Liver disease in patients with HIV

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Liver disease in patients with HIV

- Chronic (viral) hepatitis
- Liver cancer
- Drugs
- Fatty liver disease
- Vascular disease
- Opportunistic infections
- Biliary tract disease
Effect of HIV on Liver Disease

- Immune dyregulation in leads to very high viral loads and increased inflammation and fibrosis
- Stellate cell activation
- Death receptor activation
- Bacterial translocation
- Kupffer cell depletion
Effect of HIV on Liver Disease

Stellate cell activation

- HIV entry into hepatic stellate cells is CD4-independent
- HIV infection promotes stellate cell activation: increased collagen I and α-SMA mRNA
- Similar effects on incubation with gp120

Gut 2009 Sep 7
Effect of HIV on Liver Disease
Death receptor activation

- HIV and the HIV glycoprotein gp120 ligation of CXCR4 on hepatocytes up-regulates TRAIL R2 expression and increases sensitivity to TRAIL mediated apoptosis

PLoS One 2009;4:e4623
Bacterial translocation

- HIV-related CD4(+) lymphocyte depletion was strongly associated with microbial translocation across the gut wall
- Increased blood levels of LPS, LPS-binding protein, soluble CD14
- Related to HCV progression

*Gastroenterology* 2008;135: 226
Kupffer cell depletion

- Kupffer cells are the first line of defence against microbial translocation products.
- Numbers were substantially lower in persons with lower CD4+ lymphocyte counts.

AIDS 2009; 27:2397
CHRONIC (VIRAL) HEPATITIS
HIV and Chronic viral hepatitis

- Chronic hepatitis B and C viruses are often associated with HIV infection because of the common routes of infection
- HCV: 30% of patients with HIV
  - mainly IV drug abusers
- HBV: 10% of patients with HIV
  - mainly homosexual contact
HIV and Chronic viral hepatitis

• The main aetiologies are:
  HCV  82%
  HBV  2%
  HBV+HCV  3%
  HBV+HCV+HDV  7%

• The prevalence of cirrhosis different among patients with different aetiologies:
  HCV  19%
  HBV  7%
  HBV+HCV  42%
  HBV+HCV+HDV  67%

J Viral Hepat 2008;15:165
HIV AND HBV
HIV and HBV

- HBV infection persists in 25% of HIV-infected adults
- In HIV co-infection, a more severe and critical progression of HBV has been reported, and the occurrence of HCC has become a major problem

J Antimicrob Chemother 2009 Nov 8
HBV and HIV

Pre- ART

On ART
HIV and HBV

• HBV may be reactivated by advanced immunosuppression
  This may cause a lobular hepatitis
• High levels of HBV replication may be associated with cytopathic liver damage
  This may cause a fibrosing cholestatic hepatitis
HIV AND HCV
HIV and HCV

- HCV, more rapid disease in patients with HIV:
  1. More rapid fibrosis (not reversed completely by ART)
  2. Faster progression to end stage liver disease
  3. Lower clearance rates in response to therapy

Gastroenterology 2009; 137: 795
HIV and HCV

- **HIV, little difference in patients with HCV:**
  1. Little effect on progression of immune suppression
  2. Little effect on response to ART
  3. *HIV-related bacterial and mycotic infections are strongly associated with positive HCV serology and HCV-related cirrhosis*

Gastroenterology 2009; 137: 795
Clin Infect Dis 2009; 15: 612
HCV (and HIV): postinfantile giant cell transformation

J Clin Pathol 2008;61:1058
HIV and HCV
LFTs and Disease Severity

- 256 patients coinfected with HIV and HCV:
  - 9% had an ALT level within the normal range on ≥ 2 separate occasions over a 6-month period.
  - In the high ALT group F3 or F4 fibrosis was seen in 34%
  - Among patients with persistently normal ALT levels 29% had stage F2 fibrosis

Clin Infect Dis 2006;43: 640
HIV and HCV Fibrosis Progression

- 46% of patients had an increase of 1 or more Ishak stages over a period of 2.9 years
- 25% progressed 2 or more Ishak stages
  
  Cf. HCV-monoinfected patients who show progression of 2 or more Ishak stages in 10% of patients over a similar period of time
- 4.6% of patients with scores of 2 or less had cirrhosis in the second biopsy

*AIDS* 2007; 21: 2209
HIV and HCV
Fibrosis Progression

- 135 HIV-infected patients with positive serum HCV RNA, underwent two biopsies (median 3.3 years)
- Progression by 1 stage: 28% and progression by 2 or more stages: 16% (assessed using the 5 point Scheuer scoring system)

- **Slower fibrosis progression associated with:**
  1. absent-/ mild lobular inflammation at baseline
  2. response to anti-HCV treatment and
  3. effective antiretroviral therapy are associated

*Hepatology* 2009; 50: 1056
HIV and HCV

2000 2003
HIV and HCV and GBV-C

- Among people with HIV infection, the prevalence of GBV-C viraemia ranges from 14 to 43%.
- GBV-C has been associated with improved overall survival in some studies evaluating HIV-HCV infected populations.

Gastroenterology 2007; 133: 1821
J Gastroenterol Hepatol 2009; 24: 1407
**NO. AT RISK**

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HIV and HBV and HDV

- HDV usually inhabits HBV replication
- With HIV this inhibition is decreased
- With treatment of the HIV this inhibition is partially restored

HIV and HBV and HDV

HDV

HBcAg
HIV and Viral Hepatitis and .....
HIV AND AUTOIMMUNE HEPATITIS
HIV and Autoimmune hepatitis

- 3 cases
  “Liver biopsy findings were critical in establishing the diagnosis of AIH”
  J Clin Gastroenterol 2008; 42: 425

- 4 cases (2 of whom also had HCV)
- Serology and histology were consistent with AIH
- Despite appropriate therapy, all developed life-threatening infectious or adverse metabolic effects that resulted in treatment discontinuation.
  AIDS Patient Care STDS 2009; 23: 407

- AIH has rarely been reported in patients with HIV
- Should be screened for especially prior to starting interferon treatment for HCV
HIV and HCV and AIH
HIV AND LIVER CANCER
HIV and Liver cancer
HIV and Liver cancer

• All HCC patients are positive for HBsAg or have antibodies to HCV
• Lower CD4+ cell counts increased the risk for HCC especially in HBV-related HCC arising in non-injecting drug users

AIDS 2008; 22: 2135
HIV and Liver cancer

The French national Mortalité 2005 study:
• Among liver-related deaths
  HCC increased as a cause from 15% to 25%
• Among HCC-related deaths:
  in 2000, 10% had HCV
  in 2005, 25% had HCV

J Hepatol 2009; 50: 736
HIV and other liver tumours

- Cholangiocarcinoma

J Acquir Immune Defic Syndr 2005; 39: 253
Int J STD AIDS 2008; 19: 717
(Anticancer Res. 2009; 29: 3239)
ART and the lipodystrophy syndrome

- Lipoatrophy and lipohypertrophy
- Hyperlipidaemia
- Insulin resistance and clinical diabetes
- Seen with nucleoside analogues, non-nucleoside reverse transcriptase inhibitors and protease inhibitors
- 25 to 50% of HIV patients have the metabolic syndrome

Gut 2009; 58: 1579
ARV and the lipodystrophy syndrome

• Nucleoside reverse transcriptase inhibitors have been associated with morphological changes, particularly extremity fat loss, and dyslipidaemia

• Protease inhibitors have been associated with biochemical derangements of glucose and lipids as well as with localized accumulation of fat.

HCV and Insulin resistance

- Insulin resistance is commoner (especially in genotypes 1 and 4)
- Fatty change is commoner (especially genotype 3)
- Patients with insulin resistance are less likely to respond to treatment
Fatty liver hepatitis in patients with HIV and HCV

- **Apricot study**: Association with fatty change, genotype 3, hyperlipidaemia, increased hip circumference and increased fibrosis.
- Fatty liver hepatitis found in 30% of co-infected patients was related to BMI but not ART.
- Insulin resistance (related to ART) correlated with liver stiffness.
HIV AND OTHER DRUG REACTIONS
Antimicrobial therapy

1. Trimethoprim – sulphamethoxazole
2. Pentamidine
3. Isoniazid
4. Rifampacin
5. Fluconazole
6. Ketoconazole
7. Ganciclovir
HIV AND ALCOHOLIC LIVER DISEASE
HIV and Alcoholic liver disease

- Excessive alcohol consumption has been observed in one-third of patients with HIV
  Journal of Hepatology 1998; 6: 945

- Alcoholic hepatitis is more frequent and more severe
  Journal of Hepatology 2002; 36: 172

- Patients dying from liver disease had HCV in 93% of cases and moderate (30-60 g) or high (>60 g) alcohol consumption (44% and 26%, respectively)
  J Viral Hepat 2007;14:183
HIV AND VASCULAR DISEASE
HIV and Portal hypertension

- 15 case patients had endoscopically documented esophageal varices and absence of liver cirrhosis on biopsies
- Cumulative exposure to antiretroviral therapy (OR per year, 1.3) and didanosine (OR, 3.4) were longer in case patients.

Clin Infect Dis 2009; 49: 626
HIV and Portal hypertension

- 8 patients with HIV-related IPH
- 5 presented with variceal bleeding, 2 with splenomegaly, and 1 with ascites.
- All had oesophageal varices

Am J Gastroenterol. 2009;104:1707
HIV and Portal hypertension

- Median hepatic venous pressure gradient was 8 mm Hg. This is probably because of a presinusoidal component of PH and because of the presence of intrahepatic venous collaterals.
- Median liver stiffness was 8.9 kPa and was unreliable in predicting the presence of fibrosis or of oesophageal varices.
HIV and Portal hypertension

• The main histological features were absence of portal vein radicles and areas of regenerating hepatocytes.
• Six patients (75%) developed portal vein thrombosis during a 2-year follow-up.

• Pathogenesis:
  Antibodies to Protein S and C
  Direct endothelial toxicity
HIV and Thrombotic disease

• Thrombotic events occur among patients with HIV despite their relatively young ages.
• Advanced HIV disease is a risk factor for development of thromboses
• AVT is not a risk factor

AIDS Patient Care STDS 2008; 22: 771
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