Recognizing and Managing Common Adverse Drug Reactions from Anti-tuberculous Therapy

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Objectives

- How we define and monitor for adverse drug reactions
- Common types of adverse drug reactions: minor to major
- Which drugs cause which problems?
- Practical approaches to the management of specific ADRs: gastrointestinal toxicity, hepatotoxicity, skin rashes, other
Case 1

- A 63 year old Vietnamese born woman is diagnosed with smear positive pulmonary tuberculosis and is started on 4 drug anti-tuberculous 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.

Is this woman having an adverse drug reaction to her anti-TB 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

“Significant” ADRs (ASHP)

• 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
Monitoring for ADRs

• A process that starts before the initiation of treatment and continues throughout the entire treatment course
• Before prescribing anti-tuberculous medications, assess for factors that may increase risk of ADRs
  – e.g. increased age, underlying medical conditions such as preexisting liver disease, peripheral neuropathy
  – Concomitant medications and supplements
  – Behavioral risk factors: e.g. alcohol consumption
  – Barriers to effective monitoring for ADRS: language and cultural barriers, psychiatric issues
• Baseline laboratory monitoring: depends on the drugs and patient population (LTBI vs TB treatment)

Prescribing Anti-tuberculous Therapy
A Risk Benefit Analysis

• Treatment for LTBI
  – Weigh risks (toxicity) vs benefits of treatment
  – Those at highest risk for progression to TB disease should always be treated (e.g. HIV+, infant contacts, etc) despite risks
  – Risks may outweigh benefits for other groups
• Treatment for TB Disease
  – Benefits always outweigh the risks, but those at higher risk need more careful monitoring
Prospective Monitoring for ADRs

- Collaboration between patient and the TB program
- Patient education
  - Make sure they are educated about potential serious ADRs from their regimen
  - Make sure that they understand need to report them
- Staff education
  - Make sure they are aware of potential serious ADRs from the different TB medications
  - Make sure they assess for symptoms of ADRs from the patient at each interaction AND document them
- Interactions: Monthly medication pick ups, daily or twice weekly DOT visits, phone calls, any other interactions

Minor Drug Reactions

- Mild reactions
  - No lasting effects
  - Usually do not require change in the TB regimen
  - May often respond to simple interventions e.g. taking pills with food, use of an antihistamine
- Some Examples
  - Discoloration of body fluids
  - Gas, bloating, mild nausea
  - Itching and mild rash
  - Photosensitivity
  - Sleep disturbance
  - Headaches
Serious Adverse Drug Reactions

- More “severe”
- Require more intensive monitoring
- Potentially life threatening if ignored
- May require change in therapy
- May require hospitalization

- Severe N/V/diarrhea
- Liver toxicity
- Electrolyte abnormalities
- Allergic reactions
- Severe skin reactions
- Vision loss
- Neurologic damage
- Kidney damage
- Hearing loss
- Death

Consequences of Severe ADRs

- Worst case scenario: severe morbidity and even death for example: fatal hepatitis
- Need for more intensive clinical and laboratory monitoring
- Need for alternative, usually more protracted and potentially less effective treatment regimen
- 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

First Line TB Drugs
Based on Efficacy, Cost, Toxicity

- Isoniazid INH
- Rifampin RIF
- Pyrazinamide PZA
- Ethambutol EMB
- Rifabutin RFB
- Rifapentine RPT
### 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>
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### How Common are Adverse Drug Reactions During TB Treatment?

- **Treatment for LTBI**
  - Most data is for risk of INH toxicity
  - Comparative data from clinical trials comparing INH with other regimens
    - 9 mos of INH vs 12 weeks of INH plus Rifapentene
    - 9 mos of INH vs 4 mos of Rifampin
- **Treatment for TB Disease**
  - Multi-drug regimens
  - More difficult to always assign “blame” for the ADR
### Risk for INH Toxicity by Age Group:

**Table 1. Hepatotoxicity rate, adjusted for compliance with therapy, by age groups.**

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

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**Table 3. Adverse Events.**

| Outcome                                      | Isoniazid Only (N=1759) | Combination Therapy (N=6030) | P Value
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<tbody>
<tr>
<td>Permanent drug discontinuation — no./total no. (%)</td>
<td>1160/1759 (65.8)</td>
<td>713/6030 (11.8)</td>
<td>&lt;0.001</td>
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<tr>
<td>For any reason</td>
<td>661 (37.6)</td>
<td>595 (19.7)</td>
<td>&lt;0.001</td>
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<tr>
<td>Because of an adverse event</td>
<td>119/1759 (6.7)</td>
<td>106/6030 (1.8)</td>
<td>0.009</td>
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<tr>
<td>Death — no./total no. (%)</td>
<td>39/1759 (2.2)</td>
<td>31/6030 (0.5)</td>
<td>0.22</td>
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<tr>
<td>Any serious adverse event — no. (%)</td>
<td>109 (6.2)</td>
<td>64 (1.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
| ≥1 Adverse event — no. (%)
| Any                                           | 661 (37.6)               | 595 (19.7)                   | <0.001  |
| Pregnancy                                    | 71 (4.0)                 | 45 (0.7)                     | 0.005   |
| Medication error                             | 37 (2.1)                 | 27 (0.4)                     | 0.12    |
| All other adverse events                     | 584 (32.9)               | 531 (1.8)                    | 0.003   |
| Attribution — no. (%)                        |                          |                              |         |
| Related to drug                              |                          |                              |         |
| Hepatotoxicity                               | 103 (5.9)                | 18 (0.3)                     | 0.001   |
| Rash                                         | 21 (1.2)                 | 31 (0.5)                     | 0.26    |
| Possible hypersensitivity**                  | 17 (1.0)                 | 152 (2.5)                    | 0.001   |
| Other drug reaction                          | 65 (3.7)                 | 131 (2.2)                    | 0.001   |
| Not related to drug                          | 410 (23.6)               | 226 (3.8)                    | <0.001  |
| Severity of adverse event — no. (%)         |                          |                              |         |
| Grade 1 or 2                                 | 341 (19.4)               | 310 (5.1)                    | 0.03    |
| Grade 3                                      | 202 (11.5)               | 193 (3.2)                    | 0.24    |
| Grade 4                                      | 42 (2.4)                 | 36 (0.6)                     | 0.32    |
| Nongraded events                             | 31 (1.8)                 | 19 (0.3)                     | 0.05    |
Overall incidence of adverse events during TB treatment

- Montreal Chest Institute retrospective review
- 403 patients
  - Mean age 40.3 years (17-94)
  - 65% male
  - >80% foreign born
- 37/403 (9.2%) patients had major adverse reactions
  - 9 had second adverse reaction (46 events)


Incidence of major adverse events: Montreal series

- Definitions:
  - Any event that led to drug discontinuation
  - Drug-induced hepatitis: transaminases > 5 X ULN, attributed
- Rash and/or drug fever (4%)
- Drug-induced hepatitis (2.9%)
- Other GI side effects (2%)

AJRCCM 2003;167(11): 1472-1477
Incidence of serious side effects by type and drug

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

Demographic differences in adverse events:
Female > Male, Older > Younger

Sex-related differences  Age-related differences

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

- Tuber. and Lung Disease, 1996 (UK)
  - 5.1% had ADRs requiring treatment modification
  - Increase with increasing age: 2.3% 0-19, 8.3% over 60; female > male
- PLOS 1, 2011 (Lima, Peru)
  - Risks for ADRs (in the multivariate analysis)
    - Age, Obesity, anemia, smoking

Management of Some Common ADRs to anti-Tuberculous Therapy

“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
  – Bilirubin is 0.9 (normal)

The most likely explanation for her symptoms?

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

A. Stop all anti-TB 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 Toxicity

- Nausea
- Vomiting
- Diarrhea
- Bloating
- Anorexia
- Abdominal pain
- Overlap of gastrointestinal symptoms and symptoms of hepatic toxicity- need to check LFTs (ALT, AST and 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
- 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 (exception: injectables)

Management of GI Symptoms

- Initial options after excluding hepatotoxicity:
  - Change the timing of the dose
  - Give the meds with food
  - Daily dosing with fewer pills rather than intermittent therapy
  - Antacids 2hr before or after
  - Anxiolytic if the nausea occurs prior to swallowing the pills
  - Antiemetics
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
How should her symptoms be managed?

A. Stop all anti-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 new, non hepatotoxic anti-TB agents

Hepatotoxicity

• Elevation in liver enzymes: ALT more specific for liver than AST
• Confounders:
  - Other drugs/supplements, alcohol, viral hepatitis, other liver/biliary tract disease
• Spectrum of hepatotoxicity
  - Symptomatic or asymptomatic disease
  - ATS symptom related threshold for stopping therapy: ALT 3x upper limit of normal
  - ATS asymptomatic threshold for stopping therapy: ALT 5x upper limit of normal
Proposed 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 C

Spectrum of Hepatotoxicity

- Other causes: acute viral, EtOH, drugs, herbals, supplements, etc.
- Hepatic adaptation: up to 20% on INH monotherapy
- ATS Symptomatic Treatment–limiting threshold
- ATS Treatment–limiting threshold regardless of symptoms
- Drug-induced liver injury

ALT levels:
- ULN
- 3XULN
- 5XULN
- 8XULN
Management of Hepatotoxicity

Hold all meds and check LFTs

No symptoms and LFTs ≤ 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
- Interrupt treatment
- If moderate to severe TB, then continue at least 3 drugs
  - Rifampin, EMB, fluoroquinolone
  - Hepatic sparing regimen: EMB, FQ, injectable
- Assess for confounders
  - Concomitant medications, OTC, supplements, herbals, EtOH
  - Acute viral hepatitis testing:
    - IgM anti–Hep A Ab; hepatitis B surface Ag and IgM anti–Hep B core Ab; anti-HCV Ab and/or HCV RNA
Re-challenge: Practical Aspects

• Once ALT < 2 X ULN
• Many can return to original regimen
• Weigh risks based on severity of hepatotoxic event
• Different strategies:
  – Sequential re-challenge is most useful to sort out cause of hepatotoxicity if elevated LFTs recur: re-introduce drug every 7 days and monitor LFTs
    o RIF +/- EMB, INH, +/- PZA
    o If symptoms recur or LFTs increase → stop last drug added
    o If RIF and INH are tolerated, and hepatitis was severe, do not add back PZA - assume PZA was responsible

Severe Hepatitis: A Very Recent Example

• 11 year old with asthma, on no medications contact of a highly infectious TB case,
• TST “negative” as per primary pediatrician, but when seen by ID specialist a week later still had 15 mm of induration present
• No symptoms, normal exam, CXR negative, weight 54 kg
• Started on INH 300 mg daily on 1/22/13 by DOT thru Burlington Co. Health Department
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- 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

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Fulminant Hepatitis

- An uncommon but catastrophic event
- Idiosyncratic reaction
- Outcomes include death or need for liver transplant
- Rate of fatal hepatitis from older studies (pooled data) 0.43 per 1000
- Risks increased with EtOH
- Can occur later into treatment course
- ? More common in women

Severe INH liver injuries among persons being treated for LTBI in US 2004-2008

- 17 cases reported to CDC (do not have data to determine a rate)
- 5 died, 5 required liver transplantation
- Can occur anytime in treatment
- 9/17 beyond the 3rd month
- Can occur in children: 2/17
- Diagnosed by other than prescribing physician: 10/17
- Did NOT STOP the medication when symptoms developed: 8/17

MMWR 2010
Rifampin Hepatotoxicity

• Transaminitis much less common than with INH or PZA
• Most common liver injury pattern is cholestatic hepatitis
  – Elevated Bilirubin and Alk Phosphatase
  – Fever
  – Manifestation of hypersensitivity reaction

Case 3

• 64 year old Korean female with recently diagnosed presumed lymph node tuberculosis
• +PPD, enlarged cervical LN, biopsy with necrotizing granuloma and AFB
• Cultures are pending
• Started 4 drug TB regimen: RIPE
• Seen in the clinic 2 weeks later complaining of a new itchy red rash
How should this reaction be managed?

A. Stop all her anti-TB 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 her medications

Cutaneous Adverse Drug Reactions (CADRs) to Anti-tuberculous 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
  - Yee study: PZA > Rif > INH but in other studies EMB reactions also very common
- Severe CADRs more common in HIV+
  - Rifampin reactions more common in HIV+
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 Anti-TB Drug Associations

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

- Limited area
- The itching may be worse than the actual rash
- Not progressing over time
- Management
  - Generally treat symptoms with anti-histamine or a topical steroid
  - Continue anti-TB medications
  - Follow 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 Johnson syndrome
- If severe TB, use three new drugs
- Once rash significantly improved
  - Rechallenge serially
  - Reintroduce new drug every 2 – 5 days
    - R, H, E, (Z)
- Adjuvant testing: CBC (eosinophil count)
- Skin Biopsy
Petechial Rashes

- Check platelet count
- If low: presume rifampin thrombocytopenia, and stop Rifampin and monitor platelets
- Rifampin should not be restarted

Case 4

- A 56 year old Filipino male is diagnosed with smear positive pulmonary tuberculosis
- He is started on RIPE
- Susceptibility data are pending.
- He is in his 4th week of treatment and complains of severe joint pains
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 and PZA

- Arthralgias common: 8% with joint symptoms, 2% will stop drug due to this
- Treatment is NSAIDS
- Elevated uric acid on PZA occurs via decreased renal excretion of UA, EMB also increases UA, whereas rifampin decreases UA.
  - Allopurinol does not help
- PZA rarely causes acute gout flares, but history of gout is a relative contraindication to use of PZA
Other Musculoskeletal ADRs of Anti-tuberculous Therapy

- **Arthralgias:**
  - INH (much less common than PZA)
  - Fluoroquinolones
- **Gout:**
  - Ethambutol (rare)
- **Tendonitis and tendon rupture**
  - Fluoroquinolones

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**Case 5**

- 54 year old African-American male with Type 2 Diabetes mellitus and hypertension with newly diagnosed pulmonary tuberculosis
- His isolate is pan-sensitive and he completed his induction phase of therapy and is now on continuation phase therapy with INH and Rifampin 2x/week
- He is complaining 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 periphe
    neuropathies, other neurotoxic drugs, ? Slow metabol
  - Prevention: Pyridoxine 25-100 mg/day
- 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
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 this is OK continue her current TB regimen

Ocular Toxicity

- Ethambutol optic (retrobulbar) neuritis:
  - Decreased visual acuity
  - Decreased red-green discrimination
  - Can be asymptomatic
  - Risk is increased with renal insufficiency- appropriate dosage adjustment in the elderly
    - Creatinine clearance < 30 → 3 x per week dosing
- Generally does not cause pain, usually bilateral.
- Rarely INH can cause
Monitoring and Management

- Baseline/ monthly
  - Visual acuity test (Snellen chart)
  - Color discrimination test (Ishihara tests - web app available)
- Patient education
- Monthly symptoms
  - blurred vision etc
- Hold medication – for 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 twice a week therapy by DOT with INH and RIF
- He is now complaining 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 twice weekly dosing of medications
D. Stop RIF and restart PZA and EMB
Rifampin Hypersensitivity Syndromes

- “Flu-like” syndrome: 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 – rare, each < 0.1% patients: All require stopping of drug
  - Low platelet count
  - Renal dysfunction
  - Hepatotoxicity
  - Hemolytic anemia
  - Thrombotic thrombocytopenic purpura

“Possible Hypersensitivity” to Rifapentene was most Common Drug related ADR in the PREVENT TB Trial
Summary of Most Common ADRs to First Line Agents (and FQ)

<table>
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<tr>
<th>Reaction</th>
<th>INH</th>
<th>RIF</th>
<th>EMB</th>
<th>PZA</th>
<th>FQ</th>
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<tr>
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<tr>
<td>Gout</td>
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<td>X (rare)</td>
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<td>Flu-Like Syndromes</td>
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Key Points

• ADRs are common in patients on treatment for LTBI and TB disease and range in severity from minor to major
• Severe, idiosyncratic ADRs are rare but have significant implications
• Monitoring for ADRs requires risk assessment, Patient (and staff) education, open communication and careful documentation
• All suspected ADRs need to be addressed, but all do not necessarily require stopping or change in therapy