

Fourth Annual BHIVA Conference for the  
Management of HIV/ Hepatitis Co-infection



# Dr Sanjay Bhagani

Royal Free Hospital, London

Wednesday 16 November 2011, One Great George Street Conference Centre, London

Fourth Annual BHIVA Conference for the  
Management of HIV/ Hepatitis Co-infection



# Dr Sanjay Bhagani

Royal Free Hospital, London

COMPETING INTEREST OF FINANCIAL VALUE $\geq$ £1,000:	
Speaker Name	Statement
Sanjay Bhagani	Dr Bhagani has received a restricted equipment grant from Roche.
Date	3 November 2011

Wednesday 16 November 2011, One Great George Street Conference Centre, London

## **DDI associated liver disease - diagnosis and management of non-cirrhotic portal hypertension**

**Sanjay Bhagani**  
**Royal Free Hospital/UCL**

Royal Free Hampstead   
NHS Trust



### **Mr MH 38 yrs**

- 38 year old MSM
- HIV+ 1994
- Nadir CD4 120, PCP
- 1994 - 2002: AZT+3TC, d4T+ddI+NVP
- 2002: Facial lipoatrophy - Newfill
- Since 2003: Abacavir+ddI+Nelfinavir
- CD4 420, viral load < 50c/ml
- HBsAg -, Anti-HBs +, anti-HBc +, anti-HCV -
- Very little alcohol
- Occasional cannabis, no other recreational drugs

- 2003 - 2005: ALT 35-55 IU/L, ALP 240 - 280 IU/L (n<240)
- June 2005: Presented with melaena, OGD - oesophageal varices, U/S scan - cirrhotic liver and splenomegaly
- Nov 2005: transfers to the RFH
- Liver database tests: negative, including HCV RNA, HBV DNA
- Platelets 105, PT 14.5 (INR=1.3), albumin 40, ALT 43, AST 41, ALP normal, bil normal
- Repeat US Scan - nodular liver, splenomegaly, ascites
- Diagnosis: cryptogenic cirrhosis
- Triple phase CT liver

## CT-imaging



Venous phase

## Management

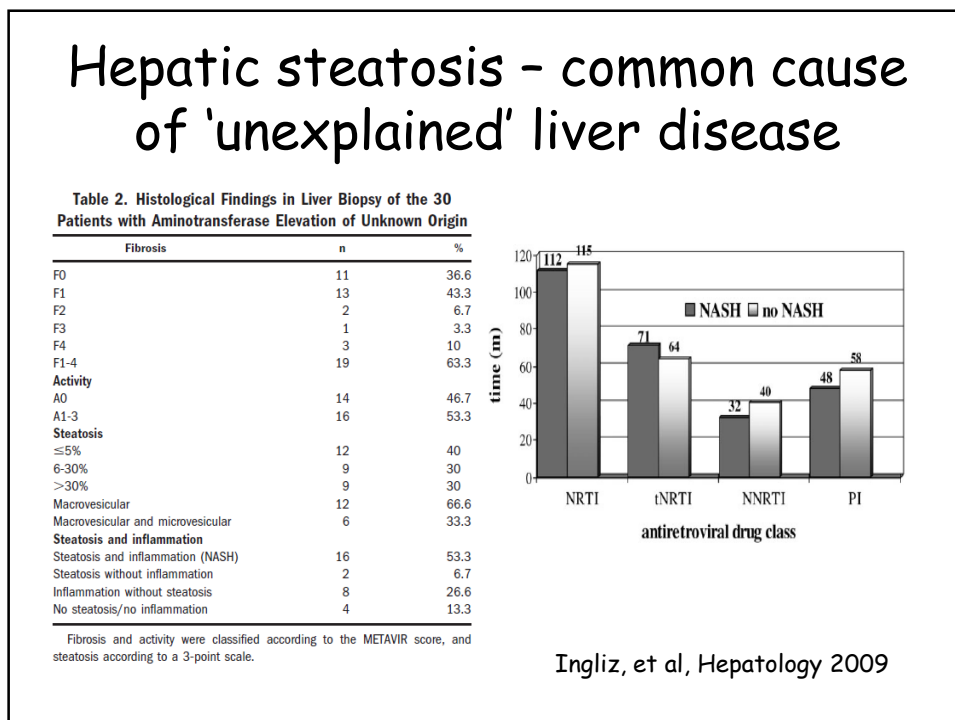
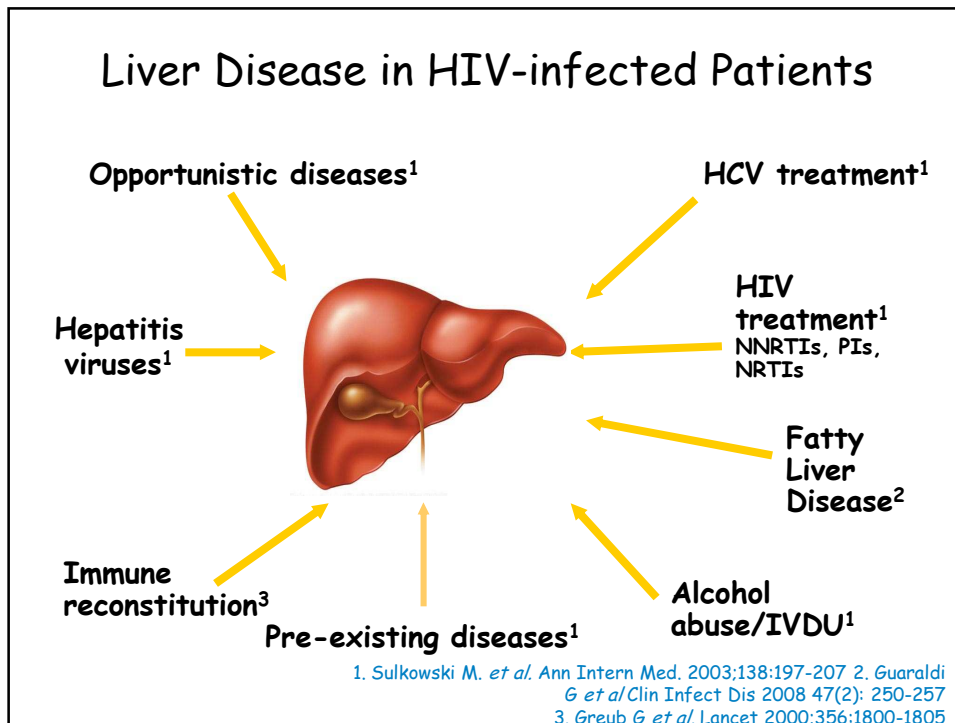
- Transjugular Intrahepatic Portosystemic Stented Shunt (TIPSS)
- Full anti-coagulation (warfarin)
- Switched to TDF+ABV+Lopinavir/r
- Progressive cachexia - listed for OLT

Successful OLT performed April 2006

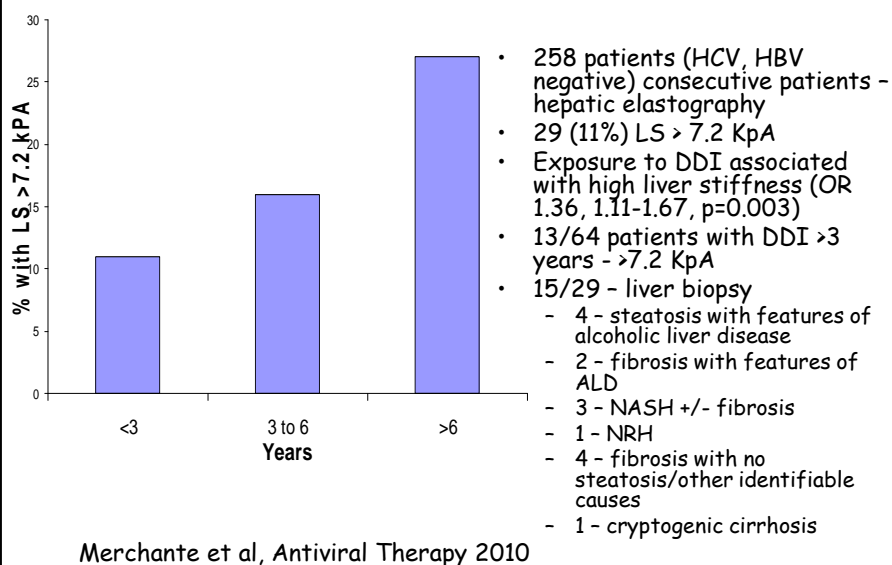
## Explant...



**Final diagnosis: Idiopathic Non-Cirrhotic Portal Hypertension  
With Partial Nodular Transformation**



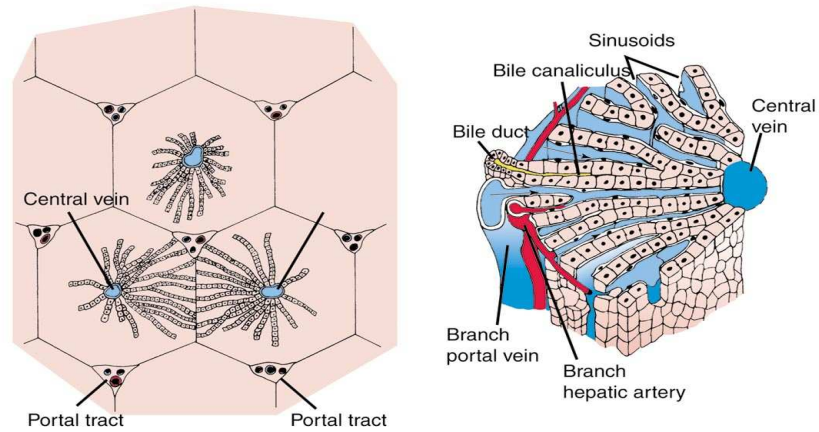
## DDI and liver stiffness



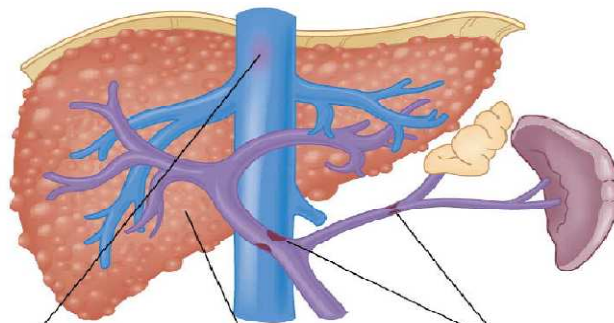
## World literature - non-cirrhotic PHT in HIV+

Author	Year	City	Cases (N)	Type	Comments (cohort entry)
Maida	2006	Seville/Madrid	17	Case-series	abnormal LEs
Mallett	2007	Paris	8	Case-series	abnormal LEs/PHT
Schiano	2007	New York	4	Case-series	Variceal bleed
Garvey	2007	London (St Mary's)	6	Case-series	PHT
Maida	2008	Seville/Madrid/Sassori	32	Case-series	Abnormal LEs Inclusive of previous?
Chang	2009	Barcelona	5	Case-series	IPH D'base
Dinh	2009	Chicago	9	Case-series	Transplant evaluation
Kovari	2009	Switzerland	15	Case-control	
Panos	2009	London (C&W)	5	Case-series	Abnormal LEs, TE
Scourfield	2011	London (C&W)	15	Case-series	Liver biopsy d'base
<b>Total</b>			<b>94</b>		

## Liver - Basic Lobule or Acini



## Portal Hypertension



- |  |  |   |
|--|--|---|
| <p><b>Posthepatic</b><br/>         Budd-Chiari syndrome<br/>         Constrictive pericarditis<br/>         Inferior vena caval obstruction<br/>         Right-sided heart failure<br/>         Severe tricuspid regurgitation</p> | <p><b>Intrahepatic</b><br/>         Presinusoidal<br/>         Idiopathic portal hypertension<br/>         Primary biliary cirrhosis<br/>         Sarcoidosis<br/>         Schistosomiasis<br/>         Sinusoidal<br/>         Alcoholic cirrhosis<br/>         Alcoholic hepatitis<br/>         Cryptogenic cirrhosis<br/>         Postnecrotic cirrhosis<br/>         Postsinusoidal<br/>         Sinusoidal obstruction syndrome</p> | <p><b>Prehepatic</b><br/>         Portal vein thrombosis<br/>         Splenic vein thrombosis</p> |
|--|--|---|

## Non-cirrhotic PHT

### Pre-sinusoidal

Developmental abnormalities  
 Idiopathic  
 Biliary diseases  
 Portal venous occlusion  
 Granulomatous lesions

### Post-sinusoidal

Veno-occlusive disease  
 Phlebo-sclerosis  
 Vascular malignancies  
 Granulomas

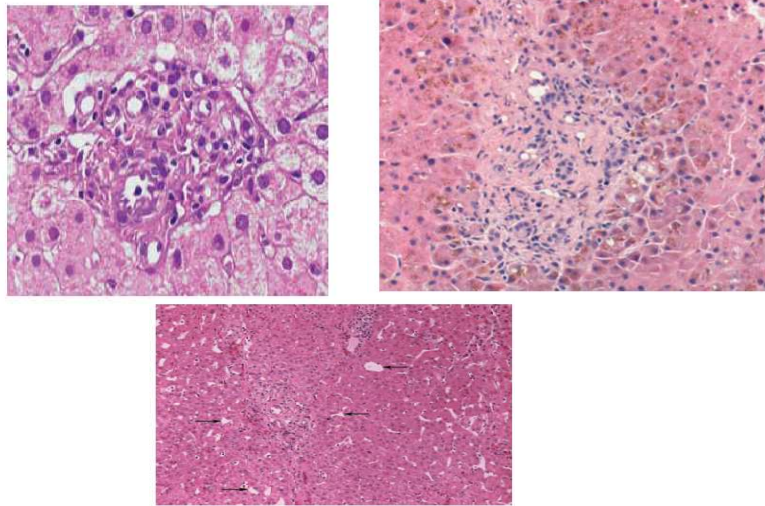
### Sinusoidal

Drugs (inc. MTX)  
 Metabolic (inc NASH)  
 Viral  
 Amyloidosis

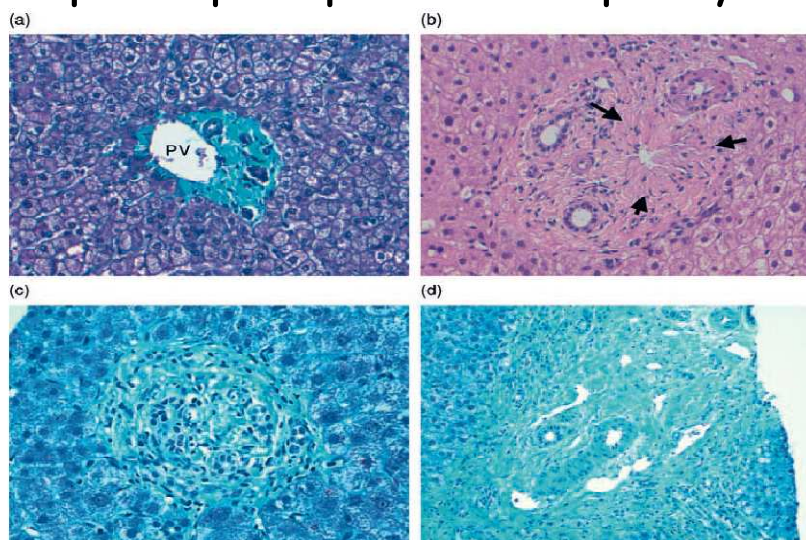
## Histological features of idiopathic non-cirrhotic PHT (INCPH)

- Idiopathic Portal Hypertension
  - Fibrous portal tracts and thin fibrous septa in the absence of cirrhosis
- Partial Nodular Transformation
  - Grossly visible parenchymal nodules visible in the peri-hilar region and around larger portal tracts
- Nodular Regeneration Hyperplasia
  - Micronodular transformation of the parenchyma with central hyperplasia and an atrophic rim in the absence of fibrosis
- Incomplete septal cirrhosis
  - Incomplete septal fibrosis that demarcates the parenchyma into nodules with small hypoplastic portal tracts and hyperplastic hepatocytes

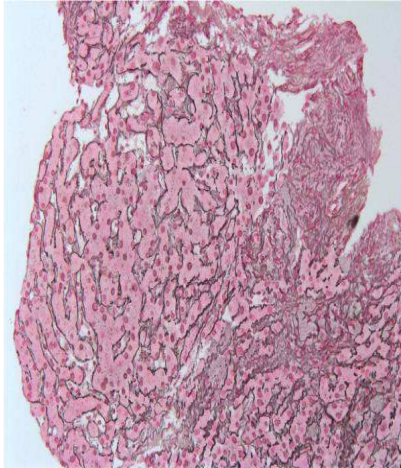
These are all a continuum of what is perhaps a portal venopathy...



These are all a continuum of what is perhaps a portal venopathy...



## Nodular transformation



## Common features in DDI-associated NCPH

	N	M (%)	LEE	DDI use (median/months)	Current DDI	Liver Biopsy	Transient Elastography
Spain Italy	32	84	All	44	27/30	2 NRH 3 Portal Fibrosis 2 Microvesicular Steatosis 1 Cholangiopathy	Median 13.8 KpA
Paris	8	50	All 5/8 cholestasis	NA All exposed	NA	7 NRH 2 Macrosteatosis 1 Perisinusoidal fibrosis	NA
Barcelona	8	50	?	48	1/8	8 Foci NRH 8 perisinusoidal fibrosis Portal Vein absence	Median 8.9 KpA (6.8 – 14.9)
C&W	15	62.5	?All	59.5	9/15	9 Portal and perisinusoidal fibrosis/dilatation 4 Fibrous tracts with septae 1 NRH 2 Steatosis	6/11 >9.6 KpA

## Complications and outcomes

	N	F/U (months)	Variceal Bleed N (%)	PVT N (%)	Ascites N (%)	Death N (%)
Swiss HIV Cohort	15	144	2 (13)			4 (26)
Barcelona	8	15		6 (75)		
C&W	16	N/A	11 (69)	4 (25)	1 (7)	2 (13)
Chicago	9	N/A	4 (44)	1 (12)	6 (75)	
St Mary's	6	24	3 (50)			1 (15)
Spain/Italy	32	12	5 (16)	8 (25)	8 (25)	
Paris	8	24	4 (50)	2 (25)	2 (25)	

## Liver and systemic haemodynamics

**Table 3. Hepatic hemodynamics, systemic hemodynamics, and liver elastography values**

Patient no:	1	2	3	4	5	6	7	8	Median or n (%)
WHVP (mm Hg)	13.0	8.0	13.0	19.5	11	11	14	18.5	13.0
FHVP (mm Hg)	5.0	4.5	6.5	5.0	3	7	6.5	5	5.0
HVPG (mm Hg)	8.0	3.5	6.5	14.5	8	4	7.5	13.5	8.0
Venovenous collaterals	N	Y	Y	N	Y	Y	Y	N	5 (63)
PAP (7–19 mm Hg)	ND	12	19.0	8	11.5	13	ND	6	11.7
PCWP (8–12 mm Hg)	ND	6.5	12.0	4	6	8.5	ND	3	6.2
MAP (80–95 mm Hg)	ND	95	83	95	86	91	ND	74	88.5
CO (4.4–8.3 l/min)	ND	5.3	7.0	6.3	6.4	10.8	ND	5.9	6.3
CI (2.5–4.0 l/min/m <sup>2</sup> )	ND	3.2	4.2	3.8	4.0	6.1	ND	4.4	4.0
SVR (900–1,440 dynessec cm <sup>-5</sup> )	ND	1,358	903	1,181	1,050	637	ND	990	1,020
SVRI (1,600–2,880 dynessec cm <sup>-5</sup> /m <sup>2</sup> )	ND	2,269	1,305	1,938	1,680	1,128	ND	1,327	1,935
Liver stiffness (kPa)	12.6	6.8	10.3	8.8	8.0	8.8	14.9	9.0	8.9

CI, cardiac index; CO, cardiac output; FHVP, free hepatic vein pressure; HVPG, hepatic venous pressure gradient; MAP, mean arterial pressure; ND, not done; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index; WHVP, wedged hepatic vein pressure. Normal values are given in parenthesis (38).

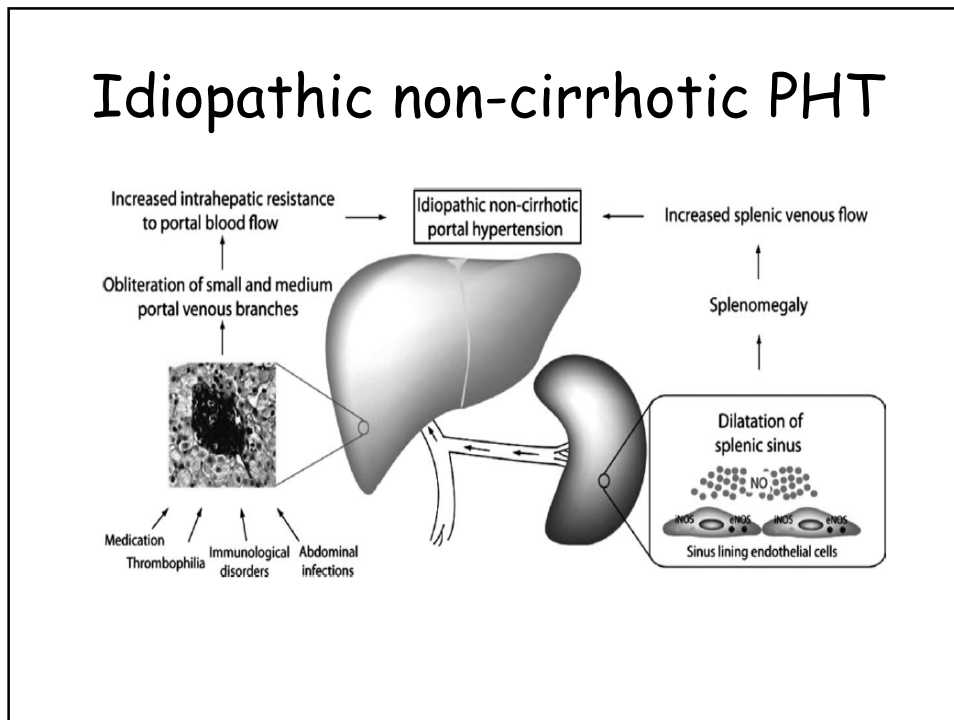
## Case-control studies; co-relates of NCPH in HIV+ patients

- **Swiss HIV Cohort** (Kowari, CID 2009; 49: 626-35)
  - Retrospective identification of NRH cases
  - 15 cases/75 controls (matched time of first visit/follow-up)
  - **Multivariate analysis**
    - DDI per yr exposure (OR 3.4, 1.5-8.1)
    - Others - Age, nadir CD4, MSM, DM
- **Lyon study** (Cotte, J Hepatol 2011; 54: 489-96)
  - Retrospective identification of NRH from liver biopsy d'base
  - 13 cases/78 controls (matched time of first visit/length of follow-up)
  - **Multivariate analysis**
    - DDI and d4T per yr exposure (OR 3.7, 1.4-10.2)
    - Others - Age, exposure to DDI, tenofovir

## Role of hereditary/acquired thrombophilia

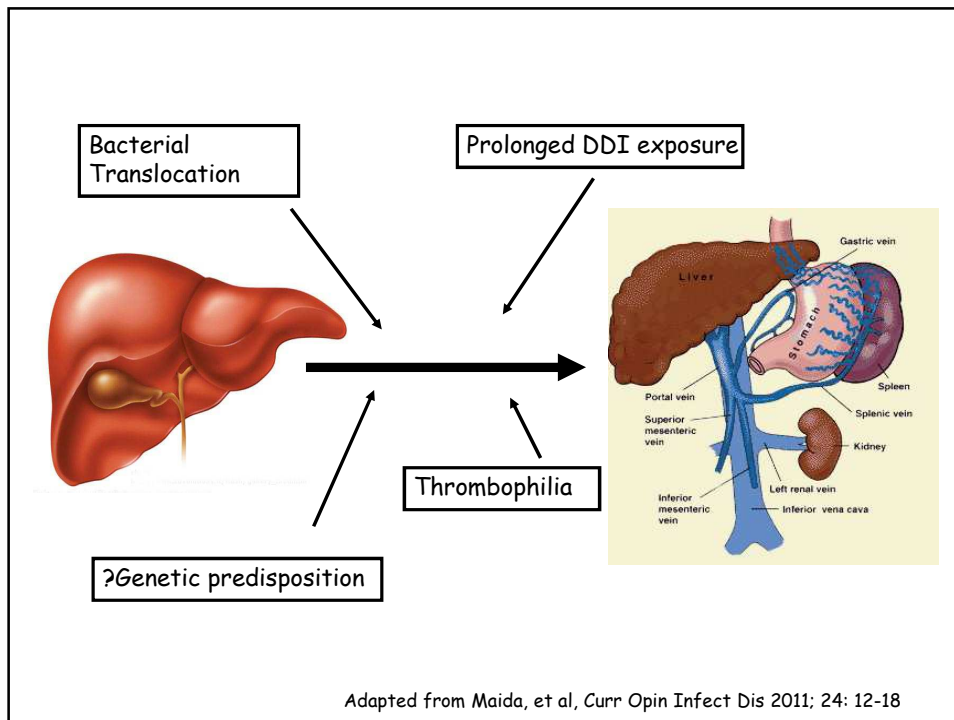
	N	Thrombophilia
St Mary's	6	4 ↓ Prot S or C or lupus aanticoagulat
C&W	16	1 ↓ Prot S level 2 ↓ ATIII level
Barcelona	8	0
Madrid	17	0
Paris	21	21 ↑ Anti-Prot S IgG
Lyon	13	4 ↓ Prot S level 2 ↓ Prot C level
New York	4	0

## Idiopathic non-cirrhotic PHT



## Hypotheses: NCPH in DDI exposed HIV+ patients

- Genetic predisposition
  - TPMT deficiency enhances Azathioprine myelosuppression
  - ITPA deficiency (SNP) protects against RBV anaemia
  - ? Genetic polymorphisms in the purine metabolism pathway and DDI
- Microbial translocation and portal vein endothelial inflammation
  - HIV-associated gut lymphocyte depletion
  - ?MSM
- Acquired thrombophilia
  - ?HIV-associated or drug associated
- Drugs
  - NCPH associated with purine analogue use in non-HIV infected patients (azathioprine, 6-mercaptopurine)
  - DDI and Abacavir associated with increased cardiovascular risk
  - ?pro-inflammatory cytokines leading to endothelial damage



## Management of NCPH in HIV+

- Close liaison with hepatology team/regional referral centre
- Preventing Gastro-Oesophageal Variceal bleed
  - Endoscopic Variceal Ligation
  - Non-selective B-blockers
  - TIPSS
- Portal Vein Thrombosis
  - Must be actively excluded especially in the context of ascites

## Management (2)

- anticoagulation
  - Risk vs. benefit
  - Reasonable in the context of PVT or thrombophilia
- Minimising further deterioration in PHT and/or hepatic function
  - Stop DDI
  - ?avoid Abacavir (all nucleos(t)ides)
  - Careful attention to hepatitis steatosis
  - Alcohol
  - ?beneficial role of CCR5 antagonists
- ?Liver Transplantation
  - Hepato-pulmonary syndrome
  - Significant synthetic dysfunction

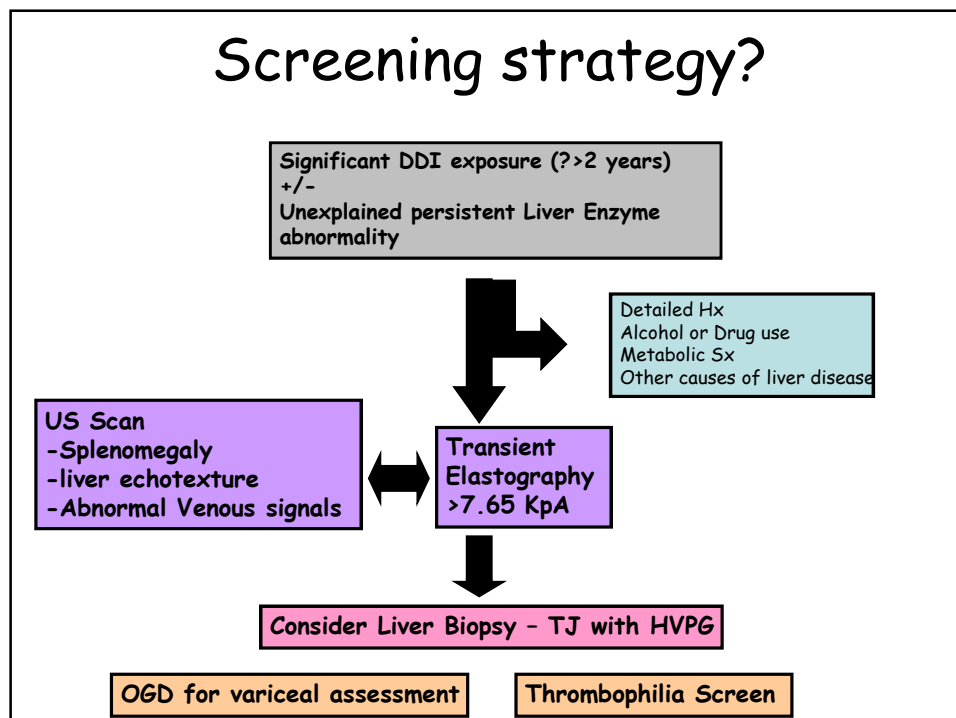
## Conclusions

- Steatosis/NASH much more common cause of liver disease in the context of DDI use
- NCPH, rare but associated with significant morbidity
- ?underlying genetic pre-disposition
- ?role of other nucleosides (d4t, abacavir, tenofovir)
- Diagnosis
  - Index of suspicion
  - Signs/Sx of portal hypertension in the absence of signs of chronic liver disease
  - ?role of Transient Elastography
  - Definitive diagnosis - demonstration of characteristic portal venopathy and histological features of peri-portal sclerosis (and associated changes) on a liver biopsy

## Conclusions (2)

- Management with hepatology team
  - Prevent OV bleed
  - Monitor for other complications
- Screening strategies
  - ?cost-effective
  - ?valid

## Screening strategy?



## Acknowledgements

- Prof Amar Dhillon
- Dr James O'Beirne
- Dr Alison Rodger
- Prof Geoff Dusheiko
- Dr Gabriella Slapak
- Mr Tom Fernandez
- Mr Fillipo Ferro
- Dr Sarah Logan