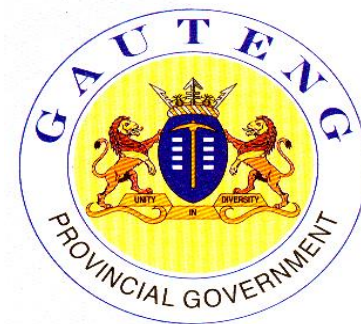# An approach to the management of drug induced liver injury in HIV-infected patients treated for TB

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Objectives of this talk:

- Concepts and definitions – that are important in the management.

- Management - a consensus statement from the Southern African HIV Clinicians Society: Eefje Jong, Francesca Conradie, Graeme Meintjes, Andrew Black, Melanie-Anne John, Rebecca Berhanu and Colin Menezes.

Cases:

- A HIV infected female diagnosed with sputum positive PTB and started on TB therapy – noted jaundice 6 weeks later. LFTs: TB 100,CB 90, ALT 50, GGT 30.

- A HIV infected male on TB therapy for EPTB for 4 months presents with abdominal pain and jaundice. LFTs: TB 80,CB 50, ALT 500, GGT 100.

- A HIV infected male on TB therapy for 5 months and ART for 7 months, presents with jaundice. LFTs: TB 90,CB 80, ALT 800, GGT 80.

Drug Induced Liver Injury (DILI)

- Liver metabolizes virtually every drug or toxin and is therefore vulnerable to injury. > 700 drugs are known to cause a DILI.

- Drugs account for 7% of reported adverse events and for 30% of all cases of fulminant hepatic failure.

- Is a diagnosis of exclusion.

- Histology specimens are often NOT obtained.

What are the mechanisms of drug toxicity?

Mechanisms of drug toxicity

- DILI may result from:
  - Direct toxicity of the primary compound (predictable hepatotoxicity).
  - Idiosyncratic (unpredictable - from an immunologically mediated response).

- Affecting:
  - Hepatocytes.
  - Biliary epithelial cells.
  - Liver vasculature.

- Knowledge of mechanisms is incomplete.

Direct / predictable reactions

- Classical e.g. paracetamol.

- Injury dose related. Often acute/subacute.

- Free radicals cause necrosis in zones furthest away from hepatic arteriole.

- Usually NO extrahepatic manifestations.

Idiosyncratic drug / unpredictable reactions

- Comprise most types of DILI.

- Include metabolic or hypersensitivity reactions.

- Largely independent of dose and may occur anytime post exposure.

- Result from genetic or acquired variations in drug biotransformation pathway.

- With synthesis or abnormally slow detoxification of a hepatotoxic metabolite.

Idiosyncratic reactions :

- Hypersensitivity:
  - Classical example: phenytoin.
  - Immunogenic drugs or its metabolites may be free or covalently bound to hepatic proteins, forming haptens or "neoantigens".
  - Response: fever, rash & eosinophilia.

- Metabolic idiosyncratic:
  - Example: INH
  - Through an indirect metabolite.

What are the clinical syndromes of a DILI?

Clinical Syndromes of DILI

Hepatic adaptation:
- Physiologic adaptive response to certain drugs e.g. rifampicin.
- Asymptomatic transient $\uparrow$ ALT & non progressive liver injury.
- No inflammation.

Acute hepatitis or hepatocellular injury:
- ± Asymptomatic or prodrome (fever, constitutional symptoms, nausea, vomiting, LOA, lethargy).
- Markedly elevated transaminases ± jaundice.
- Coagulopathy – delayed 24-36 hrs later.

NAFLD:
- Causes – HAART, DM, obesity.
- Clinical features uncommon, may get raised transaminases, $\downarrow$glucose, metabolic acidosis.
- Usually reversible but may led to steatohepatitis and higher risk of cirrhosis.

Clinical Syndromes of DILI

Granulomatous hepatitis:

- hypersensitivity reaction e.g. PZA, allopurinol, sulphonamides.
- fever, lethargy, myalgia, rash, LAD, HSM, vasculitis.
- ↑ ALT.

Cholestasis:

- bland cholestasis (no inflammation).
- due to failure of bilirubin transport.
- asymptomatic, usually reversible ↑ALP & bilirubin.

TB drug induced hepatoxicity

TB drug induced hepatoxicity

- Hepatotoxicity is one of the most important adverse drug reactions associated with anti TB drugs.

- Incidence varies between 2 – 28%. SA study: in-hospital mortality of 27%.

- All TB drugs except EMB & SM.

- Mechanism is mostly an idiosyncratic reaction.

- Best approach to management is open to debate.

Risk Factors

- difficult to predict which patient will develop hepatotoxicity.

- Important risk factors specific to TB DILI include:
  - Age > 35 years.
  - Race - blacks seem more susceptible to INH toxicity.
  - Gender - ? females more at risk
  - Genetics - ? acetylator status
  - Alcohol use.
  - Abnormal baseline transaminases.
  - Malnutrition and hypoalbuminemia.
  - HBV / HCV in isolation, more with HIV, especially on ARVs.
  - Pregnancy in 3rd trimester or 1st 3 months post partum (INH)

Rifampicin (RIF)

- Symptoms include a mildly elevated ALT and increases in bilirubin but typically a cholestatic picture. Occurs earlier i.e. within 1st month.

- Mechanisms include:
  - Conjugated hyperbilirubinaemia caused by:
    - RIF inhibiting the major bile salt exporter pump.
    - Dose-dependent competition with bilirubin for clearance at sinusoidal membrane.
    - Impeded canilicular secretion.
  - Hypersensitivity reaction - rare
    - More common with large, intermittent doses.
    - Hypersensitivity reactions in combination with renal dysfunction, heamolytic anaemia, or "flulike syndrome" have been reported.

- Potentiate hepatotoxicity of other anti-TB drugs - INH.

Isoniazid (INH)

- Biochemical mechanism remains incompletely defined. Theory : generation of reactive metabolites that bind to and damage cellular macromolecules. Acetylation by N-acetyl transferase 2 (NAT-2). Acetylator status – fast vs. slow.

- MAH: toxic through free radical generation.

- Generally occurs within weeks to months. Predominantly transaminitis. Hepatic adaption seen in 20% on INH alone.

- Nausea, vomiting, abdominal pain – 50-75%. Can get fever and rash. Recovery is complete but usually takes weeks, often not recurring on rechallenge.

Pyrazinamide (PZA)

- Most hepatotoxic. May exhibit both dose dependent and idiosyncratic hepatotoxicity.

- PZA long t/2 (10hrs) – increased to 15hrs in pre-existing hepatic disease.

- Free radical generation. There may be shared mechanisms of injury for INH and PZA, because there is some similarity in molecular structure.

- Patients who previously had hepatotoxic reactions with INH have had more severe reactions with RIF and PZA combination.

- May induce hypersensitivity reactions with eosinophilia and liver injury, or a granulomatous hepatitis.

Fluoroquinolones

- Partial metabolism by liver – moxifloxacin, ciprofloxacin.

- Excreted unchanged by kidney – levofloxacin, oxfloxacin.

- Reversible transaminitis seen in 2-3%.

- Mechanism – hypersensitivity reaction.

Clinical & Laboratory features

- Presenting clinical syndrome/LFT components?

- Highly variable, ranging from asymptomatic increase in liver enzymes to fulminant hepatic failure.

- Cholestatic injury with $\uparrow$ GGT ($\pm \uparrow$ bili) – especially RIF.

- ± hepatomegaly (tender / non tender).

- Extrahepatic manifestations: fever, rash, eosinophilia, myalgias, anorexia, nausea & vomiting.

Diagnosis & work up

- History important – drug history, identify risk factors, pre-existing liver disease.

- Clinical examination.

- Lab findings : ALT > AST $\pm \uparrow$ bilirubin.
  $\pm \uparrow$ GGT.
  INR / PTT.
  Hepatitis studies.

- $\pm$ Abdominal ultrasound to exclude other causes.

- Role of liver biopsy: only if diagnosis unclear- not routine. If no recovery, need to exclude an IRIS, other OIs.

Cases:

- A HIV infected female diagnosed with sputum positive PTB and started on TB therapy – noted jaundice 6 weeks later. LFTs: TB 100,CB 90, ALT 50, GGT 30.

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How we manage such patients?

- Only 2 clinical trials. Guidelines published by the ATS, BTS, ERS, WHO, IUATLD and HKTBS – based on expert opinion from a multidisciplinary team supported by literature searches.

- In the South African setting - HIV/TB co-infected with DILI - no clear what approach should be followed when one fails to reintroduce the first line drugs, especially INH or RIF.

- Consensus statement from the the Southern African HIV Clinicians Society – represents a consultative process with the authors and other experts in the field.

How we manage such patients?

Safety of 3 Different Reintroduction Regimens
of Antituberculosis Drugs after Development
of Antituberculosis Treatment–Induced Hepatotoxicity

Surendra K. Sharma,[1] Rohit Singla,[1] Pawan Sarda,[1] Alladi Mohan,[6] Govind Makharia,[2] Arvind Jayaswal,[3] Vishnubhatla Sreenivas,[4] and Sarman Singh[5]

The management of anti-tuberculosis drug-induced hepatotoxicity

K. Tahaoğlu, G. Ataç, T. Sevim, T. Törün, Ö. Yazıcıoğlu, G. Horzum, İ. Gemci, A. Öngel, N. Kapaklı, E. Aksoy

Monitoring process and definition of DILI according to existing guidelines

Authority	Monitoring in presence of risk factors (especially liver diseases)	Cut-off levels for DILI and stopping drugs
ATS	Yes	ALT >200 IU/l or, ALT 120 IU/l with symptoms
BTS	Yes	ALT or AST >200 IU/l, rise in bilirubin
ERS, WHO, IUATLD	-	AST > 200 IU/l
HKTBS	Yes	ALT >200 IU/l , bilirubin > 40µmol/l

LFT, liver function test; ALT, alanine transaminase; ALP, alkaline phosphatase; ATS, American Thoracic Society; BTS, British Thoracic Society; ERS; European Respiratory Society; WHO, World Health Organisation; IUATLD, International Union Against Tuberculosis and Lung Disease; HKTBS, Hong Kong Tuberculosis Service

DILI definition advocated in the South African setting:

ALT level > 120 IU/l AND symptomatic (nausea, vomiting, abdominal pain, jaundice)

OR

ALT level > 200 IU/l AND asymptomatic

OR

Total serum bilirubin concentration > 40 µmol/l

Important management principles:

- What is the clinical condition? Assess for liver failure. May need to stop all TB drugs.

- Is TB confirmed or not? Check results of TB culture and drug susceptibility testing.

- Reconsider TB diagnosis if not confirmed. If had a clinical response to the TB therapy including weight gain, improvement of "TB" symptoms and/or chest X-ray improvement then diagnosis can assumed to be correct.

- Is the patient is on the intensive or continuation phase of TB therapy.

- Consider other causes (e.g. chronic alcohol consumption, viral hepatitis, other hepatotoxic medications, TB involvement of the liver, IRIS, bacterial sepsis, pre-existing liver disease).

Summary of existing guidelines on the management of TB DILI

Authority	Stopping TB drugs if clinical or symptomatic hepatitis	When to restart TB drugs	What TB drugs to start	Recommended LFT monitoring on rechallenge	What if DILI recurs
ATS	Yes	ALT < 80	R +/- E full dose After 3-7 days H (full dose) Z only if mild DILI	Check ALT 3-7 days after H rechallenge	Stop last drug added
BTS	Yes	ALT within normal limits	S + E (if unwell or sputum smear positive within two weeks of commencing treatment) H (dose titration, every 2-3 days) R (dose titration, every 2-3 days) Z (dose titration, every 2-3 days)	Daily monitoring of LFT	Stop offending drug, alternative regimen advised by fully trained physician
ERS, WHO, IUATLD	Yes	LFT within normal limits	Start all drugs at full dosage	LFT monitoring (no recommendation on frequency)	Stop all drugs, start S + E and start other drugs one at a time
HKTBS	Yes	-	-	-	-

LFT, liver function test; ALT, alanine transaminase; ATS, American Thoracic Society; BTS, British Thoracic Society; ERS; European Respiratory Society; WHO, World Health Organisation; IUATLD, International Union Against Tuberculosis and Lung Disease; HKTBS, Hong Kong Tuberculosis Service; R, rifampicin; E, ethambutol; H, isoniazid; Z, pyrazinamide; S, streptomycin

Intensive phase: 4 presentations

- Mild DILI: Asymptomatic TB patients with elevated ALT < 200 IU/l and total bilirubin < 40 µmol/l.

- Moderate DILI: Clinically well and elevated ALT > 200 IU/l irrespective of total bilirubin.

- Moderate DILI: Isolated jaundice (ALT < 200 IU/l and total bilirubin > 40 µmol/l).

- Severe DILI: clinically NOT well (nausea, vomiting, abdominal pain).

Mild DILI: Asymptomatic TB patients with elevated ALT < 200 IU/l and total bilirubin < 40 µmol/l .

- Continue TB drugs if confirmed or probable TB.

- Continue ART if on ART.

- Repeat ALT and bilirubin in 1 week.
  - If ALT and bilirubin improved or normalized: stop monitoring.
  - If ALT and bilirubin remain elevated but stable for 4 weeks: consider referral for further workup of liver dysfunction.
  - If ALT and bilirubin increase further and manage as moderate or severe DILI.

Moderate DILI: Clinically well and elevated ALT > 200 IU/l irrespective of total bilirubin

- Stop TB therapy, co-trimoxazole and other hepatotoxic drugs.

- Start streptomycin, moxifloxacin and ethambutol.

- Stop ART. NNRTI-based regimen: stop NNRTI first and NRTIs after 5-7 days. PI-based: stop all drugs at once. If stable ART > 6 months, consider continuing ART.

- Repeat ALT and bilirubin in 2-3 days (inpatient) or 7 days (outpatient). When ALT < 100 IU/l and total bilirubin normal, rechallenge:
    - Day 1: RIF 450 or 600 mg daily depending on weight.
    - Day 3: Check ALT.
    - Day 4-6: Add INH 300 mg daily.
    - Day 7: Check ALT: ALT improving or stable.
    - Day 8: Consider PZA rechallenge (especially if TBM or intolerance/resistance to other drugs) and check ALT at day 10.
    - Monitor ALT weekly x 4 weeks after rechallenge.

Moderate DILI: Isolated jaundice (ALT < 200 IU/l and total bilirubin > 40 µmol/l)

- No need for admission. Stop RIF - the most likely cause of isolated jaundice. If on ART – continue. Stop cotrimoxazole if ALP and GGT also elevated.

- Continue INH, PZA and ethambutol and add moxifloxacin.
  - Repeat ALT and bilirubin after 7 days. If does not settle - refer.
  - Consider full dose RIF rechallenge 2-3 weeks after stopping RIF.
  - Repeat ALT and bilirubin after 7 days. If ALT and bilirubin stable, stop moxifloxacin and continue standard TB therapy.
  - If bilirubin >40 µmol/l stop RIF and continue INH, PZA, ethambutol and moxifloxacin.
  - Monitor ALT and bilirubin weekly x 4 weeks after rechallenge
  - If ALT increases > 120 IU/l, refer.

Severe DILI: Patient develops DILI and clinically NOT well.

- Admit. Consult specialist. Assess for liver failure, INR and monitor blood glucose.

- Stop TB therapy, cotrimoxazole and other hepatotoxic drugs. Stop ART. NNRTI-based regimen: stop NNRTI first and NRTIs after 5-7 days. PI-based: stop all drugs at once. If stable ART > 6 months, consider continuing ART. If in liver failure stop all ART immediately.

- Start streptomycin, moxifloxacin and ethambutol.

- Repeat ALT and bilirubin after 2-3 days. Rechallenge TB drugs when ALT< 100 IU/l and bilirubin normal.
  - Day 1: RIF 450 or 600 mg daily depending on weight.
  - Day 3: Check ALT: ALT improving or stable.
  - Day 4-6: Add INH 300 mg daily.
  - Day 7: Check ALT: ALT improving or stable.
  - Consider PZA re-challenge (especially if TBM or intolerance/resistance to other drugs).
  - Monitor ALT weekly x 4 weeks after rechallenge.

Continuation phase

- Confirm start date and response to ART/TB therapy. Consider other diagnoses.

- Similar principles:
    - If asymptomatic (elevated ALT < 200 IU/l and bilirubin < 40 µmol/l). Monitor.
    - If isolated jaundice (ALT < 120 IU/l and total bilirubin > 40 µmol/l) stop RIF, continue INH, ethambutol and moxifloxacin. Continue ART, stop co-trimoxazole if ALP and GGT also elevated. Consider full dose RIF rechallenge.
    - If moderate DILI OR severe DILI stop TB drugs, co-trimoxazole and other hepatotoxic drugs. Stop ART. Monitor ALT and bilirubin . Rechallenge TB drugs if ALT < 100 IU/l and bilirubin normal.

- If ALT and/or bilirubin worsening after RIF rechallenge: treat with INH, ethambutol and moxifloxacin.

- If ALT and/or bilirubin worsening after INH rechallenge: treat with RIF, ethambutol and moxifloxacin.

- Monitor ALT weekly x 4 weeks after rechallenge.

TB regimen with drug susceptible TB when a first line drug omitted:

Drug omitted	Intensive phase	Continuation phase
Rifampicin	Isoniazid, Moxifloxacin, Ethambutol, Streptomycin x 2 months*	Isoniazid, Moxifloxacin, Ethambutol x 16 months
Isoniazid	Rifampicin, Moxifloxacin, Ethambutol x 2 months*	Rifampicin, Moxifloxacin, Ethambutol x 10 months
Pyrazinamide	Rifampicin, Isoniazid, Ethambutol x 9 months	

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

Initiation of ART

- Patients who develop DILI while on TB medication:
  - ART-naive:
  - CD4 cell count < 100 cells/µl:

    Start ART as soon as the complete standard or alternative regimen of TB drugs are reintroduced.
  - CD4 cell count > 100 cells/µl:

    ART can be delayed until after the intensive phase of TB treatment unless the patient has other serious HIV-related conditions (e.g. Kaposi's sarcoma or HIV encephalopathy).

  - ART-experienced: Collect information on treatment history and response, and reason for treatment interruption. Discuss appropriate regimen with specialist.

  - After ART initiation monitor ALT every 2 weeks for 2 months.

Rechallenge of ART

- Patients who develop DILI while on TB medication and ART:
  - NVP: rechallenge with efavirenz after the TB drug rechallenge.
  - Efavirenz: rechallenge efavirenz if mild DILI after the TB drug rechallenge, if severe or recurrent DILI start PI-based regimen with lopinavir/ritonavir (dose adjustment if on RIF).
  - If mild DILI on efavirenz and LFTs resolve within 5-7 days after interrupting efavirenz, consider restarting efavirenz before the TB drug rechallenge to avoid stopping ART.
  - Double dose lopinavir/ritonavir: Preferred approach is to replace RIF with rifabutin 150 mg alternate days and use this with atazanavir/ritonavir (or with standard dose of lopinavir/ritonavir). If unavailable and double dose lopinavir/ritonavir with RIF used, should be recommenced with slow dose escalation over two weeks. Day 1: 400/100 mg 12-hourly, day 7: 600/150 mg 12-hourly, day 14: 800/200 mg 12-hourly.

- No need for double dose lopinavir/ritonavir if no RIF in the final regimen.
- All newer PIs or drugs from other drug classes - discuss with specialist.
- After ART rechallenge monitor ALT every 2 weeks for 2 months.

Rechallenge of co-trimoxazole

- If severe liver toxicity - should not be rechallenged.

- Use dapsone instead - but less effective in preventing PJP.

- Desirable to attempt rechallenge of co-trimoxazole in patients with previous PJP and with mild DILI after reintroduction of TB treatment and ART.

- Monitor ALT and bilirubin weekly for 1 month after rechallenge.

Other important points:

- Reintroduction of first line TB drugs preferred over use of second line drugs.

- Rechallenge not recommended in fulminant hepatitis. Once ALT < 100, bilirubin normalized, treat with MDR regimen, avoid PZA.

- If moxifloxacin not tolerated, use high dose levofloxacin, not ciprofloxacin.

- Streptomycin is contra-indicated if GFR < 60 ml/min. If streptomycin unavailable, kanamycin or amikacin should be used.

Other important points:

- If intensive phase interrupted for any period restart full course starting from the day alternative regimen is successfully reintroduced.

- Re-challenge with PZA was previously not recommended, but a recent trial has shown that most patients tolerate it. Can be considered in miliary TB, TB meningitis, drug resistance or intolerance of INH or RIF . ALT should be monitored three times weekly during rechallenge and weekly for a month following rechallenge.

- Patients with body weight patients <40kg, should have their maximal doses calculated according to their body weight.

- Monitor vision for signs of ethambutol toxicity especially if prolonged use.

Remember:

- if no improvement in LFTs, exclude autoimmune causes, liver biopsy (eg. to exclude OIs).

- No need to do full LFTs, ALT $\pm$ bilirubin sufficient, unless cholestatic pattern, do GGT.

- Educate patient to stop drugs and seek medical attention if symptoms recur.

Conclusions

- Rif & INH remain most important drugs and aim to get them on board.

- Other "liver friendly drugs" can cause hepatotoxicity.

- Confirm TB diagnosis.

- In patient management- do not rush to discharge.

- Close outpatient follow up.

- Risk of inadequate therapy- select for resistance.

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