CASE PRESENTATION
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DISCUSSION
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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 CD_4 when commencing ART (Aug 09)= 121; and

  CD_4 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
- CD_4
- Viral Load
- CXR
- Ultrasound of the abdomen

MANAGEMENT

- 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

TEST	27/07 1	30/07	01/08	04/08 1 wk	07/08	10/08 2 wks	17/08 4 wks	24/08 5 wks	31/08 6wks	07/09 7wks	21/09 8wks	28/09 9wks
LFT												
TB	**147**	158	138	168	112	97	118	102	107	98	107	98
DB	**87**	94.8	81.4	83	70	59	68.1	60	61	51	52	52
ALP	**227**	208	202	181	162	145	163	227	182	324	348	310
GGT	**494**	363	317	252	205	162	175	221	204	274	271	257
ALT	**614**	488	415	365	246	181	193	263	211	197	325	289
AST	**1145**	856	835	784	361	313	349	540	377	368	665	559
TP	**85**	78.0	74.0	67	63	52.0	59	69	66	80	87	77
ALB	**32**	27	25	23	20	16	18	22	20	24	26	24
LDH		1042	923	836	795	585	661	584	534	525	553	578
INR	**4.69**	4.24	4.4	3.60	3.92	3.17	2.21	3.08	2.4	2.64	2.14	2.51

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
- CD_4 552 (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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MANAGEMENT

- 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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AMY	108
HEPATITIS SCREEN	
HBC IgM	Neg
HBsAg	Neg
HCV IgG	Neg
HAV IgM	Neg
CMP	
Ca	1.96
Mg	0.64
PO4	0.89
ANF	Neg
Blood culture	No growth
CD4	552 (25%)
VL	<40
Preg Test	Neg
CXR	Normal
USG	Normal
CT abdomen	Enlarged liver
Liver Biopsy	Fatty liver suggestive of hepatic steatosis

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?

CASE Summary

- 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

Hepatocellular (ALT/AP >5)	Mixed	Cholestatic (ALT/AP <2)
ARVs	Sulfonamides	Amox/clav
Herbal meds	Bactrim	Macrolides
INH	Phenytoin	Phenothiazines
PZA	Phenobarbital	Tricyclics
Ketoconazole	Nitrofurantoin	Anabolic steroids
Valproate		Oral contraceptives
NSAIDS		
Allopurinol		

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

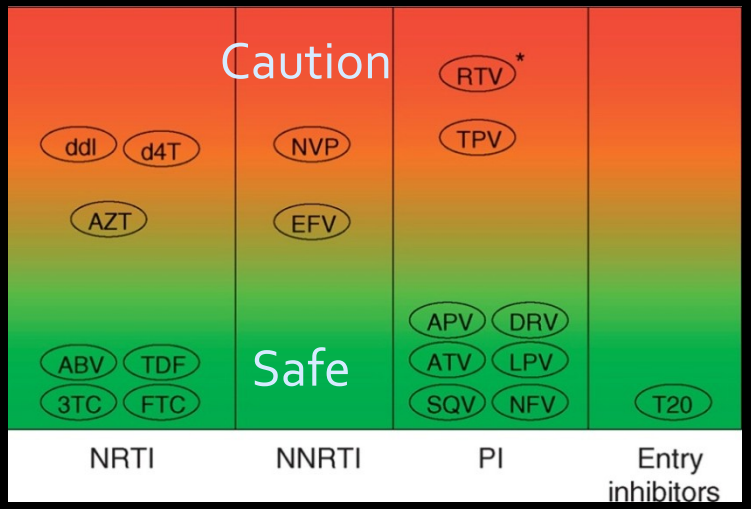
Hoffmann et al. AIDS (2007) 21: 1301
Hoffmann et al. CID (2008) 47:1479

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

[1]McGovern et al, CID 43:365



Soriano et al, AIDS (2008) 22:1

- PIs: Higher rates with TPV/rtv, RTV
- INSTI: Raltegravir: low rate[3]

[2]Clotet JAC, 2010;
[3]Rockstroh J, 17th 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

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POINTS FOR DISCUSSION

- 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

EXTRA SLIDE: Liver enzyme elevation in HIV/HBV coinfection

- 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).

[1]Wit, JID (2002) 186:23. [2]Bellini, HIV Med (2009) 10:12