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Managing LFT abnormalities in TB HIV patients

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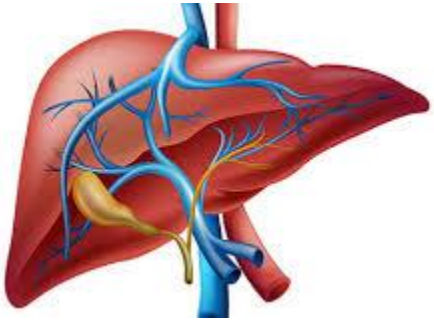


Introduction

- DILI in TB/HIV co-infected patients is a common problem in the SA setting
- Re-introduction of anti-TB drugs can be challenging for the health care workers
- The lack of studies has hindered protocols development especially in HIV confected patients
- SA HIV Clinician Society has developed a concensus statement to guide clinicians

"Let's have a show of hands. A motion has been made and seconded that it's all right to cry."

Introduction

- Liver has to perform different kinds of biochemical, synthetic and excretory functions, so no single biochemical test can detect the global functions of liver
- Liver function test is a misnomer
- Mainly determines liver injury pattern and synthetic function

Pattern of liver injury

- Raised transaminases (ALT and AST) indicate hepatocellular damage
- Raised ALP and GGT and high bilirubin

  = cholestasis
- Raised ALP plus GGT with normal bilirubin = infiltrative pattern
- Raised ALT plus ALP plus GGT plus bilirubin = mixed picture

Question 1

Which of the ff concerning liver enzymes is false

A. Alkaline phosphatase is found in liver, bone and placenta
B. Aspartate transaminase (AST) is found in red blood cells
C. The ratio of AST:ALT of 2:1 is indicative of viral hepatitis
D. Conjugated hyperbilirubinaemia is >50% of total bilirubin

Table 1: Key biochemical markers in hepatic systems and function

System or function	Marker	Site or significance
Hepatocyte integrity	Aspartate aminotransferase	Liver, heart skeletal muscle, kidney, brain, red blood cell
	Alanine aminotransferase	Liver
Cholestasis	Alkaline phosphatase	Bone, intestine, liver, placenta
	γ-Glutamyl-transpeptidase	Correlated levels with alkaline phosphatase indicate hepatobiliary origin
	Bilirubin	Elevations may indicate hepatic or extrahepatic disorder
Liver function mass	Serum albumin	Diet or liver
	Prothrombin time	Liver synthesizes vitamin K-dependent clotting factors

Question 2

- 28 yr old, RVD cd4 80 on TDF, 3TC, Alluvia ff virological failure due to non adherence. Presented with Bronchopneumonia and sputum Gene Xpert positive for M. TB and rifampicin sensitive. She was commenced on RHZE. Two weeks later she developed jaundice and ID consult sought

- Liver function
  - Total Protein 86 g/L
  - Albumin 30 g/l
  - Total Bilirubin 178 µ mol/l (>4xULN)
  - Conjugated bil 88µmol/l
  - ALT 40 g/l
  - ALP 120 g/l
  - GGT 100 IU/l
  - AST 50 IU/l
  - INR 0.9
  - Hepatitis A,B,C negative

Question 3

What is the most likely cause of the high bilirubin

A. Rifampicin
B. Isoniazid
C. Pyrazinamide
D. Ethambutol
E. Alluvia

Question 4

What would be best management

A. Stop all treatment
B. Continue treatment and watch trends of bilirubin
C. Switch Rifampicin to Moxifloxacillin
D. Stop Rifampicin and commence Streptomycin
E. Stop rifampicin and continue HZE

Isolated Bilirubin causes

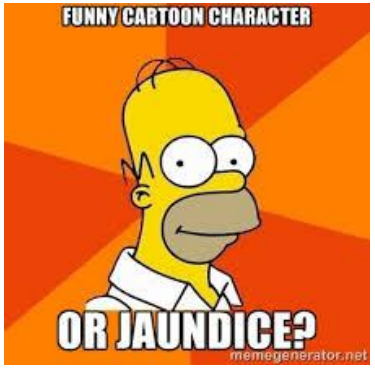
(A) Unconjugated
1. Increased bilirubin production.
- Haemolysis.
- Ineffective erythropoiesis.
- Blood transfusion.
- Resorption of haematomas.

2. Decreased hepatic uptake.
- Gilbert's syndrome.
- Drugs—for example, rifampicin.

3. Decreased conjugation.
- Gilbert's syndrome.
- Criggler-Najjar syndrome.
- Physiological jaundice of the newborn.

(B) Conjugated
1. Dubin-Johnson syndrome.
2. Rotor's syndrome.

Management of isolated hyperbilirubinemia



- Continue ART.
- Stop RIF (RIF is the most likely cause of isolated jaundice).
- Continue INH, PZA and EMB and add MOX.
- Repeat ALT and bilirubin after 7 days.
- If bilirubin does not settle, then consult an expert.

Mx of Isolated bili…

- Consider a full-dose RIF rechallenge
- Repeat ALT and bilirubin after 7 days.
- If ALT and bilirubin are stable, then stop MOX and continue with Rx
- If bilirubin increases to >40 µmol/l, stop RIF and continue INH, PZA, EMB and MOX.
- Monitor ALT and bilirubin weekly for 4 weeks after the rechallenge.

- If ALT increases to >120 IU/l, perform abdominal ultrasound and refer for further investigation

Question 5

- 35 yr old, RVD commenced TDF,3TC,EFV. A month later presented with sputum gene Xpert positive and started on antiTB meds.
- Now presents with RUQ nausea and vomiting. Bloods were done
- TP 80 Alb 20 Tbil 25 ALP 170 GGT 100 ALT 500
- Inr 1.2

Question 5

- What is the best management for this patient

A. Stop all treatment and commence liver sparing regimen
B. Stop only the TB treatment and monitor ALT
C. Do viral hepatitis screen, monitor ALT and INR
D. Stop TB rx, do viral hepatitis screen, commence liver sparing

Table 2. DILI definition advocated in the SA 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

Intensive /continuation phase of TB treatment

Mild DILI: Clinically well with elevated ALT <200 IU/l and total bilirubin <40 µmol/l

- Continue TB drugs.
- Continue ART.
- Repeat ALT and bilirubin in one week.
- If ALT and bilirubin have improved or normalised, stop laboratory monitoring.
- If ALT and bilirubin remain elevated but stable for 4 consecutive weeks, consider the other causes.

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

- Stop TB regimen.
- Start STR, moxifloxacin (MOX) and EMB
- Stop all hepatotoxic drugs.
- Stop ART. If the patient has been on a stable ART regimen for >6 months, consider continuing the therapy,
- Repeat ALT and bilirubin in 2 - 3 (inpatient) or 7 days (outpatient).
- When ALT is <100 IU/l and total bilirubin is normal, start the rechallenge.

Rechallenge Regimen

- Day 1: RIF 450 or 600 mg daily, depending on weight.
- Day 3: Check ALT.
- Day 4 - 6: Add 300 mg INH daily.
- Day 7: Check ALT.
- Day 8: Consider a PZA rechallenge (especially in the case of TB meningitis or intolerance/resistance to other drugs) and check ALT at day 10.
- Monitor ALT weekly for 4 weeks after the rechallenge

Box 4: Common causes of raised transaminases

- Alcohol.
- Medications: non-steroidal anti-inflammatory drugs, antibiotics, HMG Co-A-reductase inhibitors, antiepileptic drugs, antituberculous drugs, herbal medications, illicit drug use.
- Non-alcoholic steatohepatosis.
- Chronic hepatitis B and C.
- Autoimmune diseases.
- Haemochromatosis.
- Wilson's disease.
- Congestive cardiac failure and ischaemic hepatitis.
- α_1-Antitrypsin deficiency.
- Coeliac disease.
- Endocrine disease: hypothyroidism, Addison's disease.
- Diseases of striate muscle.
- Glycogen storage diseases.

Question 6

- 40yr old man with strong alcoholic hx, RVD on TDF/3TC/EFV on 2nd month of TB treatment presents with abnormal behaviour, hypoglycaemia and flapping tremor.
- FBC normal, U&E Na 128, K 3.5, CL 99, urea 12.4mmol/l (2.5-6.6) Cr 133mmol/l (53-115)
- LFT TP 88 Alb 20 TBIL 30 ALP 150 GGT 400 ALT 250 INR 4.5

Question 6

- What is the most likely diagnosis

A. Alcoholic withdrawal
B. Liver failure
C. TB DILI
D. Liver cirrhosis

Question 7

- What would be the best management

A. Stop TB treatment and IV dextrose
B. Stop all treatment and IV dextrose and diazepam
C. Stop all treament, IV dextrose and liver failure treatment
D. Stop all treatment, IV dextrose and liver friendly regimen

Liver Failure

- Stop all hepatotoxic drugs including ARVs
- Commence Liver failure treatment
- Supportive management
- Do not rechallenge the TB treatment
- Refer to Specialist for guidance to rechallenge

Question 8

- 39 yr old RVD cd4 69 on Alluvia/3tc/TDF with TB Abdomen based on intra abdomen lymphadenopathy and splenic abcesses presented
- LFT: TP 78 ALB 28 TBIL 30 ALP 120 GGT 100 ALT 150
- Inr 1.3
- Hepatitis B sAg positive

Question 8

- What is the best way to manage the patient

A. Commence Rifafour and monitor LFT
B. Wait until ALT normal before commencing TB rx
C. Commence liver friendly regimen
D. Do liver biopsy

- In patients with a baseline ALT >120 IU/l

  or total bilirubin >40 µmol/l, it is recommended
  - to start standard TB treatment and
  - monitor closely LFT/INR
  - to omit PZA initially in severe cases.
- If LFTs worsen on TB treatment, an alternative regimen should be started

General management principles

- Stop potentially hepatotoxic drugs
- Detailed history of screening ROH,herbal meds etc
- 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

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

Duration of treatment

Drug omitted	Total duration	Intensive phase	Continuation phase
Rifampicin	18 months	INH, Moxifloxacin, Ethambutol, Streptomycin x 2 months*	INH, Moxifloxacin, Ethambutol x 16 months
INH	12 months	Rifampicin, Moxifloxacin, Ethambutol x 2 months*	Rifampicin, Moxifloxacin, Ethambutol x 10 months
PZA	9 months	Rifampicin, INH, Ethambutol x 9 months	

TB DILI and ART Naive

ART-naive

- CD4+ count <100 cells/µl: start ART ff rechallenge
- CD4+ count >100 cells/µl: ART can be delayed until after the intensive phase of TB treatment,
- After ART initiation, monitor ALT every 2 weeks for 2 months.

TB DILI on ART

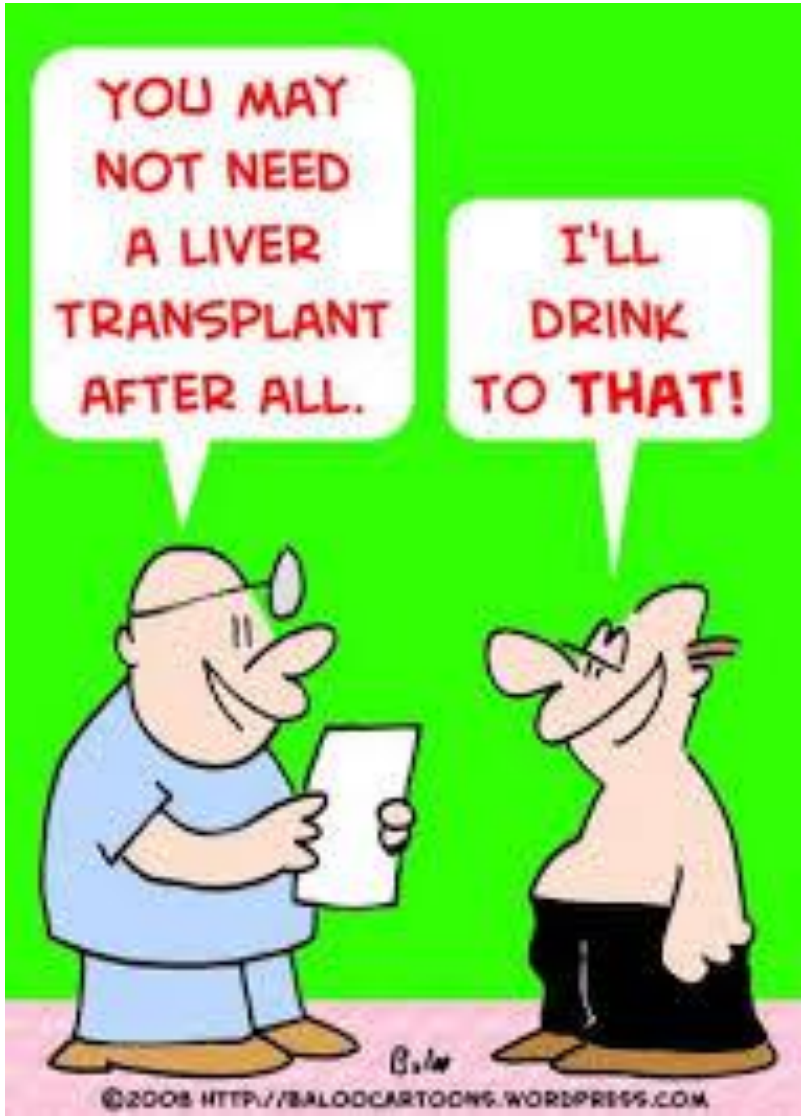
- If DILI developed on NVP, then rechallenge EFV
- If DILI developed on EFV, then rechallenge EFV in the case of mild DILI after the TB drug rechallenge.

TB DILI on ART

- If DILI developed on PI-based the preferred approach is to replace RIF with 150 mg rifabutin on alternate days and use this with atazanavir/ritonavir or alluvia
- After full TB Rx re challenged, LPv/r with slow-dose escalation over 2 weeks: i.e.
  - day 1 – 400/100 mg 12-hourly;
  - day 7 –600/150 mg 12-hourly;
  - day 14 – 800/200 mg 12-hourly.

Cotrimazole re challenge

- Co-trimoxazole therapy should not be rechallenged who experience severe liver toxicity
- Dapsone should be used instead
- Co-trimoxazole in patients with previous *P. jirovecii* pneumonia and with mild DILI after re-introduction of TB treatment and ART can be considered
- ALT and bilirubin weekly for 1 month


YOU MAY NOT NEED A LIVER TRANSPLANT AFTER ALL.
I'LL DRINK TO THAT!
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