Adverse Reactions to TB Meds: What do I Stop? What and When do I Restart?

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Objectives

• Understand how we define and monitor for adverse drug reactions from TB medications
• Recognize the most common types of adverse drug reactions: minor → major
• Understand which medications most commonly cause which types of problems
• Provide practical approaches to managing the most common ADRs including GI toxicity, hepatotoxicity, skin rashes, and others
Case 1

• A 63 year old Vietnamese born woman is diagnosed with smear positive pulmonary tuberculosis and is started on 4 drug anti-tuberculocous therapy with RIPE. She is receiving her treatment by DOT. About one week into treatment she complains to her clinic nurse that the medications are “making her sick” and she wants to stop them
Q1. Is this woman having an adverse drug reaction to her anti-tuberculous therapy?

A) No, these are expected side effects of treatment and treatment should not be stopped

B) Yes, these is definitely an adverse drug reaction and will require change in her therapy

C) It is an adverse drug reaction only if her liver enzymes are elevated

D) Can’t tell, she will need further evaluation
What is an ADR?

• Several different definitions used

• World Health Organization definition: “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease”

• Side effects vs. ADRs

  – “Side effect” is a less precise term, often refers to milder, predictable effects of taking a medication. Example: orange urine from RIF
What is a “Significant” ADR?*

- Requires discontinuing the drug
- Requires changing the drug therapy
- Requires modifying the dose
- Necessitates admission to a hospital
- Prolongs stay in a health care facility
- Necessitates supportive treatment
- Negatively affects prognosis
- Results in temporary or permanent harm, disability, or death

*Am. Soc. Of Health-System Pharmacists (ASHP)
Monitoring for ADRs

• A process starting before initiating treatment and continuing through the entire treatment course
• Assessment for factors increasing risk of an ADR
  – or delay recognition if occurs
  – e.g. increased age, underlying medical conditions: liver disease, peripheral neuropathy
  – Concomitant medications and supplements
  – Behavioral risk factors: e.g. alcohol
  – Barriers to effective monitoring: language/ cultural, psychiatric issues
• Baseline laboratory monitoring
Prescribing anti-Tuberculous therapy: A risk benefit analysis

• Treatment for TB Disease
  – Benefits always outweigh the risks, but those at higher risk need more careful monitoring

• Treatment for LTBI
  – Weigh risks (toxicity) vs benefits of treatment
  – Those at highest risk of progression to TB disease should always be treated (e.g. HIV+, infant contacts) despite risks of therapy
  – But: risks may outweigh benefits for some groups

➤ Baseline evaluation incorporates risk assessment

Source: h.fraitmow
We know what the benefits of Rx are, Can we modify the risks?

By choice of regimen: eg. less hepatotoxic
Behavioral interventions: eg. alcohol
By having a good monitoring plan
By reacting quickly if problems do arise
Prospective Monitoring for ADRs

• Collaboration between client and TB program
• Client education
  – Make sure they are educated about potential serious ADRs from their regimen *but how to educate*
  – Make sure they understand the need to report them
• Staff education
  – Make sure they are aware of potential serious ADRs from different TB meds
  – Make sure to assess for symptoms of ADRs at each and every interaction AND document them
• Interactions: Monthly medication pick ups, daily or other DOT visits, phone calls, any other interactions
Minor vs Serious Drug Reactions

- Mild reactions
  - No lasting effects
  - Usually do not require change in the TB regimen
  - May respond to simple interventions e.g. taking pills with food; antihistamines
  - eg: gas, bloating, itching, HA

- More “severe”
  - Require more intensive monitoring
  - Potentially life threatening if ignored
  - May require change in therapy
  - May require hospitalization
  - eg: liver toxicity, severe skin reactions
Consequences of Severe ADRs

• Worst cases: severe morbidity and even death *example:* *fatal hepatitis*

• Need for more intensive clinical and laboratory monitoring

• Need for alternative, more protracted and potentially less effective treatment regimen
  
  ➢ *Treating TB in those with multiple ADRs as challenging as treating MDR disease*

• Potential impact on compliance and treatment outcome
Most Common Types of Drug Toxicity

- Gastrointestinal toxicity
- Hepatotoxicity
- Hypersensitivity (allergic) reactions
- Other dermatologic reactions
- Joint symptoms
- Neuropathy
- Visual symptoms
- Drug fever
- Other: nephrotoxicity, hearing loss
## What Drug can do what?
### ADRs to First Line Agents and FQ*

<table>
<thead>
<tr>
<th>Reaction</th>
<th>INH</th>
<th>RIF</th>
<th>EMB</th>
<th>PZA</th>
<th>FQ</th>
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<tbody>
<tr>
<td>Gastrointestinal</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Hepatotoxicity</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<td>Cutaneous</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
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<td>Periph. Neuropathy</td>
<td>X</td>
<td></td>
<td>X (rare)</td>
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<td>Optic Neuritis</td>
<td>X (rare)</td>
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<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Arthralgia</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Gout</td>
<td></td>
<td>X (rare)</td>
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<td>X</td>
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<td>Tendonitis</td>
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<td>X</td>
</tr>
<tr>
<td>Flu-Like Syndromes</td>
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<td>X</td>
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<td></td>
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<tr>
<td>Thrombocytopenia</td>
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<tr>
<td>CNS</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Drug Fever</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Levofloxacin or Moxifloxacin*
How Common are ADRS to TB Meds?

• LTBI Treatment Regimens
  – Generally healthy, limited number of drugs
  – Lots of historical data for risk of INH toxicity, some (fewer) for risk with other regimens
  – Comparative data from some recent large clinical trials and from meta-analyses
    • 9 mos of INH vs 12 weeks of INH plus Rifapentine
    • INH vs Rifampin

• TB Disease Treatment Regimens
  – Multi-drug regimens, overlapping toxicites
  – More difficult to assign “blame” for ADRs
Table 1. Hepatotoxicity rate, adjusted for compliance with therapy, by age groups.

<table>
<thead>
<tr>
<th>Age range</th>
<th>Adjusted incidence hepatoxocity per 1000</th>
</tr>
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<tbody>
<tr>
<td>0 – 19</td>
<td>0.8</td>
</tr>
<tr>
<td>20 – 34</td>
<td>2.8</td>
</tr>
<tr>
<td>35 – 54</td>
<td>9.1 (or 17.2*)</td>
</tr>
<tr>
<td>&gt; 54</td>
<td>31.0</td>
</tr>
</tbody>
</table>

Adjusted incidence by age group (criteria from Table 2 applied to age subgroups). References [28-36] were used.

*Reference [29] included in 35 – 54 group (based on mean age of participants = 50). If this study is excluded, rate for 35 – 54 is 17.2.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Isoniazid Only (N = 3759)</th>
<th>Combination Therapy (N = 4040)</th>
<th>P Value†</th>
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</thead>
<tbody>
<tr>
<td>Permanent drug discontinuation — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For any reason</td>
<td>1160/3745 (31.0)</td>
<td>713/3986 (17.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Because of an adverse event</td>
<td>139/3745 (3.7)</td>
<td>196/3986 (4.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Death — no./total no. (%)</td>
<td>39/3745 (1.0)</td>
<td>31/3986 (0.8)</td>
<td>0.22</td>
</tr>
<tr>
<td>Any serious adverse event — no. (%)‡</td>
<td>109 (2.9)</td>
<td>64 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥1 Adverse event — no. (%)§</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Any</td>
<td>661 (17.6)</td>
<td>595 (14.7)</td>
<td>&lt;0.001</td>
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<tr>
<td>Pregnancy</td>
<td>71 (1.9)</td>
<td>45 (1.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Medication error</td>
<td>37 (1.0)</td>
<td>27 (0.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>All other adverse events</td>
<td>584 (15.5)</td>
<td>531 (13.1)</td>
<td>0.003</td>
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<tr>
<td>Attribution — no. (%)¶</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Related to drug</td>
<td>206 (5.5)</td>
<td>332 (8.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>103 (2.7)</td>
<td>18 (0.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Rash</td>
<td>21 (0.6)</td>
<td>31 (0.8)</td>
<td>0.26</td>
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<td>Possible hypersensitivity**</td>
<td>17 (0.5)</td>
<td>152 (3.8)</td>
<td>&lt;0.001</td>
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<tr>
<td>Other drug reaction</td>
<td>65 (1.7)</td>
<td>131 (3.2)</td>
<td>&lt;0.001</td>
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<tr>
<td>Not related to drug</td>
<td>410 (10.9)</td>
<td>226 (5.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Severity of adverse event — no. (%)†</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 or 2</td>
<td>341 (9.1)</td>
<td>310 (7.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Grade 3</td>
<td>202 (5.4)</td>
<td>193 (4.8)</td>
<td>0.24</td>
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<tr>
<td>Grade 4</td>
<td>42 (1.1)</td>
<td>36 (0.9)</td>
<td>0.32</td>
</tr>
<tr>
<td>Nongraded events</td>
<td>31 (0.8)</td>
<td>19 (0.5)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Incidence of adverse events during TB treatment – Montreal Chest Institute

• Retrospective review of 403 adult patients

➢ 9.2% (37/403) patients had major ADRs that lead to drug discontinuation
  – 9 had second adverse reaction (total 46 events)

• Rash/fever 4%, Hepatitis 2.9%, other GI 2%

• Risks:
  – Female > Male
  – Age > 60

Incidence of serious side effects by type and drug

Shaded columns, isoniazid; cross-hatched columns, rifampin; open columns, pyrazinamide; dotted columns, ethambutol.

AJRCCM 2003;167(11): 1472-1477
Demographic differences in adverse events: Female > Male, Older > Younger

Sex-related differences

Age-related differences

AJRCCM 2003;167(11): 1472-1477
ADRs: Some other studies

• Tuber. and Lung Disease, 1996 (UK)
  – 5.1% ADRs requiring treatment modification
  – over 60 4x > under 19
  – female > male

• PLOS 1, 2011 (Lima, Peru)
  – Risks for ADRs: Age, Obesity, anemia, smoking

• Int. J. of Env. Res. Pub. Health 2016 (China)
  – 462 pts: 22.1% ADRs, 3.1/100 patient mo.
  – 37% hepatic, 24% other GI toxicit

➢ Why such variability in the rates of toxicity?
“Don’t take any of these red pills, and if that doesn’t work, don’t take any of the blue ones”
Patient 1

• When further interviewed, the patient says that when she takes her TB pills, she feels “sick to her stomach” and can’t eat. She has not vomited and does not have abdominal pain. She denies dark urine.
  – She has blood drawn for liver enzymes
  – ALT is 58 (upper limit of normal 55, baseline was 27 before treatment); AST is normal
  – Total Bilirubin is 0.7 (normal)
Q2. The most likely explanation for her symptoms is:

A) Gastrointestinal toxicity from INH
B) Hepatotoxicity from INH
C) Gastrointestinal toxicity from PZA
D) Gastrointestinal toxicity from any of her anti-tuberculous medications
Q3. How would you try and manage her symptoms?

A) Stop all anti-tuberculous medications and re-introduce them one at a time
B) Try giving medications with food or at a different time
C) Try giving medications with an anti-emetic
D) Stop the PZA and see if symptoms resolve
Gastrointestinal (GI) Toxicity

- Nausea
- Vomiting
- Diarrhea
- Bloating
- Anorexia
- Abdominal pain

- Overlap of GI and hepatotoxicity symptoms
- Can’t tell without LFTs (ALT, AST, bilirubin)
Which Drugs are Most Likely to Cause GI toxicity (and When?)

- Almost any drug can potentially cause GI toxicity
- Often occurs early (first few weeks) of Rx
- Hierarchy: PZA > INH > RIF > EMB
- Fluoroquinolones can also cause GI toxicity but less commonly than PZA or INH
- Many of the other 2nd line drugs cause gastrointestinal toxicity (rarely injectables)
Management of GI Symptoms (after excluding hepatotoxicity)

- Change the timing of the dose
- Give meds with food (how much food?)
- Daily dosing with fewer pills rather than intermittent (3x per week) therapy
- Antacids 2hr before or after
- Anxiolytic if the nausea occurs prior to swallowing the pills
- Anti-emetics: odansetron, promethazine, prochlorperazine, hydroxyzine
Antiemetic Options

• Ondansetron (Zofran)
  4 to 8 mg PO twice daily prn
• Promethazine (Phenergan)
  12.5 to 25 mg every 6 hours prn
• Prochlorperazine (Compazine)
  5 to 10 mg every 6 hours prn
• Hydroxyzine (Vistaril or Atarax)
  25 to 50 mg every 6 hours prn
Case 2

- 34 yo from Ecuador with pleural TB diagnosed 6 weeks post partum. She was started on RIPE and is in her 5th week of treatment. She complains of some mild nausea on her clinic visit. She looks mildly jaundiced, her abdominal exam is normal.

- Her LFTs are:
  - ALT 732 (ULN 55)
  - AST 444 (ULN 50)
  - Bilirubin 3.4
Q4. How should her symptoms be managed?

A) Stop all TB medications until LFTs return to 2X ULN
B) Stop INH and follow LFTs
C) Stop INH and PZA and follow LFTs
D) Stop INH, RIF and PZA, continue EMB and add 2 non-hepatotoxic anti-tuberculous agents
Hepatotoxicity

- Elevation in liver enzymes: ALT (AST, Bili)
- Confounders: Other drugs/supplements, alcohol, viral hepatitis, other liver/biliary tract disease
- Spectrum of hepatotoxicity (Drug Induced Liver injury aka DILI)
  - Symptomatic or asymptomatic
    - Asymptomatic mild AST ↑ in up to 20% on INH,
    - ATS *symptom related* threshold for stopping Rx: ALT 3x upper limit of normal
    - ATS *asymptomatic* threshold for stopping Rx: ALT 5x upper limit of normal
  - Fulminant Hepatitis (rare)
Some Risk Factors for Hepatotoxicity from Anti-tuberculous Therapy

- Increasing age
- Malnutrition or hypoalbuminemia
- PZA in regimen
- Other hepatotoxic agents
- Alcohol
- Pregnancy or post-partum
- Elevated baseline ALT
- HIV infection
- Multiple medical problems
- Pre-existing chronic liver disease
- Chronic Hepatitis: B and/or C
Managing Suspected Hepatotoxicity

Hold all meds and check LFTs

- No symptoms and LFTs $\leq 5X$ ULN: Continue therapy
- No symptoms and LFT $> 5X$ ULN: STOP therapy
- Symptomatic and LFT $>3X$ ULN: STOP therapy

Note: Patients with underlying cirrhosis may not demonstrate typical elevations in ALT and AST, must rely on other clues
Treatment Limiting Thresholds

- ALT > 3 X ULN with nausea, vomiting, or abdominal pain
- ALT > 5 X ULN in all, regardless of Sx
- Interrupt treatment, but how to do it? Stop everything?
- If moderate/severe TB, then continue at least 3 drugs
  - Rifampin, EMB, fluoroquinolone
  - Hepatic sparing regimen: EMB, FQ, injectable
- Assess for confounders
  - Concomitant meds, OTC, supplements, herbals, EtOH
  - Acute viral hepatitis testing: Hep A, B, C
  - Role for liver Biopsy?
- In rare instances, ↑LFTs can be due to the TB disease

From: Am J Respir Crit Care Med. 174; 935–52, 2006
So now we’ve stopped, what then?
Practical aspects of re-challenge

- Can restart once ALT < 2 X ULN
- Many can even return to original regimen
- Weigh risks based on severity of hepatotoxicity
- Different strategies:
  - Sequential re-challenge: most useful to sort out cause of hepatotoxicity if recurs; re-introduce drug q. ~7 days with careful LFT monitoring
    - RIF +/- EMB, then INH, +/- PZA
    - If symptoms or LFTs ↑ stop last drug added
    - If RIF and INH are tolerated, and hepatitis was severe, do not add back PZA
Severe Hepatitis: A Recent Example

- 11 year old with asthma, on no medications, household contact of an infectious TB case
- TST “negative” per primary pediatrician, but noted as 15 mm a week later by an ID specialist
- No symptoms, well appearing, normal exam, CXR negative, wt. 54 kg
- Started on INH 300 mg daily on by DOT (due to concerns about parental compliance) thru local Health Department
- DOT after a month transitioned to school nurse
Severe Hepatitis: A Very Recent Example

• No complaints or issues when seen for DOT visits or follow-up pediatric visit a month later
• 4/10/13 (~ 3 mos of Rx) brought to ED by mom with “yellow eyes”, now reports some decreased appetite, nausea and fatigue x 1 week
• On exam, icteric but otherwise normal exam, no abdominal tenderness
• Labs: AST 2158 ALT 2234 Bilirubin 7.8 Alk Phos 361, Albumin 4.0, INR 1.2
• Acute hepatitis serologies all negative
Severe INH liver injuries among persons being treated for LTBI in US 2004-2008
MMWR 2010

• 17 cases reported to CDC (no denominator)
  Rate of fatal hepatitis from older studies (pooled data)
  0.43 per 1000

• 5 died, 5 required liver transplantation

• Can occur anytime in treatment
  – 9 of 17 beyond the 3rd month

• Can occur in children: 2/17

• Diagnosed by other than prescriber: 10 of 17

• Did NOT STOP the medication when symptoms developed: 8 of 17
What about Rifampin Hepatotoxicity?

- Transaminitis much less common than hepatotoxicity from INH or PZA
- Most common liver injury pattern is cholestatic hepatitis
  - Elevated Bilirubin and Alk Phosphatase
  - Often Fever
  - Often other Manifestations of hypersensitivity reaction
  - Generally have to stop the drug
Case 3

- 64 year old Korean male with recently diagnosed presumed lymph node tuberculosis
- +TST, enlarged cervical LN, biopsy: necrotizing granuloma and AFB, Cultures pending
- Started on RIPE
- Seen in clinic 2 weeks later complaining of a new itchy red rash
Q5. How should this reaction be managed?

A) Stop all his anti-tuberculous medications until the rash subsides
B) Obtain more history about the rash
C) Treat with antihistamines
D) Check for fever, mucous membrane involvement or generalized erythema and if any of these stop his medications
Cutaneous Adverse Drug Reactions (CADRs) to Antituberculous Drugs

• Can be confined to the skin or part of a systemic hypersensitivity syndromes

• Epidemiology and rates of CADRs less well defined than for other toxicities
  – Montreal Chest Institute study: PZA > Rif > INH but in other studies EMB skin reactions also very common

• Severe CADRs more common in HIV+ and in those with multiple drug allergies
Question??

• Does it matter what the rash looks like?
Drug Rashes: The 4 W’s

- **Where**…
  - did it start?
  - has it spread?
- **What**…
  - does it look like?
  - makes it better or worse?
- **When** did it start?
- **Who** has it?

DDx of skin rashes

- Insect bites, scabies. Bed bugs
- Other drugs
- Contact dermatitis
- Acne/folliculitis
- Immunologic/hypersensitivity reactions
- Sunburn
- Pellagra
- Eczema
- Dry skin
- Infections
Skin reactions and Specific Anti-TB Drug Associations

- Acne (INH)
- Photosensitivity (PZA, FQ)
- Purpura (RIF, INH)
- SLE-like syndrome (INH)
- Pellagra (INH)
- Urticaria (Any)
- Exfoliative dermatitis (Any)
- Toxic epidermal necrolysis (Any)
- Stevens-Johnson syndrome (Any)
Minor rashes

- Affects only a limited area
- The itching may be worse than the actual rash
- Not progressing over time
- Management
  - Generally treat symptoms with anti-histamine or a mild topical steroid
  - Continue anti-TB medications
  - Follow closely for any worsening
Generalized Erythematous Rashes

- Any drug can cause this
- Stop all drugs immediately
  - Especially if fever and/or mucous membrane involvement
  - Concern for toxic epidermal necrolysis/ Steven Johnsons
- If severe TB, use three new drugs
- Once rash significantly improved
  - Re-challenge serially
  - Reintroduce new drug every 2 – 5 days- slow better if you have time
    - R, H, E, (Z)
- Adjuvant testing: CBC: eosinophils
- Derm Evaluation and Skin Biopsy
Petechial Rashes

- Check platelet count
- If low: presume rifampin is the culprit for thrombocytopenia, stop Rifampin and monitor platelets
- Rifampin should not be restarted
My Patient had an ADR to Rifampin- What can I do?

- Rifamycins remain our most important drug - much longer regimens without

- Can I give them rifabutin if they?
  A) Yes most of the time it’s OK
  B) Yes but you better monitor them carefully
  C) No, you really shouldn’t
  D) Depends on the reaction
Case 4

• A 56 year old Filipino male is diagnosed with smear positive pulmonary tuberculosis. Susceptibility data are pending.

• History of DM, Chronic Kidney Disease and Coronary artery Disease. Ht 68 inches, wt. 134 lbs., Creatinine 1.7 (Calc Cr.Cl ~35).

• Started on INH 300 mg, RIF 600 mg, PZA 1500 mg, EMB 1200 mg and B6 daily

• He is in his 4th week of treatment and complains of severe joint pains
Q6. How should his symptoms be managed?

A) Check a uric acid and stop PZA if Uric Acid is elevated
B) Start allopurinol
C) Check an ANA (lupus) test and stop INH if positive
D) Continue all medications and treat symptomatically with an NSAID
Joint Complaints: PZA and other

• Arthralgias common with PZA:
  – 8% with joint symptoms,
  – 2% will stop drug
  – Elevated uric acid common
  – Treatment is NSAIDS, allopurinol generally not helpful

• PZA can cause acute gout flares, so history of gout a relative contraindication to use, but an elevated uric acid alone is not a contraindication
Other Musculoskeletal ADRs of Anti-tuberculous Therapy

- **Arthralgias:**
  - INH (much less common than PZA)
  - Fluoroquinolones

- **Gout:**
  - Ethambutol (rare)

- **Tendonitis and tendon rupture**
  - Fluoroquinolones!!!
  - Risk higher with Increased age, corticosteroids
  - **Now a Black box warning**
Case 5

• 54 year old African-American male with Type 2 Diabetes mellitus and hypertension and newly diagnosed pulmonary TB.
• His isolate is pan-sensitive, he completed his initial phase of therapy and is now on continuation therapy with INH and Rifampin 3X per week by DOT
• At his 4 month visit, he complains of numbness and tingling in his hands and feet
Peripheral Neuropathy

- Most common cause: INH
- Dose/duration of treatment related
- Incidence: Overall < 0.2%
- Risk Factors:
  - EtOH, Diabetes, renal failure, pregnancy, other peripheral neuropathies, other neurotoxic drugs, ? Slow metabolizers
  - Prevention: Pyridoxine 25-100 mg/day

Also seen with fluoroquinolones, very rarely reported with EMB
Case 6

- 86 year old woman with diabetes and thyroid disease who is found to have a solitary pulmonary nodule suspected to be cancer. Biopsy of the nodule shows caseating granulomas and cultures grow Mycobacterium tuberculosis. She is being treated with RIPE pending susceptibilities.

- She complains of severe pain and decreasing vision in the right eye.
Q7. How should she be managed?

A) Ophthalmology evaluation as soon as possible
B) Stop her Ethambutol
C) Stop her Isoniazid and Ethambutol
D) Check her color vision, if OK, continue her current TB regimen
Ocular Toxicity

• Ethambutol optic (retrobulbar) neuritis:
  – Decreased visual acuity
  – Decreased red-green discrimination
  – Can be asymptomatic- clients may not notice
  – Risk is increased with renal insufficiency-
    appropriate dosage adjustment in the elderly
    • Creatinine clearance < 30 → 3x per week EMB dosing

• Generally painless, usually bilateral.

• Rarely can be caused by INH

➢ TB involvement of eye: uveitis and other
Monitoring and Management

• Baseline/ monthly
  Visual acuity test (Snellen chart)
  Color discrimination: Ishihara tests (web app available)

• Patient education

• Monthly symptoms
  – blurred vision etc

• Hold medication if any symptoms, but Ophthalmology evaluation ASAP
Case 7

• A 48 year old Mexican immigrant is diagnosed with smear positive pulmonary tuberculosis, pan sensitive. He completed 40 doses of INH, RIF and PZA and has been recently been started on 3X a week therapy with INH and RIF by DOT.

• He now complains of severe “flu-like” symptoms of headache, fever and chills starting about 2 hours after each dose of medication, that resolves by that evening.
Q8. How should these symptoms be managed?

A) Stop INH and RIF and start 2 new drugs
B) Send sputum to assess for relapse of tuberculosis
C) Change back to daily rather than 3x weekly dosing of medications
D) Stop RIF and restart PZA and EMB
Rifampin Hypersensitivity Syndromes

• “Flu-like”: fever, chills, headache, myalgias
  ◦ 1-2 hrs after dose, resolves spontaneously after 6-8 hrs
  ◦ Associated with intermittent and higher doses
  ◦ If mild, consider daily dosing (including weekend)

• Other severe immunologic reactions – all rare, < 0.1% of those on Rx: All require stopping of drug
  ◦ Haematologic: Low platelet count, Haemolytic anemia, Thrombotic thrombocytopenic purpura
  ◦ Renal dysfunction
  ◦ Hepatotoxicity (usually cholestatic enzymes)
  ◦ Severe rash

“Possible Hypersensitivity” to Rifapentene was most Common Drug related ADR in the PREVENT TB Trial
Key Points

• ADRs common in patients on treatment for LTBI and TB disease and vary in severity
• Severe, idiosyncratic ADRs are rare but have significant implications for ongoing treatment
• Monitoring for ADRs requires risk assessment, client and staff education and awareness, open communication and careful documentation
• All suspected ADRs need to be addressed, but do not always require stopping or modifying Rx
• Sorting out causes of ADRs if on multiple meds may require stopping and serially rechallenging