A practical approach to the management of TB drug-induced liver injury

Graeme Meintjes
University of Cape Town
Imperial College London

HOPE Conference, 27 August 2013
1) Aetiology is complex and multifactorial

- 3 potentially hepatotoxic TB drugs in first line
- Each of these drugs has multiple metabolites
- Systemic inflammation may influence immune response in liver
- Nutritional status (serum albumin)

- Hepatic TB and TB-IRIS
- Co-treatments may be hepatotoxic
  - ART
  - Co-trimoxazole
  - Fluconazole
  - Alternative remedies
- Previous or current alcohol abuse
- Hepatitis B and hepatitis B IRIS
Figure 1 Proposed isoniazid metabolic pathways. Solid lines, major metabolic pathways; dashed lines, speculated pathways. [O], oxidation.
Model of drug-induced hepatocyte injury
Causes

- **1st line TB medication**
  - PZA, INH, Rifampicin

- **Drug resistant TB medication**
  - Ethionamide, fluoroquinolones, PAS

- **ART**
  - Nevirapine most hepatotoxic
  - Also Efavirenz and PI’s (especially double dose Lopinavir/ritonavir)

- **Several other drugs used in HIV+ patients**
  - Co-trimoxazole, Fluconazole

- **Always consider other causes**
  - Viral hepatitis
    - ART can induce exacerbation of chronic viral hepatitis B and C (IRIS)
  - Sepsis
Patterns of liver injury

- **Hepatocellular injury**
  - Fever, nausea and vomiting and anorexia
  - May be asymptomatic
  - Transaminitis
  - If jaundiced: worse prognosis

- **Cholestasis**
  - Asymptomatic
  - Reversible elevation of bilirubin
  - Disruption of bilirubin transport, no inflammation
  - Rifampicin

- **Cholestatic hepatitis**
  - Elevations in bilirubin and cholestatic enzymes
  - Inflammation in/around bile canaliculi
  - May be irreversible
  - Co-trimoxazole, Flucloxacillin
TB DILI: Major risk factors

- Age
  - Over 35 years
- Females more severe DILI
- Malnutrition
  - Low albumin
- More extensive TB
- HIV
- Chronic hepatitis B and C
- Genetic polymorphisms
  - NAT2 slow-acetylator genotype and INH DILI

2) Timing of TB DILI

- Most idiosyncratic DILI events occur within 3 months of starting the drug
- Turkish study
  - Mean 17 days (range 6-102)
- Indian studies
  - Median 23 days (IQR 14-44)
  - 75% within first two months

Tahaoglu, IJTLID 2001
Sharma, Clin Infect Dis 2010
Devarbhavi, J Gastroenterol Heaptol 2012
3) Only two clinical trials and most guidelines are based on “expert” opinion

RCT of rechallenge regimens in India

- 175 HIV-negative patients randomised to receive 1 of 3 rechallenge regimens

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm I</td>
<td>H, R, and Z at maximum dosages from day 1</td>
</tr>
<tr>
<td>Arm II</td>
<td>R at maximum dosage from day 1, H at maximum dosage from day 8, and Z at maximum dosage from day 15</td>
</tr>
<tr>
<td>Arm III</td>
<td>H at dosage of 100 mg/day from day 1, maximum dosage from day 4; R at dosage of 150 mg/day from day 8, maximum dosage from day 11; and Z at dosage of 500 mg/day from day 15, maximum dosage from day 18</td>
</tr>
</tbody>
</table>

**NOTE.** Maximum dosage was determined according to body weight, as follows: H, 5 mg/kg; R, 10 mg/kg; and Z, 25 mg/kg. H, isoniazid; R, rifampicin; Z, pyrazinamide.

Sharma, Clin Infect Dis 2010
## Results

<table>
<thead>
<tr>
<th>Arm</th>
<th>Recurrence rate</th>
<th>Median time to relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>8/58 (14%)</td>
<td>14 days</td>
</tr>
<tr>
<td>II</td>
<td>6/59 (10%)</td>
<td>21 days</td>
</tr>
<tr>
<td>III</td>
<td>5/58 (9%)</td>
<td>21 days</td>
</tr>
</tbody>
</table>

No significant difference in recurrence rate by arm (p=0.69)

Pretreatment albumin was only independent predictor of recurrence (not severity of initial DILI)

Median “normalization period” was 18 days (IQR 14-28)

No deaths

Sharma, Clin Infect Dis 2010
Randomised trial in Turkey
HIV-negative patients, n=45

<table>
<thead>
<tr>
<th>Group</th>
<th>Retreatment</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I (n=20)</td>
<td>With <strong>HRES, gradually increasing</strong> number and dosages of drugs</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Group II (n=25)</td>
<td>With <strong>RHZE</strong>, in same dosages throughout</td>
<td>6 (24%)*</td>
</tr>
</tbody>
</table>

* 5/6 later rechallenges with strategy of Group I

Tahaoglu, IJTL 2001
Several guidelines

1. American Thoracic Society
2. British Thoracic Society
3. European Respiratory Society; WHO; IUATLD, International Union Against Tuberculosis and Lung Disease
4. Hong Kong Tuberculosis Service
5. SA HIV Clinicians Society Consensus Statement
   – In press with SA J HIV Med
   – Will be available at: http://www.sahivsoc.org
4) Significant mortality

**Burden of antituberculosis and antiretroviral drug-induced liver injury at a secondary hospital in South Africa**

Charlotte Schutz, Zahiera Ismail, Charles John Proxenos, Suzaan Marais, Rosie Burton, Chris Kenyon, Gary Maartens, Robert J Wilkinson, Graeme Meintjes


All patients seen at referral hospital during 6 month period with:

- $\text{ALT} \geq 200$
- or
- $\text{Bilirubin} \geq 44 \mu\text{mol/l} \text{ (2.6 mg/dl)}$
TB treatment/ART DILI patients (n=71)

- 85% HIV infected (97% tested)
- Median CD4 = 75 (IQR 28-189)
- 11% HepBsAg+ (80% tested)
- 45% receiving ART
- 83% receiving TB treatment
- 28% receiving ART & TB treatment
Clinical Presentation

- Transaminitis: 44%
- Cholestasis: 79%
- Both: 23%
- Hepatic encephalopathy: 21%
- Median ALT: 157
- Median bilirubin: 88
- Median INR: 1.7

Management

- **TB Treatment:**
  - 49% interrupted
  - 64% liver safer regimen
  - Median 16.5 days off optimal TB treatment
  - Optimal treatment NOT restarted in 46%

- **ART:**
  - 34% interrupted
  - 72% changes made to regimen
  - Median 25 days off optimal ART
Died during initial admission = 27% (median 8 days)
Died within 3 months = 35%
Causes of death in patients who died during admission

- Cardiomyopathy
- DILI and sepsis
- Liver failure
- MDR TB
- Multi-organ failure
- Sepsis
- Sepsis and disseminated TB
- Unknown

$n=19$
Bangalore, India

• 269 cases (1997-2011)
• 8% HIV-infected
• 71% jaundice; 26% acute liver failure
• 90-day mortality
  – Overall: 23%
  – Jaundice: 30%
  – Encephalopathy: 70%
  – Ascites: 51%

Devarbhavi, J Gastroenterol Hepatol 2012
Reasons for high mortality?

• DILI and complications
• Interruptions & suboptimal Rx of TB & HIV
• DILI in patients with underlying poor prognosis

• Probably a combination of factors
5) Differentiate hepatic adaptation from DILI

- Mild transient asymptomatic transaminitis (ALT < 200) is common with the introduction of many drugs
  - With TB drugs estimated to be ~ 20%

- This is known as hepatic “adaptation” and is not a reason for interrupting drugs.

Hepatic “adaptation”

• Physiological adaptive responses to certain drugs
  – Induction of survival genes (anti-oxidant, anti-inflammatory and anti-apoptotic)
  – Hepatocyte proliferation
  – Metabolic enzyme induction

• Asymptomatic, transient elevations of ALT may reflect slight, non-progressive injury to hepatocyte mitochondria, membranes and other structures

• Rarely leads to inflammation, cell death or significant histological changes
TB DILI definition

- ALT level > 120 AND symptomatic (nausea, vomiting, abdominal pain, jaundice)
  OR
- ALT level > 200 AND asymptomatic
  OR
- Total serum bilirubin concentration > 40μmol/l*

*40μmol/l = 2.3 mg/dl

SA HIV Clinicians Society Consensus Statement, in press
6) Significant ALT (or bilirubin) elevations with symptoms of hepatitis = serious clinical problem.

- Jaundice
- Nausea and vomiting
- Anorexia
- Right upper quadrant pain
- Other features of hypersensitivity (e.g. rash, fever, systemic symptoms)

- Interrupt culprit drugs at lower thresholds if symptoms accompany ALT elevations
Hy’s law

- Proposed by Hy Zimmerman who studied DILI in general

- The combination of hepatocellular liver injury leading to jaundice is a marker of severe DILI – mortality 10-50%
Key practice points

• If a patient on TB treatment and/or ART complains of hepatitis symptoms, then examine for jaundice and send blood for urgent ALT & ensure urgent follow-up of result

• Interrupt drugs and consider referral if patient jaundiced or with significant symptoms
7) TB dissemination to the liver can cause LFT derangement and this may worsen with TB-IRIS

- Dissemination to liver more likely in HIV+ patients with lower CD4 counts
- Hepatomegaly (+/- tender)
- Typically Alk Phos and GGT elevated with minor elevation of transaminases
  - Rarely clinical jaundice
HEPATIC TB-IRIS CASE

- 4 months treatment for drug-sensitive pericardial TB
- Clinically improved, then started ART
- 3 weeks later presented with fever and hepatomegaly
- LFT: Bil 52, CBil 31, Alk Phos 1081, GGT 1468, ALT 82, AST 88
- CD4 rise from 64 to 221
- Biopsy AFB- and TB culture -

Case courtesy of Mark Sonderup
Hepatic TB-IRIS vs DILI

Hepatic TB-IRIS

- RUQ pain, nausea and vomiting
- Tender hepatomegaly
- Cholestatic LFT derangement
- +/- mild jaundice
- Usually other TB-IRIS manifestations

Drug-induced liver injury

- Similar symptoms
- Typically not hepatomegaly
- Transaminitis +/- jaundice
- Absence of other TB-IRIS features

Patients may present with clinical picture between these two
- Biopsy or treat as DILI

Two conditions may co-exist
8) Rifampicin rechallenge important for success of TB treatment

- British MRC trials in 1970’s: addition of rifampicin to TB regimen allowed treatment shortening from 18 months to 8-9 months
- Predictable cures in >95%
- Capacity of rifampicin to kill mycobacteria undergoing sporadic metabolism
  – This “sterilising effect” prevents relapse

Iseman, ERJ 2002
9) General management principles

• Stop potentially hepatotoxic drugs
• Use 3 alternate TB drugs and continue these as a backbone during rechallenge
  – Ethambutol, moxifloxacin, aminoglycoside
• Rechallenge when ALT <100 and symptoms/jaundice resolved
• Rechallenge Rifampicin then INH
  – Consider PZA
• Frequent ALT monitoring
Western Cape Academic Hospitals
TB DILI Guidelines

• Discontinue current TB treatment
• Review basis for TB diagnosis
• Commence 3 drugs with no/low hepatotoxic potential
• Selected patients may be rechallenged when
  – Hepatitis symptoms resolved
  – Bilirubin normal
  – Transminases < 100
• Drug susceptibility testing whenever possible
Rechallenge regimen*

– Background therapy: Strep, Etham, Moxi
– Day 1: Rif 450 or 600mg daily depending on wt
– Day 3: Check ALT
– Day 4: Add INH 300mg daily
– Day 7: Check ALT
– Day 8: Consider PZA rechallenge in patients with severe TB (miliary, TBM) or drug resistance
– Monitor ALT 3x/week during rechallenge

*Based on American Thoracic Society guidelines, Am J Respir Crit Care Med 2006; 174: 935-52
Rechallenge of ART

• Generally after TB drug rechallenge*

• Restart ART drugs all at once

• Do not rechallenge Nevirapine. Efavirenz rechallenge can be considered unless DILI was severe

• If DILI occurred on double dose Lopinavir/ritonavir with Rifampicin
  – Replace with Rifabutin and Atazanavir/ritonavir (or standard dose Lopinavir/ritonavir) if possible, otherwise gradual dose escalation

* If mild DILI and efavirenz interrupted and LFTs settle within 5-7 days may consider efavirenz re-introduction before TB rechallenge

SA HIV Clinicians Society Consensus Statement, in press
9) TB treatment regimen for patients with drug susceptible TB when a first-line drug is omitted

<table>
<thead>
<tr>
<th>Drug omitted</th>
<th>Total duration</th>
<th>Intensive phase</th>
<th>Continuation phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampicin</td>
<td>18 months</td>
<td>INH, Moxifloxacin, Ethambutol, Streptomycin x 2 months*</td>
<td>INH, Moxifloxacin, Ethambutol x 16 months</td>
</tr>
<tr>
<td>INH</td>
<td>12 months</td>
<td>Rifampicin, Moxifloxacin, Ethambutol x 2 months*</td>
<td>Rifampicin, Moxifloxacin, Ethambutol x 10 months</td>
</tr>
<tr>
<td>PZA</td>
<td>9 months</td>
<td>Rifampicin, INH, Ethambutol x 9 months</td>
<td></td>
</tr>
</tbody>
</table>

* May consider PZA rechallenge and use during intensive phase particularly if DILI occurred early during intensive phase

SA HIV Clinicians Society Consensus Statement, in press
10) When not to rechallenge?

• Rechallenge is **NOT** recommended for those who have had fulminant hepatitis (defined as hepatic encephalopathy with coagulopathy).
  – Once LFT resolves, treat with MDR regimen avoiding PZA (substitute it with ethambutol).

• In patients hospitalized with DILI check the INR
  – A raised INR is a marker of significant liver damage
11) Recurrence of DILI upon rechallenge

- Median time to recurrence was 14 days in those patients rechallenged simultaneously
  
  Sharma, Clin Infect Dis 2010

- Thus monitor ALT weekly x 4 weeks after rechallenge
  
  – Also monitor clinically for recurrent symptoms and jaundice

- Last drug re-introduced not necessarily culprit
12) Drug-induced cholestasis

- Bilirubin and/or cholestatic enzyme elevation
- Variety of underlying processes

Table 1. Classification of Drug-Induced Cholestasis Syndromes

<table>
<thead>
<tr>
<th>I. Intrahepatic Drug-Induced Cholestasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Acute</td>
</tr>
<tr>
<td>i. Cholestasis without hepatitis (pure, simple, canalicual, or bland cholestasis)</td>
</tr>
<tr>
<td>ii. Cholestasis with hepatitis (hepatocanalicual hepatitis or mixed cholestatic hepatitis)</td>
</tr>
<tr>
<td>iii. Cholestasis with bile duct injury (ductular, cholangiolar, or cholangiolytic cholestasis)</td>
</tr>
<tr>
<td>b) Chronic (Cholangiopathies)</td>
</tr>
<tr>
<td>i. Mild, nonspecific bile duct injury</td>
</tr>
<tr>
<td>ii. VBDS</td>
</tr>
<tr>
<td>iii. PSC-like</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>II. Extrahepatic Drug-Induced Cholestasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. Cholelithiasis</td>
</tr>
<tr>
<td>ii. PSC-like</td>
</tr>
</tbody>
</table>

Padda
Hepatology 2011;53:1377
Cholestatic LFT derangement in HIV-TB
Consider the following:

- Hepatic TB or TB-IRIS
- HIV cholangiopathy
- Biliary obstruction (eg. TB nodes)

- Rifampicin disrupting bilirubin transport
  - Inhibition of major bile salt exporter pump -> conjugated hyperbilirubinaemia
  - Or interference with bilirubin clearance across sinusoidal membrane -> unconjugated hyperbilirubinaemia
  - Consider switch to Moxifloxacin and assess response

- Co-trimoxazole associated cholestatic hepatitis
  - Enzymes +/- bilirubin elevation

- Less frequently other drugs causing cholestatic hepatitis

Saukkonen, AJRCCM 2006
Acknowledgements

• Co-authors of SA HIV Clinicians Society Consensus Statement
  – Francesca Conradie
  – Andrew Black
  – Melanie-Anne John
  – Rebecca Berhanu
  – Colin Menezes
  – Eefje Jong

• Charlotte Schutz
• Mark Sonderup