Advanced Update in HIV Medicine
Durban, South Africa
October 1 and 2, 2009

Presented by:
Dr B I Gosnell
HPI:

- 29 yr old male
- Seen at ID clinic for routine Follow-up
- Found to be deeply jaundiced
- Patient was asymptomatic - no symptoms to suggest hepatitis or biliary obstruction
- Patient’s first monthly follow-up visit to ID after having spent 6 months in hospital, 5 of which under the care of the ID team.
PMH

- **RVD:**
  - Diagnosed Nov 2008
  - Commenced ARVs (AZT, 3TC, EFV) 12/5/09
  - No interruptions.
  - Baseline CD4: 25 cells 5/09, VL 48000 c 1/09

- **PTB**
  - Diagnosed by CXR and sputum culture:
    Pan-sensitive MTB
  - Commenced on intensive phase on 20/04/09
  - Received intensive phase for 3/12
  - Un-interrupted continuation phase Rx up current admission.
PMH

- **Pancytopenia:**
  - BMAT demonstrated poorly formed granulomas with scanty AFB
  - Likely secondary to TB bone marrow.
- FBC from last admission
  - Worst FBC: Hb 4.9 g/dL, WCC 1.3 /nL, Plt 55 /nL
  - On discharge: Hb 12.1 g/dL, RCC 4.02 , WCC 3.2 /nL, Plt 128 /nL
- Transfused once 2 units of packed Red Cells
- **Recurrent Salmonella septicaemia:**
- Episodes in March, April and May ’09 – treated each time for 10 days with ceftriaxone iv.
- **Schistosomiasis:**
  - Diagnosed on rectal biopsy in July ’09
  - Treated with stat dose of praziquantel
- **Cryptococcal meningitis:**
  - Diagnosed in March 2009
  - Treated with Amphotericin B x 2/52
  - then Fluconazole
PMH

- **Hepatitis B Infection:**
  - HBs Ag +, HBe Ag –, HBc Ab –; HA & HC Ab –
  - Interpreted as chronic carrier

Worst LFT: March 09 prior to ARVs + TB tx
- Bili 20 µmol/L (n 0-17), +ALP 329 U/L (n 42-121), GGT 1192 U/L (n 10-60), *ALT 130 U/L (n 10-45)

Best LFT: June 09 on ARVs + TB tx
- Bili 13 µmol/L, ALP 277 U/L, GGT 762 U/L, ALT 39 U/L
Hepatosplenomegaly:
- Liver function abnormalities not helpful
- Liver biopsy: mild inflammation + mild steatosis, HBs + HBc Ag +, Activity grade 3/18, Stage 1/6
- Presumed 2° to TB which was missed due to incomplete sampling or cirrhosis with portal hypertension or 2° to HIV

CMV:
- IgM positive

Severe debilitating peripheral neuropathy:
- Improved with symptomatic treatment and ARVs
- Was walking without and aid on discharge
Meds on this admission:

- Rifampicin 600 mg/INH 300mg dly
- Pyridoxine 25 mg dly
- Lamivudine 150 mg BD
- Zidovudine 300 mg BD
- Efavirenz 600 mg nocte
- Co-trimoxazole 1d/s daily
- Gabapentin 300 mg TDS
- Amitryptiline 50 mg nocte
PE:
Deep jaundice, shotty lymphnodes, not pale, no thrush, no oedema
Chest: clear
CVS: Not in failure, BP 96/61, P118
Abdomen: soft, hepar 2 cm, smooth edge spleen 2 cm, no ascites, no signs of chronic liver disease.
CNS: Lucid, Cranial nerves intact, no meningism, no signs of liver failure
Studies:

- Hb 11.7g/dL normochromic, normocytic, WCC 2.2 /nL, Plt 97 /nL
- Na 137 mmol/L, K 3.4 mmol/L, Cl 107 mmol/L, CO₂ 22.0 mmol/L, Urea 2.2 mmol/L, Creatinine 66 µmol/L,
- Prot 78 g/L, Albumin 29 g/L, Bili 176 µmol/L, (10x ULN), +ALP 94 U/L(n), GGT 407 U/L(6.8x ULN) (3.3x ULN), *ALT 243 U/L (5.4x ULN), INR 1.94

+alkaline phosphatase *alanine aminotransferase
Trends GGT, ALT, total Bilirubin

Trends

EFV, 3TC, AZT

AZT, 3TC only
Initial CXR in March: prior to ATT
CXR 4 months into TB Tx this admission
Diagnostic testing

- June: Mild lobular and portal tract mixed inflammation with focal mild interface hepatitis. Mild steatosis, no cholestasis, no granulomas, AFB, or neoplastic infiltrate identified. Positive for HBsAg and HBcAg. Activity grading index and staging index suggest mild disease HBV disease. Cannot exclude cirrhosis due to poor specimen
Questions for discussion:

1. How should this patient be managed further:
   a) For HIV
   b) For TB
   c) For secondary prophylaxis of crypto meningitis

2. Is it important to determine the underlying cause of the HBV flare (HBV drug resistance vs. HBV IRIS)

3. How should the HBV be managed – is there any value to using steroids?
Trends GGT, ALT and tot Bili

Trends

upper limit of normal multiples

06-Sep 07-Sep 08-Sep 09-Sep 10-Sep 11-Sep 12-Sep 13-Sep 14-Sep 15-Sep 16-Sep 17-Sep 18-Sep 19-Sep 20-Sep 21-Sep 22-Sep 23-Sep 24-Sep 25-Sep 26-Sep 27-Sep 28-Sep

EFV, 3TC, AZT
AZT, 3TC only
Tenofovir added
Discussion

HBV Flare
Pathogenesis of HBV CLDx

- Hepatic damage ⇒ predominantly immune mediated - cytotoxic T cells
- HBV specific peptides presented on the infected liver cell surface ⇒ recognized by Ag specific CD8 T cells ⇒ hepatocellular inflammation and necrosis.
Natural history in face of HIV:

- Higher rates of hepatitis HBeAg positivity
- Higher levels of HBV DNA
- Lower ALT levels
- Reduced necroinflammatory activity on histology
- More rapid progression of liver disease.
Definition of HBV IRIS

- Rapid worsening of LFT
- Soon after commencement of HAART
- Evidence of immune reconstitution (decrease VL, increase CD4 count)
- Absence of alternate explanation:
  - Hepatotoxic effects of treatment
  - Withdrawal of HBV active agent
  - Resistance of HBV to HBV active agent
  - Superimposed, unrelated acute liver disease
HBV IRIS

- Immune reconstitution is a “double-edged sword” in patients infected with HBV.
  - Hepatocyte injury
  - Viral clearance.
Chronic Asymptomatic HBV infection

- Is a result of a fine balance between viral replication and intensity of immune response to virus

Acute Flare

Due to alteration in balance:
- Treatment interruption / withdrawal
- HBV resistance to treatment
- Immune reconstitution (favorable)

AWACC 2009
How to prevent flares

Know HBV status!
How to prevent flares

- Control active HBV replication.
- The most prudent approach would be combination of 3TC & TDF:
  - More effective at reducing HBV VL
  - ↓ risk of HBV drug Ω (50% - 2 yrs, 90% - 4 yrs)
- Particular care with significant underlying liver disease.
Take Home Message

- Cannot commence HAART without the knowledge of your patients HBV status
- Cannot withdrawal HAART without knowledge of your patients HBV status.
- Must be aware of the dual purposes of lamivudine, tenofovir, and emtricitabine
- If suspect underlying liver disease then need to evaluate patient further
Final Diagnosis

Exacerbation of Hepatitis B in Patient 4 months on HAART

Contributors:

Prof MYS Moosa (infectious diseases)

Dr Ramdial (Histology)