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

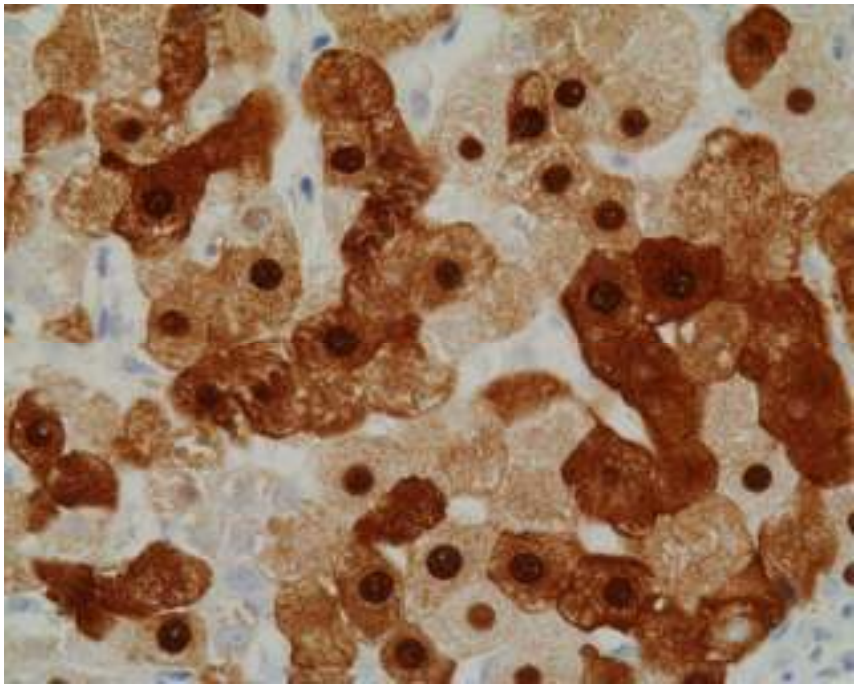
HIV and HBV

- 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

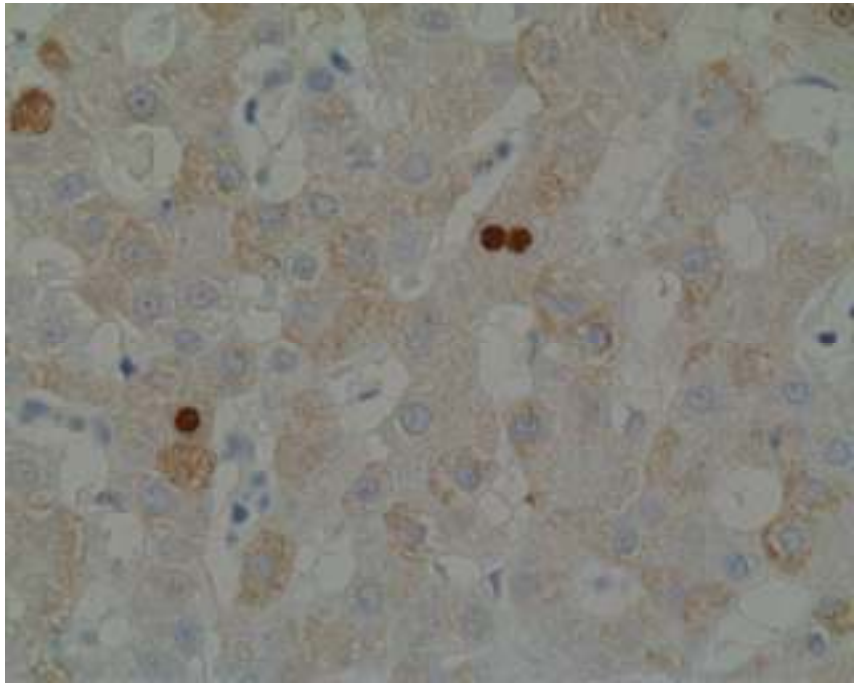
J Antimicrob Chemother 2009 Nov 8

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

Clin Infect Dis. 2009; 49: 1274

HIV and HCV

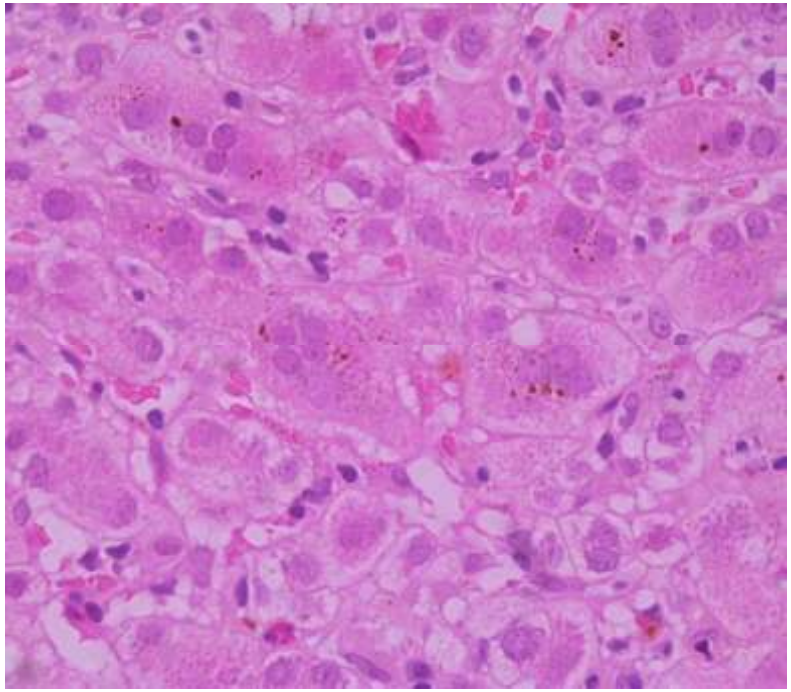
- **HIV, little difference in patients with HCV:**

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 > or = 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 / more Ishak stages over a period of 2.9 years
- 25 % progressed 2 / 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)

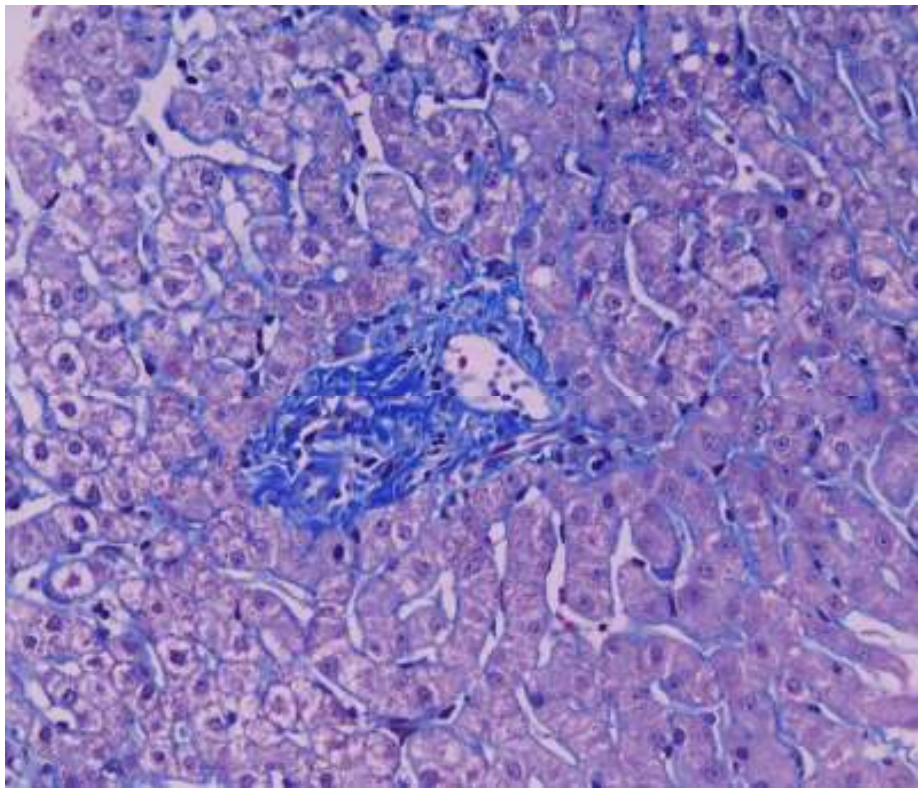
- **Slower fibrosis progression associated with:**

1. absent-/ mild lobular inflammation at baseline
2. response to anti-HCV treatment and
3. effective antiretroviral therapy are associated

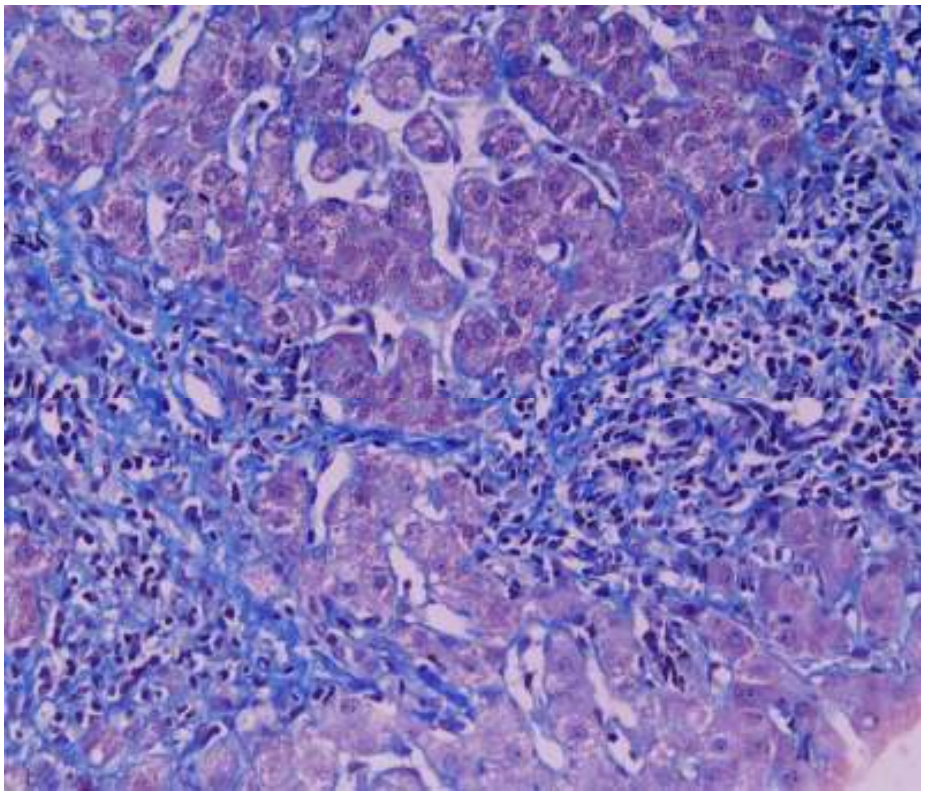
Hepatology 2009; 50: 1056

HIV and HCV

2000



2003

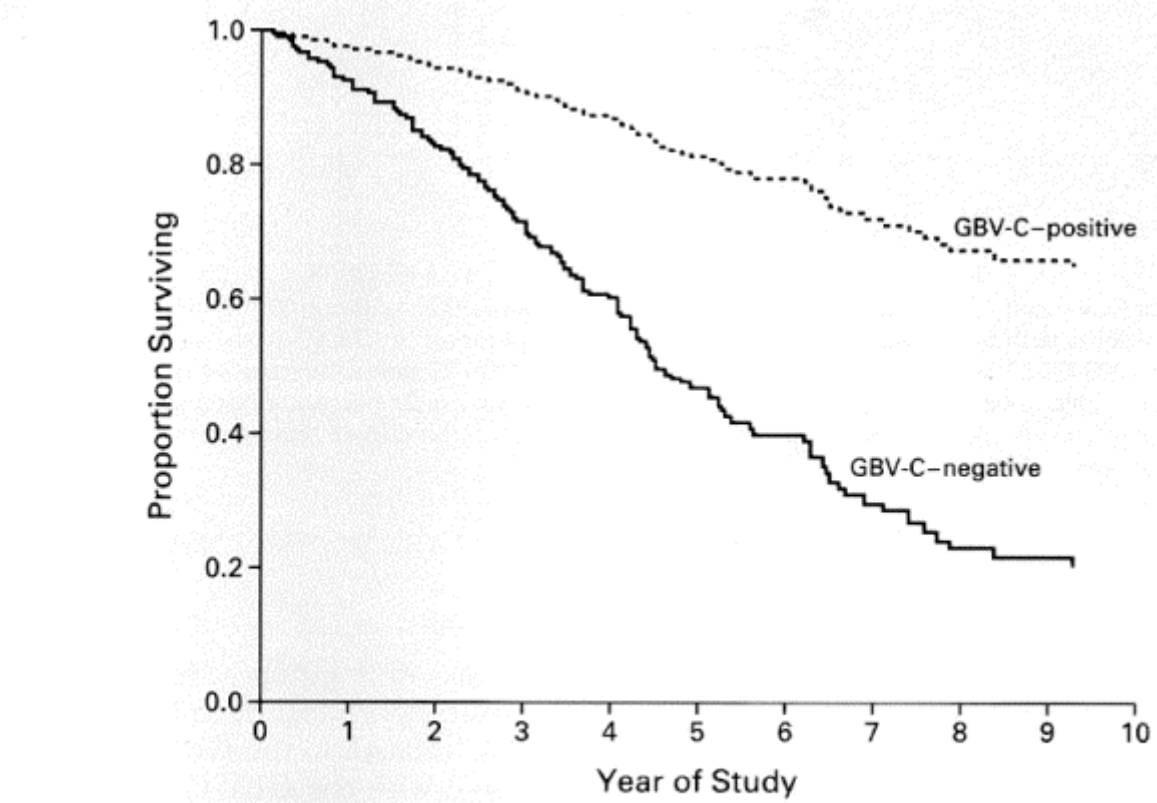


HIV and HCV and GBV-C

- 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

Gastroentrology 2007; 133: 1821

J Gastroenterol Hepatol 2009; 24: 1407



No. at Risk						
GBV-C–positive	144	135	111	68	43	20
GBV-C–negative	218	156	91	42	20	12

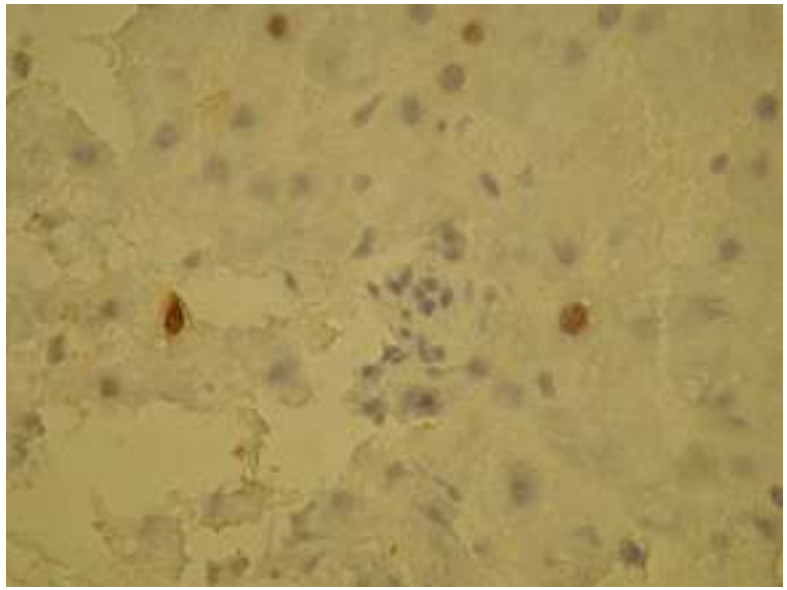
HIV and HBV and HDV

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

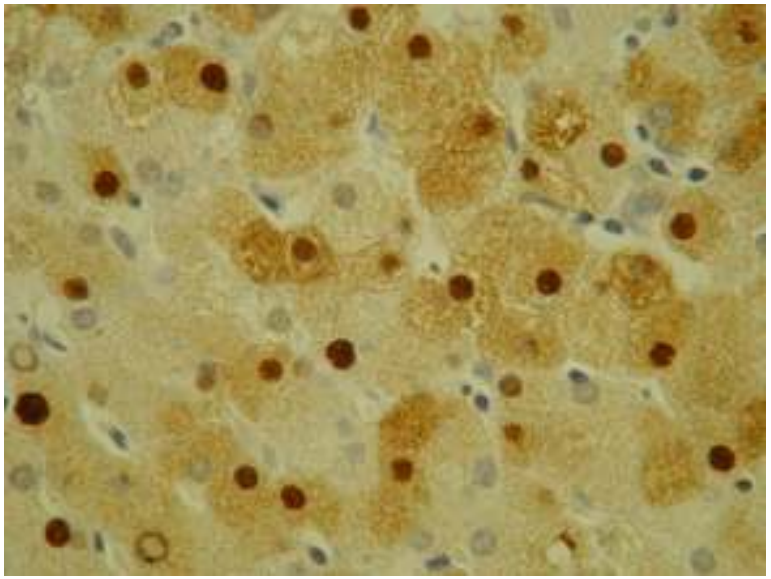
Scand J Infect Dis. 2008; 40: 928

HIV and HBV and HDV

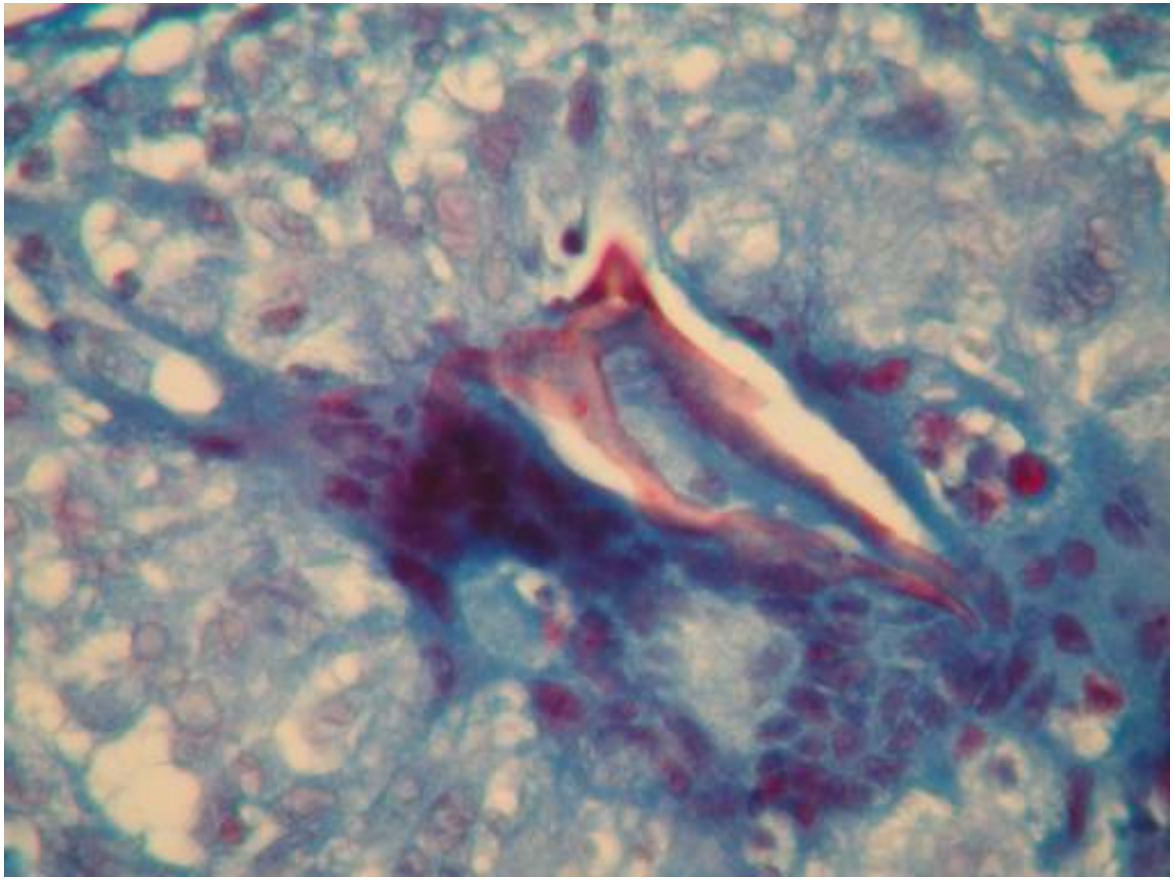
HDV



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”

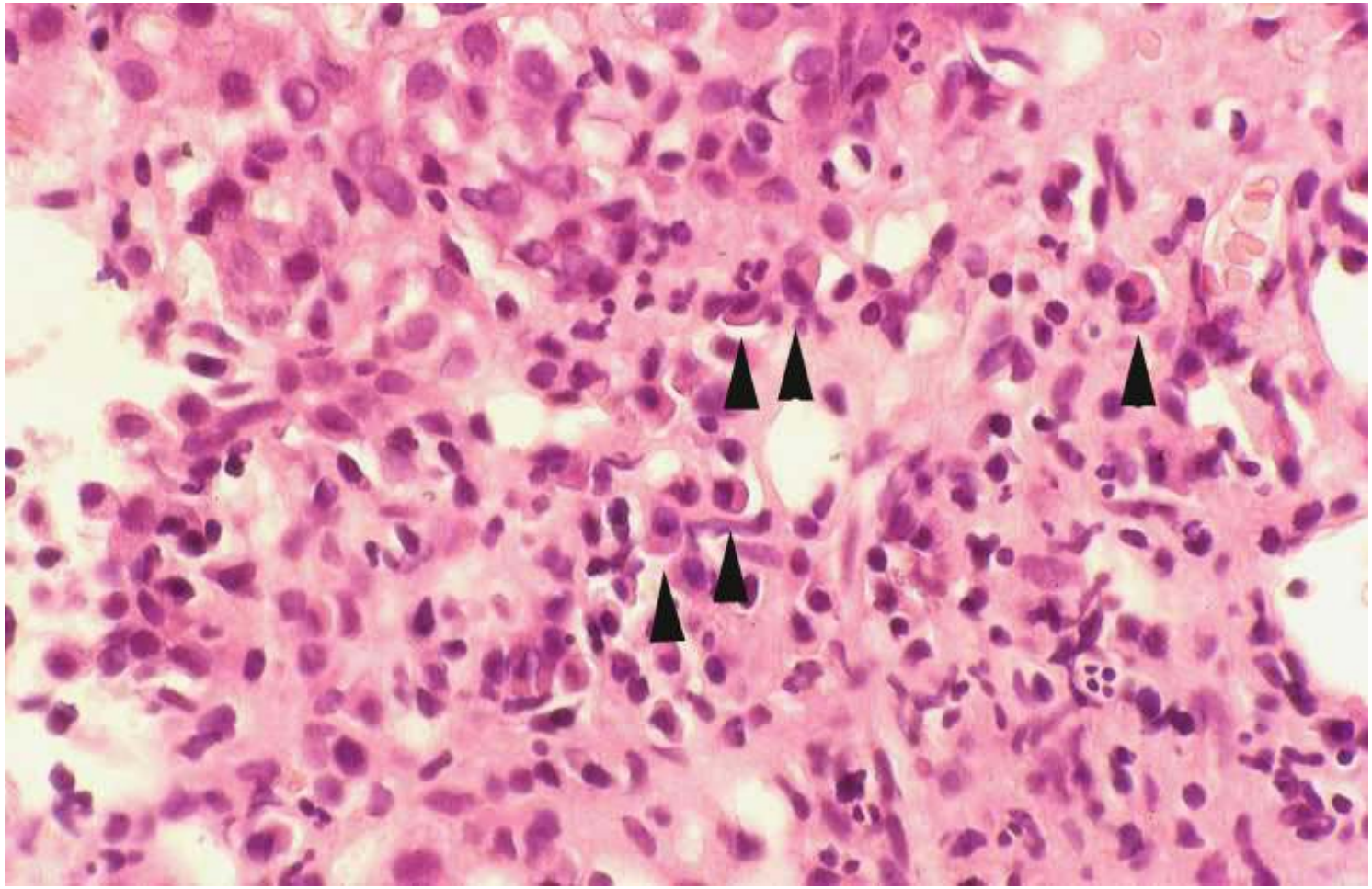
J Clin Gastroenterol 2008; 42: 425

- 4 cases (2 of whom also had HCV)
- Serology and histology were consistent with AIH
- Despite appropriate therpay, all developed life-threatening infectious or adverse metabolic effects that resulted in treatment discontinuation.

AIDS Patient Care STDS 2009; 23: 407

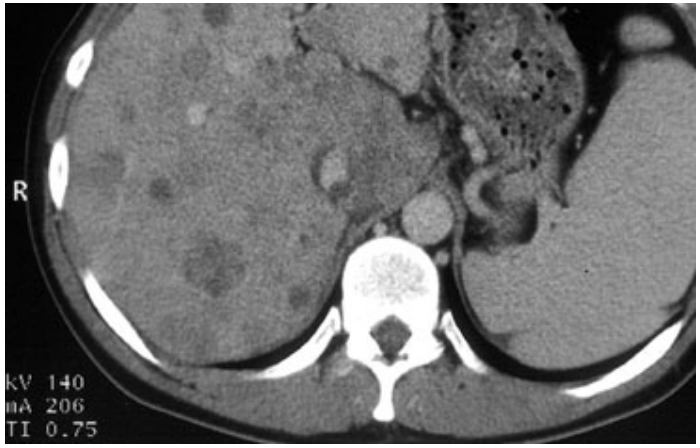
- AIH has rarely been reported in patients with HIV
- Should be screened for especially prior to starting interferon treatment for HCV

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)

HIV AND FATTY LIVER DISEASE

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.

J Antimicrob Chemother. 2008;62:648

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

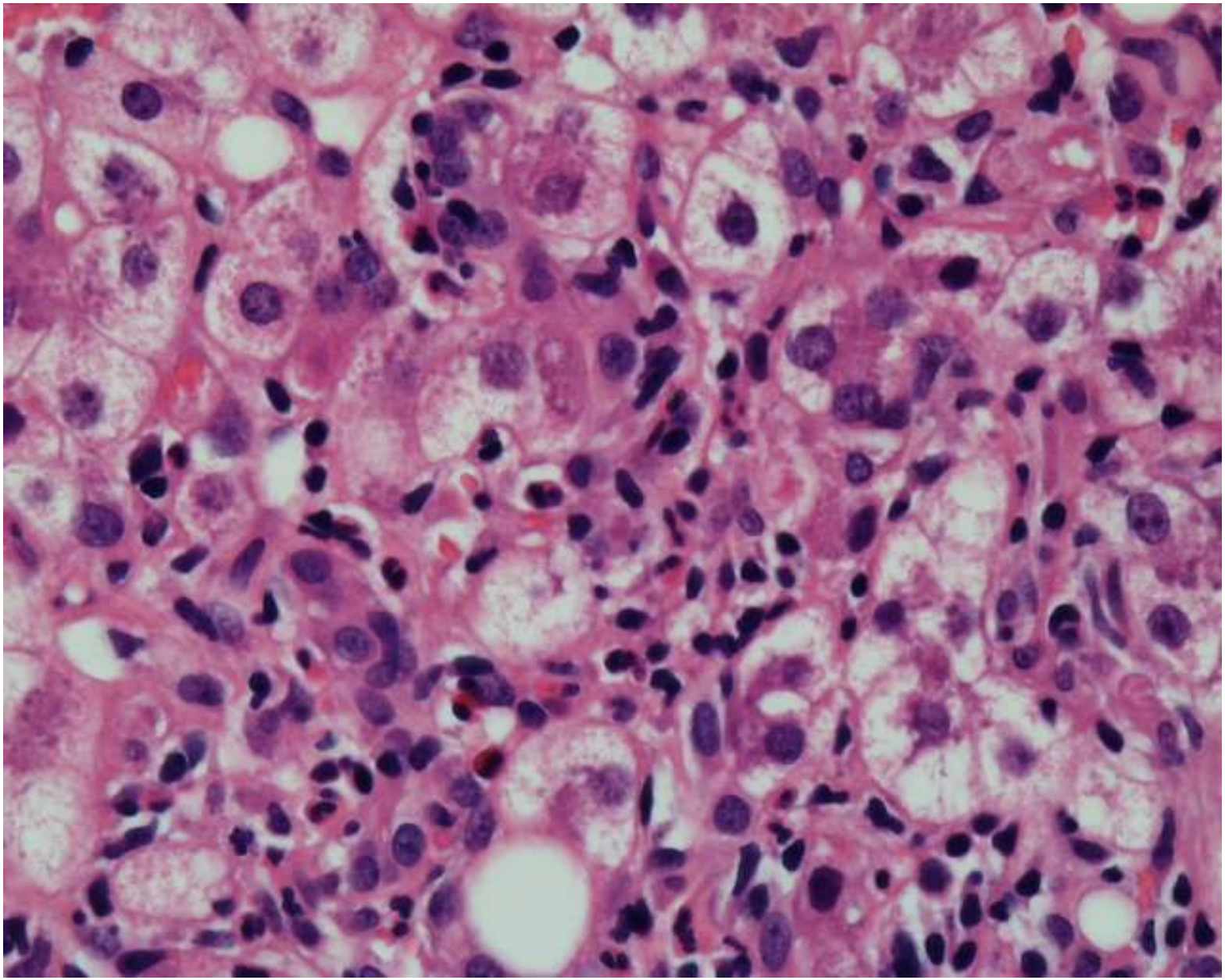
Fatty liver hepatitis in patients with HIV and HCV

- **Apricot study** : Association with fatty change, genotype3, 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. Ketaconazole
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

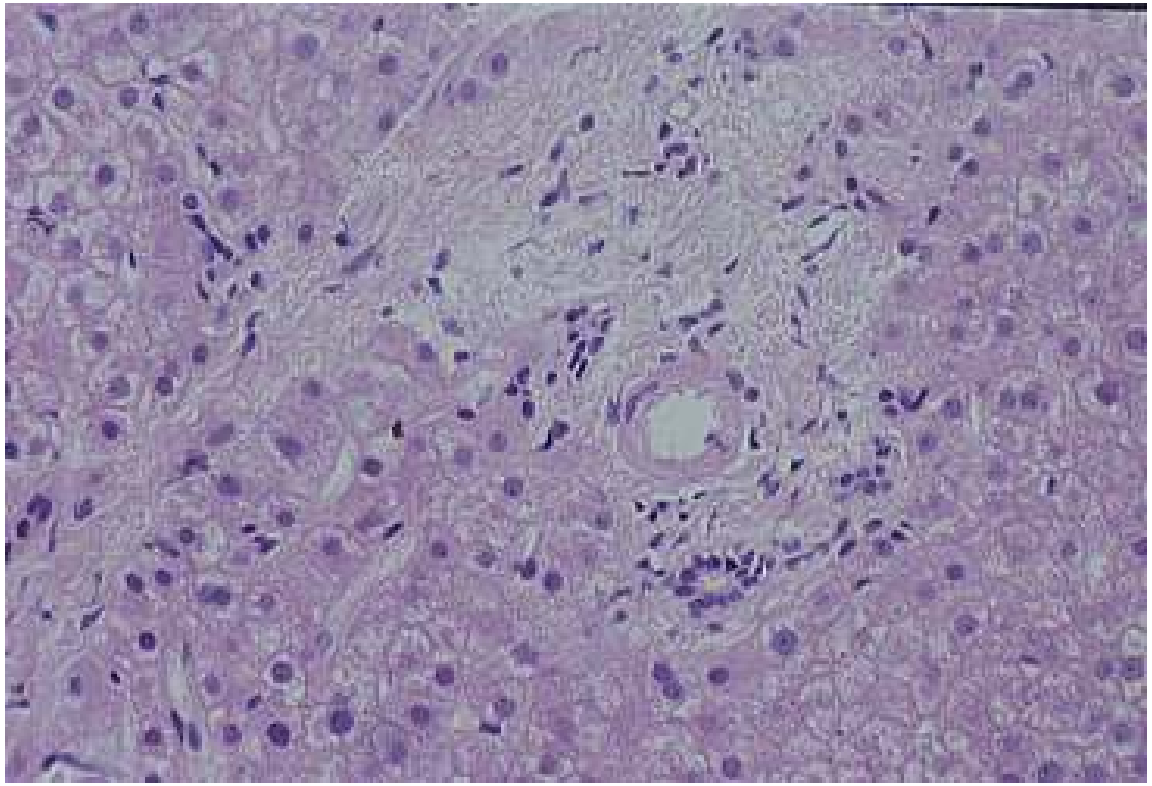
- Median hepatic venous pressure gradient was 8 mm Hg. This is probably because of a presinusoidal component of PH and because of the presence of intrahepatic venous collaterals.
- Median liver stiffness was 8.9 kPa and was unreliable in predicting the presence of fibrosis or of oesophageal varices

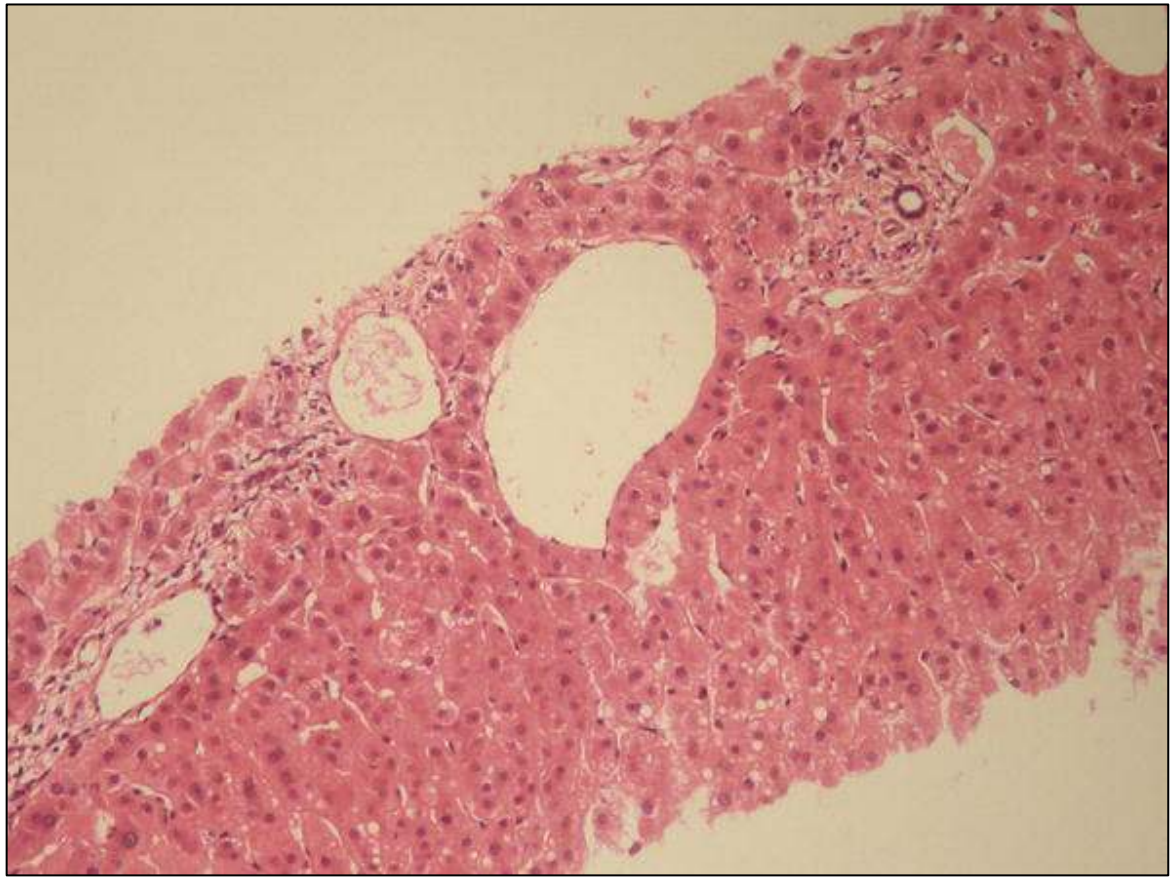
HIV and Portal hypertension

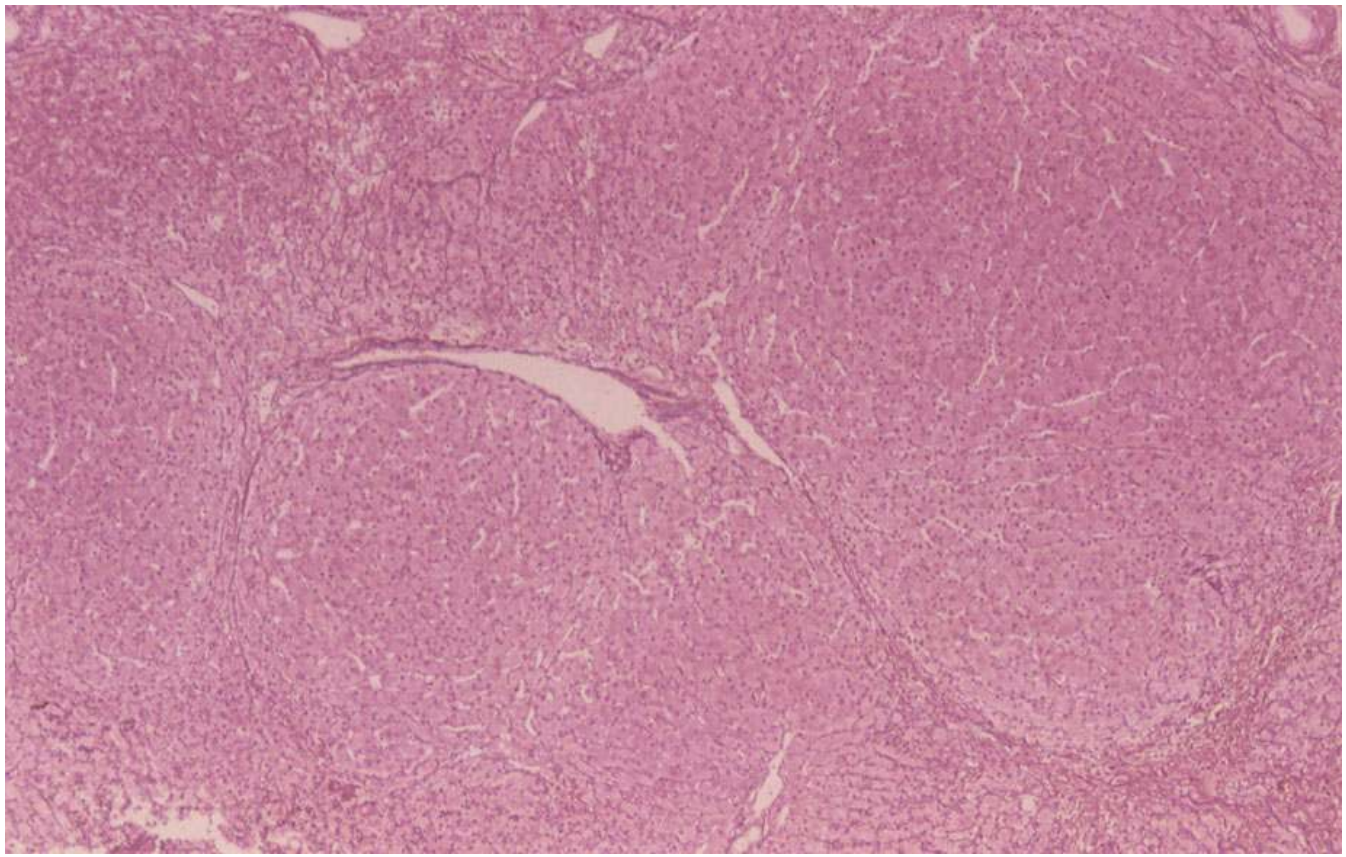
- The main histological features were absence of portal vein radicles and areas of regenerating hepatocytes.
- Six patients (75%) developed portal vein thrombosis during a 2-year follow-up
- **Pathogenesis:**

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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