- Modify drug delivery
- Stop the drug(s) (e.g. temporarily) and follow clinically
- Re-challenge after symptoms abate
- Use different drug(s)
- Measure drug levels
- Desensitization for difficult cases
- Hospitalize during medication re-challenge
## Common Side-effects of TB drugs

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<th>Drug</th>
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<td>Visual changes, eye pain, change in color vision</td>
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Section I

Understanding common drug toxicities

- 1st step: identify the most likely offending drug by understanding drug profiles:
  → Brief review of more common TB drug toxicities:
Isoniazid (INH) – Adverse reactions

- **Hepatotoxicity / hepatitis** - not related to acetylation status
  - Increased in HIV (4x), HCV (5x) or both HIV-HCV (14x) co-infections
  - Usually in 1st 4-8 weeks of therapy – typically 0.1-1% risk without underlying liver disease
  - *Rapid improvement* (AST/ALT) after stopping drugs - clue to INH toxicity

- Note transient **asymptomatic elevation** of AST/ALT in 10-15% (usually in 1st 4-8 weeks of therapy) – usually resolves
Isoniazid (INH) – Adverse reactions

- **Peripheral neuropathy** – “stocking glove” process, numbness / tingling
  - Give vitamin B6 (25-50 mg/d) to at risk patients:
    - i.e., diabetes, pregnancy, renal insuff., alcoholism, seizure disorder, malnutrition, and HIV-infection
- Other:
  - Hypersensitivity – (+) ANA (< 20%); lupus-like reaction (≤10%)
  - Arthralgias, pellagra, acidosis
  - **Drowsiness** – therefore favor admin. at evening time
  - CNS - toxic psychosis, behavioral changes, seizure / gen. convulsions
Novel INH drug interactions

• INH can increase phenytoin (Dilantin) and carbamazepine serum concentrations
  • Higher risks of drug toxicity
• In relatively high doses, INH can also increase effect of theophylline and warfarin
• Isoniazid inhibits metabolism of selected benzodiazepines and vitamin D
• Food notably decreases isoniazid bioavailability

Rifampin – Adverse reactions

• Hepatotoxicity / hepatitis
  • \( \uparrow \text{increased bilirubin} \) is a clue to RIF toxicity
  • \( \uparrow \text{AST/ALT} \) can also occur

• Cytopenias - \( \downarrow \text{WBC, Plts} \) (*bleeding problems)

• Light chain proteinuria / nephrotoxicity

• Influenza-like syndrome; myalgias

• Hypersensitivity reactions (lupus-like reactions can occur with rifamycins)
**Rifampin – Adverse reactions**

**Orange discoloration** of body fluids including Urine and tears

- NOT a drug toxicity; an expected finding
- Can permanently stain soft contact lenses
- Ask pts about orange urine during f/u evaluations:
  - Can be a marker of drug compliance (for pts on SAT)
Rifampin – Adverse reactions

- **Drug interactions** - induces Cyt. P450 system and will *decrease* levels of:

  - Steroids
  - Coumadin
  - Digoxin
  - OHAs
  - OCAs/estrogen
  - Methadone
  - Quinidine
  - Azoles
  - Protease inhibitors
  - Theophylline
  - Dapsone
  - Ca2+ channel block
Novel Rifamycin problems

Rifampin

• Flu-like syndrome: 0.4-0.7% pts
  • More common patients taking BIW 600mg
  • Less common with daily dosing 600 mg

Rifabutin

• Polyarthralgia in 1-2% pts on standard 300 mg/d
  • More common in higher doses
Rifabutin

• Less hepatic CYP 450 induction effect
  • Still occurs but to lesser degree

• RBT is a substrate of CYP 450 3A4
  • Other drugs metabolized via CYP 450 isoenzyme cascade can bump up / increase RFB drug levels
  • May require RBT dose reductions
  • Examples:
    • Triazoles – including: fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole
    • *Protease inhibitors (HIV infection)
Rifamycins (class)

• The Rifamycin class produces *an induction* of hepatic CYP 450 isoenzyme metabolism
  • But to differing degrees

Rifampin > rifapentine > rifabutin

*Stronger/more potent Hep CYP induction*

*Weaker / less potent Hep CYP*
Rifamycin “Take Home Points”

Remember:

• Counsel patients on the *expected* Orange discoloration of urine

• Always review patients' *other medications* for drug-drug interactions with the Rifamycin class
Pyrazinamide (PZA) – Adv rxns

- Hepatotoxicity / hepatitis – modest rises in transaminases
  - Slow hepatic/transaminase recovery is clue to PZA toxicity
- Hyperuricemia – can be used as a marker of drug compliancy
  - Development of gout is rare; but can worsen pre-existing gout
- *Arthralgias - particularly of shoulders
- Other: GI upset, Rash, Glucose dysregulation
Pyrazinamide (PZA)

• Asymptomatic Hyperuricemia
  • Expected effect of the drug; does not predictor of gouty attacks (in pts without history of gout)
  • Acute gout is RARE (except in pts with pre-existing gout)
  • Can be a marker / measure of drug compliance

• Non-gout Polyarthralgia
  • May occur in up to 40% pts on daily PZA
  • Shoulders commonly affected
  • Rarely requires dose adjustment drug modification
  • Usually controllable with NSAIDs
# Pyrazinamide and Gout

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<tr>
<th>Problem</th>
<th>Action</th>
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<tbody>
<tr>
<td>Arthralgia</td>
<td>NSAIDS if needed</td>
</tr>
<tr>
<td>Uric acid elevation</td>
<td>nothing if asymptomatic</td>
</tr>
<tr>
<td>Flare of gout</td>
<td>stop PZA if possible, try to lower uric acid levels</td>
</tr>
<tr>
<td>Persistent arthritis</td>
<td>look for another cause of inflammation</td>
</tr>
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Note: Isoniazid can lead to joint inflammation as a manifestation of SLE syndrome
Ethambutol – adverse reactions

- **Retrobulbar / optic neuritis**
  - ↓ visual field, ↓ red-green color discrimination
  - Monitoring - Visual acuity & color vision (baseline and monthly)

- **Contraindications:**
  - Pre-existing optic neuritis (from any cause)
  - Inability (i.e. young pt. age) to report visual disturbances (relative contraindication)
Monitoring for EMB toxicity

• **Monthly** office examinations
  • Visual acuity:
    • E.g. read while pages of phone book
  
  • Color vision – color chart
    • E.g. Via iPhone app

• **Every 3 mo.** formal funduscopic evaluation
Ethambutol – adverse reactions

• Retrobulbar / optic neuritis
  • Higher risk with renal failure, dose > 15 mg/kg, or duration > 2 months
    • Dosing should be 15 mg/kg for prolonged course (more than 2 months)
  • If visual disturbance suspected, discontinue drug immediately and refer for Ophthalmology evaluation
    • Severe and permanent vision loss possible if ethambutol not stopped

• Other:
  • peripheral neuropathy (rare) - occasionally in legs
  • hyperuricemia (rare)
  • hair loss (rare)
Section II
Management strategies for the more common drug toxicities
Approach to Drug-Associated Hepatitis

General Principles:

• Not unusual for patients just starting combination TB therapy to experience upset stomach
  • Pts need counseling that this is **NOT uncommon**
  • INH, Rifampin, PZA all can produce gastritis
    • Symptoms can be similar to hepatitis, but LFTs **remain normal**

• Patients who develop anorexia, nausea, vomiting, abdominal pain, jaundice – more concerning
  • Stop all medications promptly, examine patient and check LFTs
# Gastrointestinal Upset

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<th>Action</th>
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| Gastric discomfort | Give medication with food  
                     Change time of administration  
                     Acid suppression  
                     Check for H. pylori  
                     Discontinue drugs and follow response |
| Nausea             | Discontinue drugs and follow response  
                     Check for hepatitis  
                     Anti-emetics |
| Aversion to pills  | Crush pills  
                     Liquid form of medication  
                     Split the dose |
**Approach to Drug-Associated Hepatitis**

**General Principles (cont’d):**

- ALT is more specific for hepatocellular injury
  - AST can also be produced from muscle, heart, etc.
- If AST > ALT, assess for excessive alcohol intake
- 10-20% of patients on INH will have asymptomatic rise in transaminases
  - Tends to occur during 1st few months on INH
  - Not a toxicity and does not require cessation of therapy
  - Improves with continuation of therapy
Approach to Drug-Associated Hepatitis

Follow-up assessments - I:

Stop all TB meds promptly with:

• Any abnormal LFTs and the **presence of adverse symptoms**
  - Some guidelines state adverse symptoms and transaminases $\geq 3 \times$ upper limits of normal range
• AST or ALT $> 5\times$ upper limits (ULN) of normal
• If bilirubin is elevated, with or without symptoms
  - Note that rifamycins may mildly increase bilirubin (and not necessarily a toxicity – requires *clinical context*)
Approach to Drug-Associated Hepatitis

Follow-up assessments - II:

• Then patient should have LFTs checked 1-2x weekly
  • If symptoms persist > 2 weeks off TB medications or if LFTs continue to worsen, then consider progressive hepatitis and/or an unrelated cause of hepatitis – patient may need hospitalization
    • Underlying HCV, HBV, acute HAV infection
    • Other medications (non-TB)
    • Alcoholism (usually AST >ALT)

• As soon as hepatitis is identified, a hepatitis viral profile should be ordered
Approach to Drug-Associated Hepatitis

Important notes:

• If the patient has extensive pulmonary, meningeal or disseminated TB – then may not be able to temporarily observe off therapy:

• Consider using a temporary “liver sparing” combination drug regimen while awaiting LFTs to improve:
  • E.g. Fluoroquinolone, ethambutol, amikacin

• Add other drugs as LFTs improve to constitute appropriate regimen
Important notes:

Pattern of LFT abnormalities – clues to offending agent

- RFP usually produces a **cholestatic pattern** (bilirubin & Alk phos. out of proportions to AST/ALT)
- INH, RFP, PZA may produce **hepatocellular pattern** (AST/ALT elevated out of proportion to bilirubin or Alk phos)
Approach to Drug-Associated Hepatitis

Restarting Medications after LFTs normalize or significantly improve:

- **Hepatocellular pattern:**
  - Start with Ethambutol and Rifampin x 1 week
    - Recheck LFTs – if stable/improved:
  - Add INH or PZA *(which drug to add is debated; favor adding INH)*
    - Recheck LFTs – if they remain stable:
    - Continue with EMB / Rifampin / INH or EMB / Rifampin / PZA for the duration of therapy
      - At least monthly LFTs (more frequently early on)

- **Notes:**
  - INH and PZA are most commonly associated with hepatotoxicity
  - Some reports implication PZA more frequently
  - Combination using PZA may be more problematic
  - PZA less important in combination TB drug regimen

AJRCCM 2003 167:1472-77
Approach to Drug-Associated Hepatitis

Restarting Medications after LFTs normalize or significantly improve:

- **Cholestatic pattern:**
  - Start with INH and ethambutol x 1 week
    - Recheck LFTs – if stable/improved:
  - Add PZA
    - Recheck LFTs – if they remain stable:
    - Continue with INH/EMB/PZA – favor adding FQ
      - At least monthly LFTs (more frequently early on)
      - More prolonged duration of therapy without rifamycin used

- *Note (given importance of rifamycins) - might consider graded introduction of rifabutin or rifampin cautiously (judgement call)*

- If symptoms are not related to TB drugs, then restart entire drug regimen promptly and observe
# Specific Drug-Associated Liver Effects

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<th>Effects on Liver</th>
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<td>Typically more hepatocellular (ALT/AST); usually fairly rapid reversibility if INH stopped at onset of symptoms</td>
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<td>• Increased risk with other hepatic metab. Medications (e.g. Rifampin, PZA)</td>
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<tr>
<td>Rifampin</td>
<td>Cholestatic picture more common (↑ Bili); ALT/AST may also be elevated (less common)</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Hepatoxicity not uncommon; can be severe are more prolonged / slower resolution</td>
</tr>
<tr>
<td>Less common:</td>
<td>Occasionally implicated with hepatotoxicity</td>
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<tr>
<td>Ethionamide</td>
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<tr>
<td>Para-aminosalicylic acid</td>
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<tr>
<td>Not commonly associated with hepatotoxicity</td>
<td>Consider using these drugs when TB therapy cannot be held in cases of hepatotoxicity (e.g. severe TB)</td>
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<tr>
<td>Ethambutol</td>
<td>• Especially <em>early in therapy</em> for disseminated, miliary or meningeal TB</td>
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Restoring Anti-TB Medications in Patients with Drug-Induced Hepatitis

Patient taking anti-TB drugs has symptoms consistent with hepatitis

- Discontinue medications: Check LFTs and Hepatitis Screen
  - Normal LFTs*/Negative Hepatitis Screen: whether symptoms improve or not related to anti-TB drugs
    - Restart same regimen
  - Abnormal LFTs*/Negative hepatitis screen
    - Is treatment absolutely essential?
      - Yes: Give EMB, SMN, FQ
        - Follow LFTs weekly
      - No: Discontinue treatment
        - Follow LFTs weekly

- Cholestatic LFT pattern initially
  - Rechallenge with INH, EMB for 1 week
    - Repeat LFTs
    - If LFTs stable, add PZA
      - Repeat LFTs
      - If LFTs stable, treat with INH, EMB, PZA* (assume RIF-induced hepatitis)
  - If LFTs stable, treat with INH, EMB, PZA* (assume RIF-induced hepatitis)
    - Consider trial of Rifabutin*3
      - Repeat LFTs, if LFTs stable
      - Follow LFTs, monthly for remainder of treatment

- Hepatocellular LFT pattern initially
  - Rechallenge with RIF and EMB (if not on it already) for 1 week*4
    - Repeat LFTs
    - If LFTs worsen, discontinue RIF (and EMB) for 1 week
      - When LFTs stable, rechallenge with EMB and INH for 1 week
      - Repeat LFTs
      - If LFTs stable, add INH for 1 week
        - Repeat LFTs
        - If LFTs stable, add PZA for 1 week
          - Repeat LFTs
          - If LFTs stable, treat with EMB, RIF, PZA, ± FQ if extensive disease (assumed RIF-induced hepatitis)
            - Follow LFTs, monthly for remainder of treatment

Note: *Treat with INH, EMB, PZA* (assume RIF-induced hepatitis)

Summary - algorithm

Clinical Policies and Protocols
Bureau of Tuberculosis Control
New York City Department of Health and Mental Hygiene
4th ed. 2008
Other *select* drug reactions:

- CNS changes
  - Behavioral
  - Seizures
- Peripheral neuropathy
- Skin Rash
  - Mild skin rash
  - TEN / SJS
- Hypothyroidism
CNS changes

• Depression
  • Cycloserine
  • Ethionamide
  • INH (in patient with baseline *unstable* or untreated mental health problems)
    • Need to check pt’s mental health history
    • Can cause sleepiness (best to give at night / before bedtime for LTBI therapy)

• Psychosis: Cycloserine, INH

• Seizures: INH, ethionamide

• Remember:
  • **Pyridoxine (Vit B6)** required with Cycloserine and Ethionamide; used with INH in pts with select risk factors
  • Add 50 mg Vit. B6 for each 250 mg of cycloserine (variable) OR 100 mg/d total with CYC
Peripheral Neuropathy

- Symmetric polyneuropathy
  - Early: paresthesias
  - Late: sensory loss, ↓reflexes, ↓proprioception
- Predisposed in patients with:
  - Alcoholism, diabetes, HIV infection, malnutrition
- TB drugs implicated:
  - Isoniazid, ethionamide, cycloserine, linezolid
  - **Note:** overly high Vit. B6 doses (≥ 200 mg/d) can occasionally produce neuropathy
- Treatment
  - Start Vit. B6 if not already done so (typically 100-150 mg/d)
  - Stop/change TB drug therapy (if possible)
  - Low dose TCAs or gabapentin (if refractory)
Skin lesions - I

Maculopapular rash & Itching

- Typically develop early / during first few weeks of therapy
- Patient otherwise feeling fine/well
- For *mild cases*: May resolve with cautious continuation of all medications
Skin lesions - II

Maculopapular rash & Itching

- Moderate / severe: need to stop drugs
- Reported with all 1st line TB drugs
- Mgmt approach
  - Ensure no other non-TB drugs were started
    - E.g. OTC agents, herbal drugs; other prescriptions drugs
  - For non-type I reactions (non-anaphylaxis / non-angioedema):
    - Reintroduce TB medications 1 at a time – observing for recurrence of skin lesions
    - Start with most important TB drugs: Rifampin – then INH – then PZA or EMB
    - Space drug introductions by 3-5 days
Skin lesions – III (more serious)

SJS, TEN, DRESS

- Early or delayed onset
- Progressive skin lesions; often with mucosal involvement (SJS/TEN)
- Often with fever, and often multi-organ involvement; +/- lymphadenopathy (DRESS; SJS, TEN)
Skin lesions – III (more serious)

• Management approach:
  • Immediate stop all medications
    • Avoid restarted offending agent – if known
  • Dermatology consult (may need to be inpatient)
    • Skin biopsies occasionally recommended – depending appearance of skin lesions
  • Mgmt can be very challenging if offending drug not identified and/or limited drug options (MDR TB)
Hypothyroidism

• TB drugs implicated:
  • Ethionamide
  • Para-aminosalicylic acid (PAS)

• Risk increased when both drugs used together (at least 40% incidence; possibly higher)
  • A reversible endocrine effect

• Monitoring:
  • Monthly clinical assessments
  • Check sTSH baseline and q 3 months
  • Replace with thyroid hormone (Synthroid) if sTSH rises
    • Do not need to stop TB drugs
Antimicrobial Agents
General Principles - 2nd Line Agents

Less Effective

More Toxic

More Expensive
2nd - line Anti-Tuberculosis Drugs

- Aminoglycosides
  - Streptomycin, Amikacin & Kanamycin
- Capreomycin
- Thioamides
  - Ethionamide
  - Prothionamide
- Fluoroquinolones
  - Moxifloxacin
  - Levofloxacin
  - Ciprofloxacin
- Cycloserine (and Terizidone)
- Para-Aminosalicylic Acid (PAS)
- Other:
  - Linezolid
  - Bedaquiline (TMC 207) – FDA approved 12/2012; a new diarlyquiline
  - Clofazimine
Streptomycin

Adverse reactions:

- Vestibular toxicity - monitor for HA, nausea, vomiting, tinnitus, imbalance
- Auditory toxicity (hearing loss) – less than other aminoglycosides
- Nephrotoxic
- Rare: Hemolytic anemia
  Thrombocytopenia
  Agranulocytosis, lupus reactions
Amikacin & Kanamycin

• Audio-toxicity - high frequency hearing loss (irreversible)
• Vestibular dysfunction (irreversible)
• Nephrotoxicity - reversible
• Eosinophilia

Monitoring:
• Renal function / Creatinine
• Weekly serum levels
• Monthly Audiograms / Balance testing
**Fluoroquinolones**

- “Newer” fluoroquinolones preferred: *Moxifloxacin, Levofloxacin*
  - More active compared to ciprofloxacin, ofloxacin
- Generally *well tolerated* among 2\(^{nd}\) line TB drugs

- Notable side effects:
  - Tendonitis; tendon rupture (Achilles tendon most common)
  - QTc prolongation
    - Higher risk when given with other QTc prolonging drugs – e.g. bedaquiline, clofazimine, Zofran, azole-antifungals, etc.
  - Contraindicated in patients with Myasthenia Gravis
  - Insomnia, lightheadedness, dizziness
  - Peripheral neuropathy
Linezolid

• An oxazolidinone
• 600 mg once daily dosing preferred
  • Twice daily dosing recommended for MRSA and other drug-resistant Gram-positive bacteria

• Select Toxicities include:
  • Myelosuppression
  • Peripheral neuropathy
  • Ocular toxicity
  • Mitochondrial toxicity; hyperlactatemia
  • Serotonin toxicity - when administered in combination with a SSRI or a nonselective MAO inhibitor
    • LZD is structurally similar to tolaxotone, a known MAO inhibitor
    • Two of its metabolites are structurally related to moclobemide - a reversible MAO-A inhibitor and has been reported to cause serotonin toxicity

Ethionamide

- *GI intolerance – (high likelihood) N/V, diarrhea, dysgeusia; metallic taste
- Arthralgias
- **Endocrine disorders:** *Hypothyroidism
  *Glucose intolerance
  Sexual dysfunction ↓ Libido
  Erectile dysfunction       Menstrual Abnor.

- Peripheral neuropathy (with prolonged therapy) - reversible
- Hepatitis (10% cases) - rarely serious
- Caution with co-administration of:
  - PAS (GI distress, hypothyroidism)
  - Isoniazid (peripheral neuropathy, hepatitis)
Cycloserine

• CNS toxicity
  • Inability to concentrate and lethargy
  • Seizure, depression, psychosis, and suicidal ideation
    • usually occur at peak concentrations > 35 mcg/ml
    • Can also be seen in the normal therapeutic range
    • Need to give Vitamin B6, 100 mg/d

• Other Toxicities:
  • peripheral neuropathy
  • Skin problems include lichenoid eruptions and Stevens-Johnson syndrome
Para-aminosalicylic acid (PAS)

Delayed-release PASER granules (acid-resistant outer coating)

- Bulky, unpleasant taste
- *GI disturbance - anorexia, nausea, vomiting, abdominal discomfort
- Hypothyroidism, goiter (PAS has anti-thyroid effect); *Caution when administering with Ethionamide
- Hepatic dysfunction
- Hypersensitivity reaction / skin rash
Dose Escalation Strategies: Ethionamide, Cycloserine, PAS

- Ethionamide & cycloserine
  - Start with 250 mg daily x a few days
  - Increase to 250 mg bid x a few days
  - Increase to 250 mg/qAM and 500 mg q/PM
    - Check serum level

- PAS (Paser granules, sachet packets)
  - Start with 2 gm bid x a few days
  - Increase to 2 gm/qAM and 4 gm qPM x few days
  - Increase to 4 gm bid
    - Check serum level
Bedaquiline

- Increased risk of death (11.4% vs. 2.5% in comparator group)
- Elevated QTc (although not felt to be a major risk by CDC group meeting)
  - May be additive with other QTc prolonging drugs - *caution by FDA
- Higher hepatic adverse reactions
- Drug interactions via Hepatic CYP 3A
  - M2 is major metabolite (4-6x less potent)
  - BDQ does not increase or decrease 3A4 activity
  - Rifampin will decrease BDQ levels (via accelerated 3A4 metabolism)
- Limited data in HIV co-infected patients

CDC RTMCC meeting January 14-15, 2013
Clofazimine

• Used for MDR TB, Leprosy

• Side effects include:
  • Bronze skin pigmentation (75-100%)
  • GI / stomach upset; N/V (40-50%)
  • QTc prolongation potential
    • Monitor ECG when given with quinolones and/or BDQ
  • Ocular: Conjunctival and corneal pigmentation due to crystal deposits

• No longer commercially available in the United States
  • Clofazimine can be obtained by submitting an IND through the National Hansen’s Disease (Leprosy) Program (NHDP)
The End

Questions?