CASE PRESENTATION
BY: DR C NARASIMOOLOO

DISCUSSION
BY: DR RAJ GHANDI

ABNORMAL LIVER ENZYMES IN AN HIV POSITIVE PATIENT ON ART

AWACC CONFERENCE 2010
Case History

- 28 year old female
- Diagnosed HIV positive in January 2009
- Started ART in August 2009 (Truvada (TDF / FTC) + EFV)
- Admitted to MCH on 27/07/10 with a complaint of
  - Jaundice
  - Abdominal pain
  - Vomiting
Jaundice

- Noticed for a week prior to presentation
- Sudden onset
- Progressively deepening
- Discolouration of sclera, mucous membranes and skin
Abdominal pain

- Began 2 months prior to admission
- Initially waxing and waning type of pain which became progressively worse and constant at presentation
- Non radiating
- Not associated with food
- No associated with movement
- Normal bowel habits
- Normal stools
Vomiting

- Preceded the abdominal pain
- 2 months duration
- Began with nausea and progressed to vomiting in mornings
- Now vomiting after every meal
- No hematemesis
Negative history

- No dysuria
- No fever
- No headache
- No dark urine
- No pale stools
- No pruritis
- No previous admissions
- Not on any other medication other than ART and bactrim
Other history

- She displayed good insight into her HIV and was fully compliant with her medication.
- According to the patient, her CD4 when commencing ART (Aug 09) = 121; and CD4 after 6 months of ART (Mar 10) = 17.
- She admitted to taking traditional medication, but that was for a few weeks in 2009 and then she stopped.
- No history of alcohol or drug abuse.
- No previous TB/autoimmune disease.
- No drug allergies.
- She is married with 2 children. Both children are HIV negative
- Her husband lives away from home and is HIV positive
- He is not on ART as his CD4 count is more than >200
- They do not use condoms
EXAMINATION FINDINGS

- **DAY 1**
  - She was not acutely ill
  - Comfortable at rest
  - Obvious yellow tinge to her skin and eyes
  - Moderately built and nourished

- **Vitals:**
  - fever (38*)
  - tachycardia (110/min)
  - BP and RR were normal
- Icterus – sclera, mucous membranes and skin
- No pallor, clubbing, cyanosis, LAD, oedema
- Oral thrush
- Mild dehydration
- CVS: NAD
- RS: NAD
- P/A: soft, not distended, tender in RUQ, no peritonism, no organomegaly, BS normal
- CNS: NAD
ASSESSMENT

- Hepatitis
  - ? Drug induced
  - ? Viral

- ? Immunological Failure on ART
INVESTIGATIONS

- FBC
- U&E
- LFT
- CMP
- Amylase
- INR
- ANF
- Hepatitis screen
- Blood cultures
- Pregnancy Test
- CD4
- Viral Load
- CXR
- Ultrasound of the abdomen
IV fluid was ordered
Nystatin oral suspension for oral thrush
Ponstan for fever and pain
Maxalon for vomiting
The ART and bactrim was continued pending results
DAY 2 of admission

- Review of results showed a marked transaminitis
- Normal FBC, U&E, CMP, amylase
- INR was raised to 4.6
- CXR normal
- USG abdomen was normal
- Pregnancy test was negative
# RESULTS

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MANAGEMENT

- ART was stopped
- Patient was commenced on Vitamin K
- Lactulose
- Flagyl and ciprofloxacin
- Fresubin protein energy supplements
- Blood sugar levels monitored closely
- Daily INR and regular LFTs’ were ordered
Day 7

- Afebrile
- Doing well
- Ambulant
- Tolerating foods, no longer vomiting
- Abdominal pain still constant
- AST / ALT levels had dropped by approximately 60%
- INR 3.6
- ANF negative
- Hepatitis screen negative
- Blood cultures negative
- CD4 552 (25%)
- VL <40
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MANAGEMENT

- Immunological failure was unlikely
- Hepatitis of a viral cause was ruled out
- ART was planned to be reintroduced once the liver enzymes had normalised
- A CT scan of the abdomen was ordered
- A Liver biopsy was proposed once the INR had settled to normal
Day 14

- Patient was well
- Now pain free
- The AST/ALT had dropped by 70%
- The CT scan was normal apart for an enlarged liver
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Patient was booked for a plugged liver biopsy (gel foam technique) at another hospital, for the following week.

Patient was discharged and asked to be reviewed with the biopsy results.
3 weeks after admission: OPD review

- Liver biopsy showed: fatty liver suggestive of hepatic steatosis
- A decision was made to recommence ART since the hepatic steatosis was probably pre-existing prior to commencing ART (TDF / FTC / EFV)
- Patient would be reviewed after a week with LFT’s
Week 4 and 5 after admission

- The liver enzymes began an upward climb with the transaminitis getting progressively worse (this is 2 weeks of recommencing ART)
- A decision to change EFV to alluvia (LPV/r) was made, however, since the patient was on medical aid, she need authorization to make this change.
- This was denied
Week 8 after admission

- Patient still has a raised INR and a transamintis
- She is not on ART or bactrim
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</table>
POINTS FOR DISCUSSION

- The diagnostic approach to pts with abnormal liver enzymes post ART.
- What are good ART options?
- Which regimen should be recommended for this patient?
- What is the management of hepatic steatosis in the HIV positive patient?
- How do we work up and manage the HIV patient with jaundice pre and post ART?
- How do we manage drug toxicity caused by TB and or ART?
28 yo F with HIV (initial CD4 <200), started on TDF/FTC/EFV and bactrim in 8/09, presents in 7/10 with jaundice, abdominal pain, vomiting

Exam notable for icterus, oral thrush, RUQ abdominal pain

Studies: markedly elevated transaminases and cholestasis, with evidence of synthetic dysfunction (elevated PT, low albumin). CT: enlarged liver. HBsAg, HCV Ab, HAV IgM negative. Liver bx: hepatic steatosis. CD4 552, VL<40.

Transaminases initially improve after stopping ART, but then begin to slowly climb again
LFT Abnormalities After Starting ART: Differential Diagnosis

- Drug-induced liver injury
  - ART hepatotoxicity
  - Other: bactrim, amox/clav, azoles, alcohol, alternative medications
- Immune Reconstitution Inflammatory Syndrome
  - HBV
  - Opportunistic infections, e.g. MAC, TB (granulomatous hepatitis)
- Superinfection
  - HAV, HCV, HDV, HEV (chronic HEV has been reported in an HIV-infected patient\(^1\))
  - EBV, CMV, HSV
  - Syphilis
- Hepatitis B flare

\(^1\)Dalton, NEJM (2009) 361:1025
Drug-induced liver injury (DILI)

- May result from direct toxicity of the drug or from an immunologically-mediated response
- Clinical diagnosis of exclusion
- Generally occurs within a few months of initiating a drug
- Treatment is usually withdrawal of drug and supportive care
  - N-acetyl cysteine used in acetaminophen (paracetamol) overdose
  - Intravenous carnitine used in valproate-induced mitochondrial injury
Typical patterns of liver injury with drugs

<table>
<thead>
<tr>
<th>Hepatocellular (ALT/AP &gt;5)</th>
<th>Mixed</th>
<th>Cholestatic (ALT/AP &lt;2)</th>
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<tr>
<td>ARVs</td>
<td>Sulfonamides</td>
<td>Amox/clav</td>
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<td>Herbal meds</td>
<td>Bactrim</td>
<td>Macrolides</td>
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<tr>
<td>INH</td>
<td>Phenytoin</td>
<td>Phenothiazines</td>
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<td>Phenobarbital</td>
<td>Tricyclics</td>
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<td>Nitrofurantoin</td>
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<td>Valproate</td>
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<td>Oral contraceptives</td>
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<td>Allopurinol</td>
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Navarro & Senior. NEJM 354: 7
ART hepatotoxicity

- 14-20% of HIV+ pts starting ARVs have elevations in LFTs
- 2-10% need to interrupt ART because of significant hepatotoxicity
- Risk factors:
  - Female gender
  - Elevated baseline transaminases
  - Concomitant hepatotoxic drugs (anticonvulsants, bactrim, amox/clav, azoles)
  - HCV
  - HBV: 3-fold increased risk of severe hepatotoxicity, primarily in those with high HBV DNA levels or those with CD4 cell count <200

Hoffmann et al. CID (2008) 47:1479
Audsley J, 17th CROI (2010), abs 691
ART hepatotoxicity (Htox)

- **NRTI**: esp. d-drugs
  - Hepatic steatosis
  - May be related to inhibition of mitochondrial DNA pol-
  - d4T/ddI>AZT>ABC, TDF

- **NNRTI**: NVP > EFV
  - ETR: low rate\(^2\)
  - Early NVP Htox (6-18 wks): rash, systemic sx; Risks: female, CD4 >250

- **PIs**: Higher rates with TPV/rtv, RTV
- **INSTI**: Raltegravir: low rate\(^3\)

\(^1\)McGovern et al, CID 43:365
\(^2\)Clotet JAC, 2010;
\(^3\)Rockstroh J, 17\(^{th}\) CROI (2010), abstract 662
Conclusions

- In a HIV+ patient with liver test abnormalities after starting ART, consider:
  - Worsening of underlying liver disease, e.g. alcohol-related
  - Drug-induced liver injury
    - ARVs
    - Other drugs
  - IRIS
    - Particularly if fever, adenopathy, hepatomegaly, other sites of disease
  - Superinfection
  - Flare of HBV or HBV IRIS
POINTS FOR DISCUSSION

- The diagnostic approach to pts with abnormal liver enzymes post ART.
- What are good ART options?
- Which regimen should be recommended for this patient?
- What is the management of hepatic steatosis in the HIV positive patient?
- How do we work up and manage the HIV patient with jaundice pre and post ART?
- How do we manage drug toxicity caused by TB and or ART?
The diagnostic approach to pts with abnormal liver enzymes or jaundice post ART.

- Consider drug-induced liver injury (ARVs, bactrim), alternative medications, alcohol
- Check synthetic function (albumin, PT, platelet count)
- U/S. In cases of jaundice, r/o biliary dilatation; r/o thrombosis
- Look for adenopathy, hepatomegaly, new CXR findings—to suggest IRIS
- Hepatitis serologies: HAV, HBV
- Rule out EBV, CMV, HSV, syphilis
- Evaluate for hemolysis given high LDH
- Liver bx: review for signs of drug-induced liver injury (eosinophils); granulomatous inflammation; infection
POINTS FOR DISCUSSION

- What are good ART options? Which regimen should be recommended for this patient?
  - Have her abdominal pain and vomiting resolved?
  - Is she still on bactrim?
  - Does she have any evidence for TB or IRIS?
  - If her symptoms have resolved, there’s no evidence for TB or IRIS and her LFTs remain elevated after stopping bactrim, then would restart ART with new regimen, e.g. TDF/FTC/Alluvia; TDF/FTC/raltegravir
POINTS FOR DISCUSSION

What is the management of hepatic steatosis in the HIV positive patient?

- Potential causes: obesity, d-drugs, viral hepatitis (HCV), HIV
- Treatment
  - Address underlying cause
  - Pioglitazone
  - Vitamin E
POINTS FOR DISCUSSION

- How do we manage drug toxicity caused by TB and or ART?
  - If patient is HBV- or HCV-positive, treat the underlying viral hepatitis
  - Choose agents that are less likely to be hepatotoxic
  - If possible, avoid concomitant hepatotoxic medications
Discontinuation of 3TC, FTC, TDF may lead to HBV flare
- Incidence after 3TC-withdrawal: 22%\(^1\)
- ~5% have elevation of ALT >5x ULN, usually peaking 1-3 months after stopping 3TC\(^2\)

Flares in transaminases may also be due to:
- Breakthrough of drug-resistant HBV
- Seroconversion of HBeAg
- Immune reconstitution against HBV (HBV IRIS)
- Superinfection with HDV, HCV, HAV, EBV, CMV
- Drug-induced liver injury
  - Liver histology may distinguish drug toxicity (presence of eosinophils) from viral hepatitis (portal inflammation).