British HIV Association
BHIVA

Professor Sharon Lewin

Alfred Hospital and Monash University

Melbourne, Australia

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Sharon Lewin	Acts in a Consultancy capacity for ViiV Healthcare and Gilead Sciences and as a speaker at company-sponsored events for ViiV Healthcare, Gilead Sciences and Merck. She has also received funding for investigator initiated research grants from Gilead Sciences, Merck and Janssen. All payments were made to the Alfred Hospital and Monash University
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Pathogenesis of liver disease in HIV-HBV co-infection

Sharon R Lewin

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Autumn British HIV Association (BHIVA) meeting, London, October 2-4, 2012

Burnet Institute
Medical Research. Practical Action.

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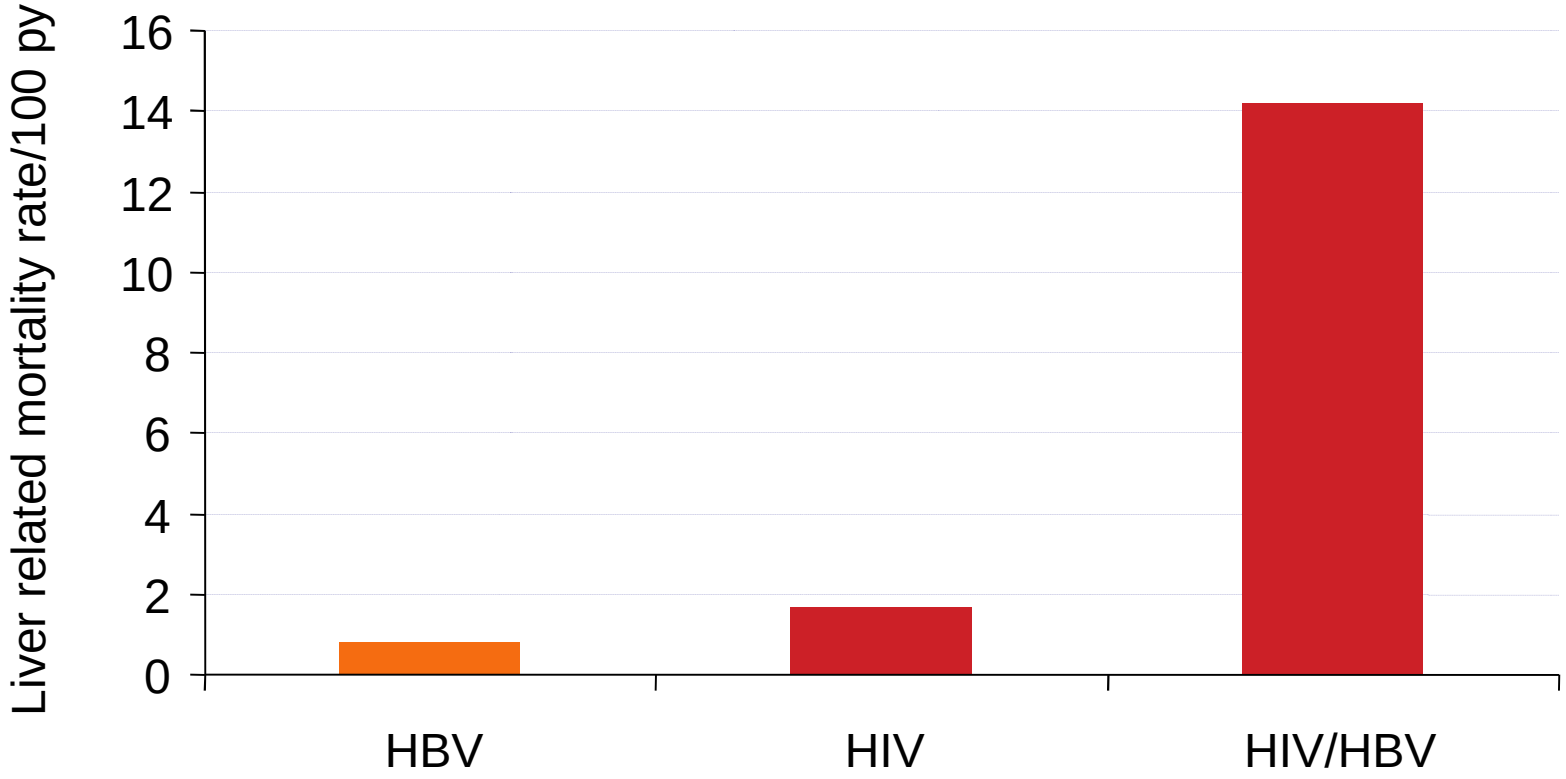
Liver related mortality in HIV/HBV co-infection



Thio et al *Lancet* 2002; 360:1921;

Outline

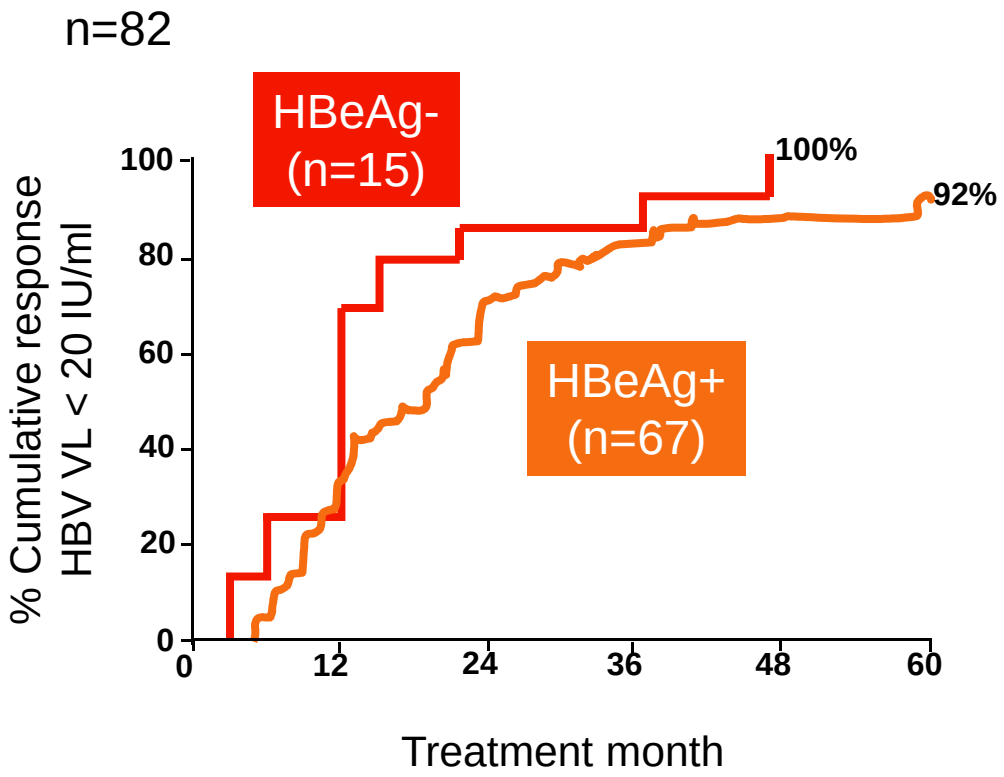
- Natural history of HIV-HBV co-infection
  in the era of HBV-active HAART
- Pathogenesis of liver disease on HAART
  - –Viral factors
  - –Immune activation
  - –Immune recovery
- Emerging research issues

natural history in the era of HBV-active HAART

Treatment options for HIV-HBV

Drug	HBV
3TC / FTC	++
Tenofovir	+++
Adefovir	++
Entecavir	+++
Telbivudine	+++
IFN / PEG-IFN	+++

Excellent HBV virological control on tenofovir



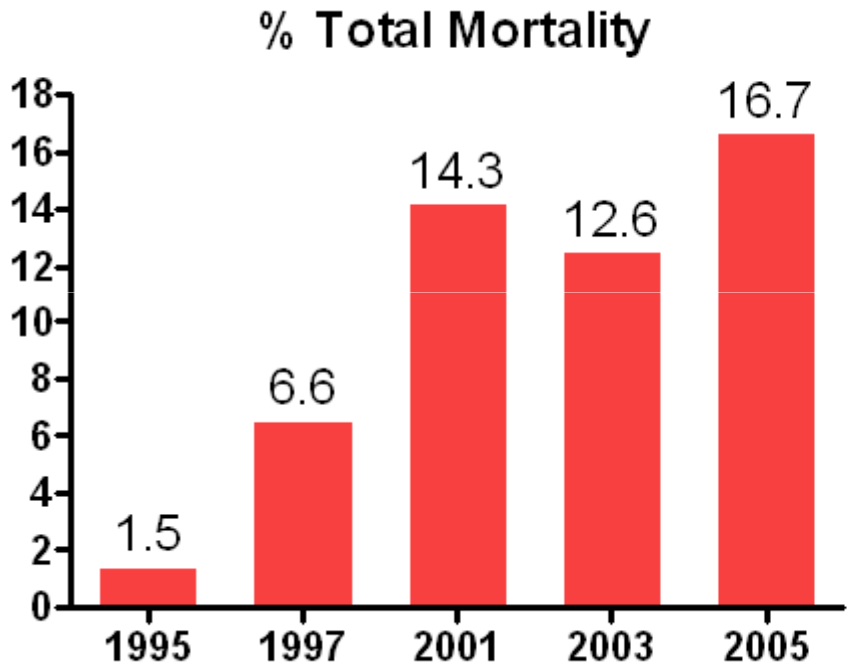
Over 5 years, HBeAg loss 46% and HBsAg loss 12%

de Vries-Sluijs et al Gastroenterology 2010;139(6):1934-41

Zhoutendyk et al., J Infect Dis 2012; 206:974; Matthews et al., Plos One 2012 (re-submitted)

Contribution of HBV to liver disease associated mortality is decreasing

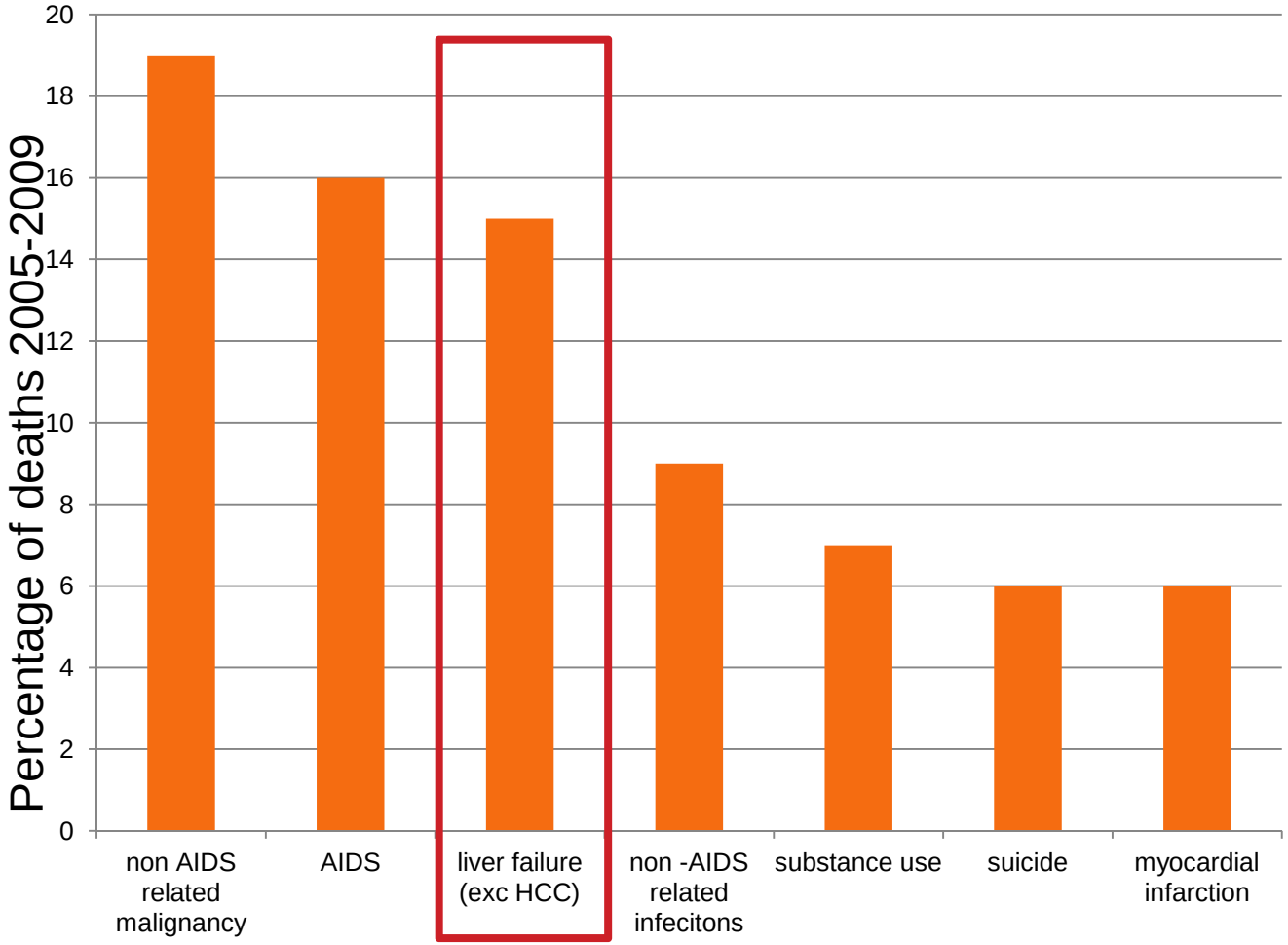
Liver disease associated mortality



Periodic cross sectional survey of 34 French hospitals; total n=24,000
Estimated national coverage of 70% (CI 62-78%)
Deaths from HCC increased from 5% (1995) to 25% (2005)

Rosenthal E et al *J Viral Hepat* 2007; Rosenthal et al., *HIV Med* 2009

Total morality increased in HIV-HBV co-infection in Swiss cohort



Risk of death multivariate model (95% CI)

Active HBV
1.6 (1.12-2.27)

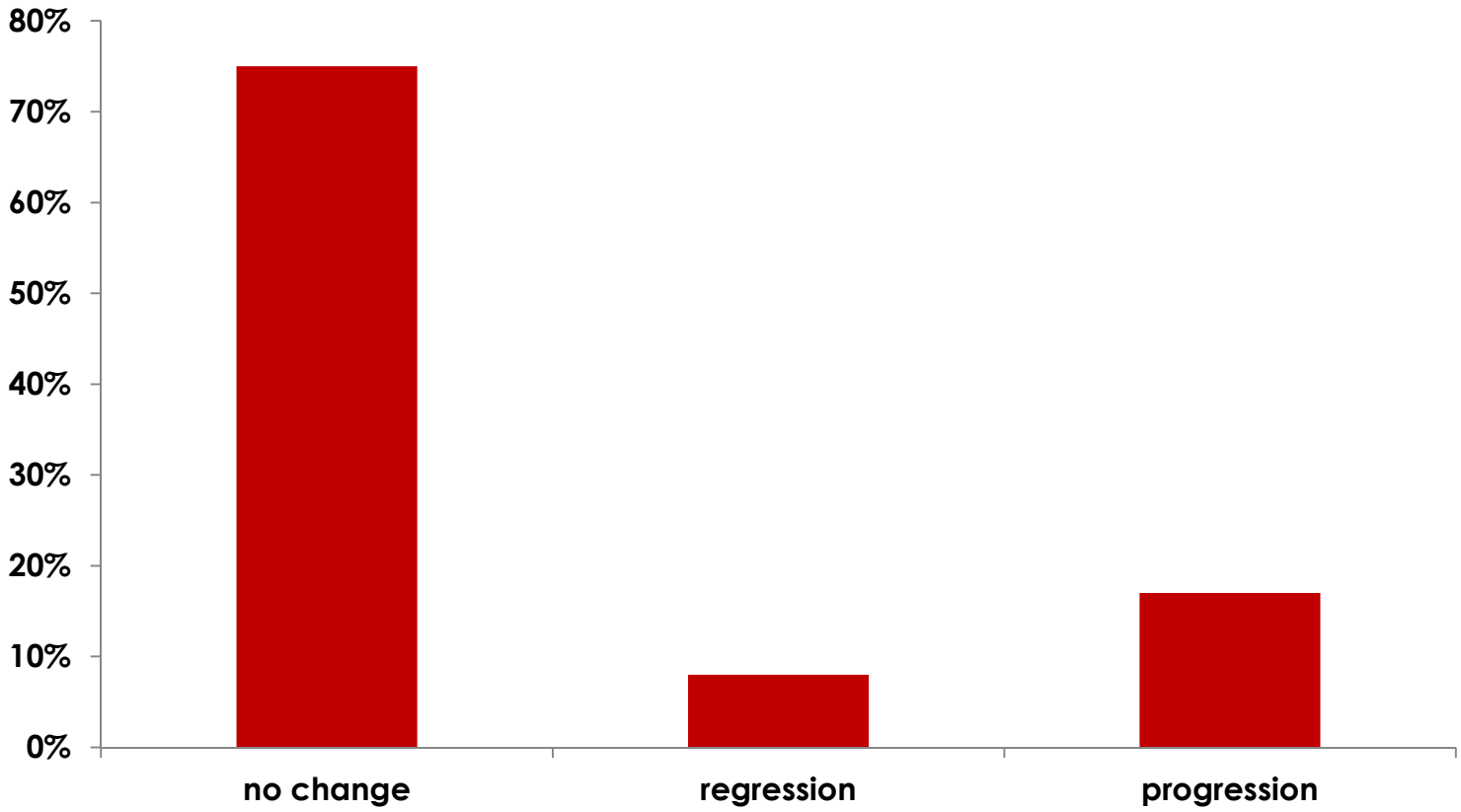
Active HCV
1.49 (1.07-2.07)

Male injecting drug suer
2.05 (1.39-3.03)

Swiss Cohort 2005-2009; n=9053; deaths = 549; HBsAg+ = 11%; HCV+ = 44%

Weber et al., HIV Med 2012 (in press)

Liver disease progression in HIV-HBV co-infection: fibroscan



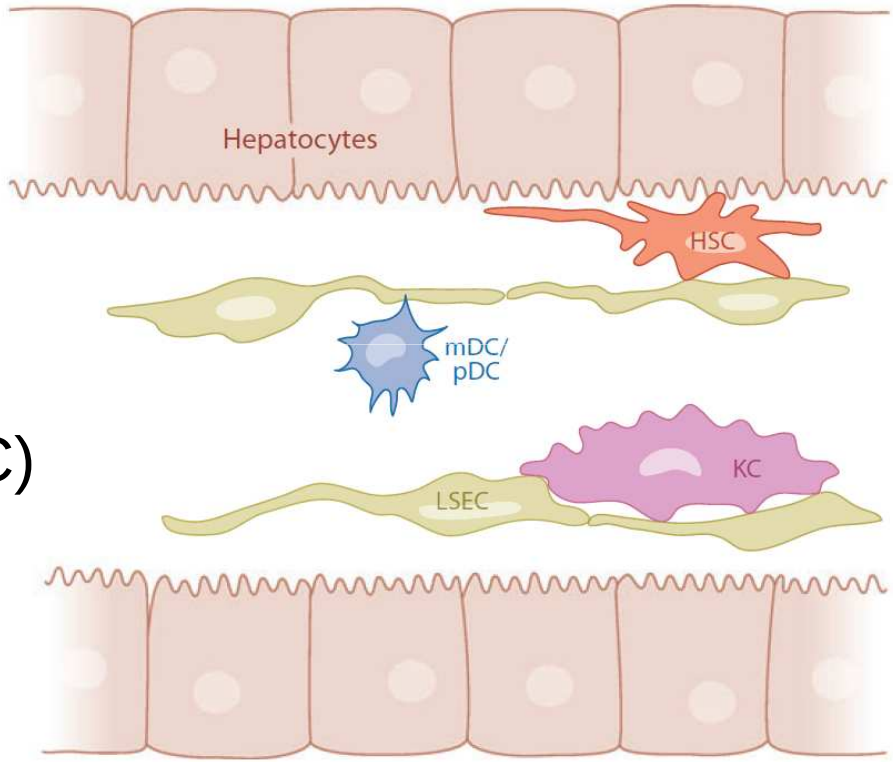
n = 92; retrospective study; HBeAg+ = 46%; genotype A and D; delta virus = 20%; HCV RNA+ =15%; received tenofovir = 82%; null or mild fibrosis = 48%

Martin-Carbonero et al *AIDS* 2011

viral factors: HIV and the liver

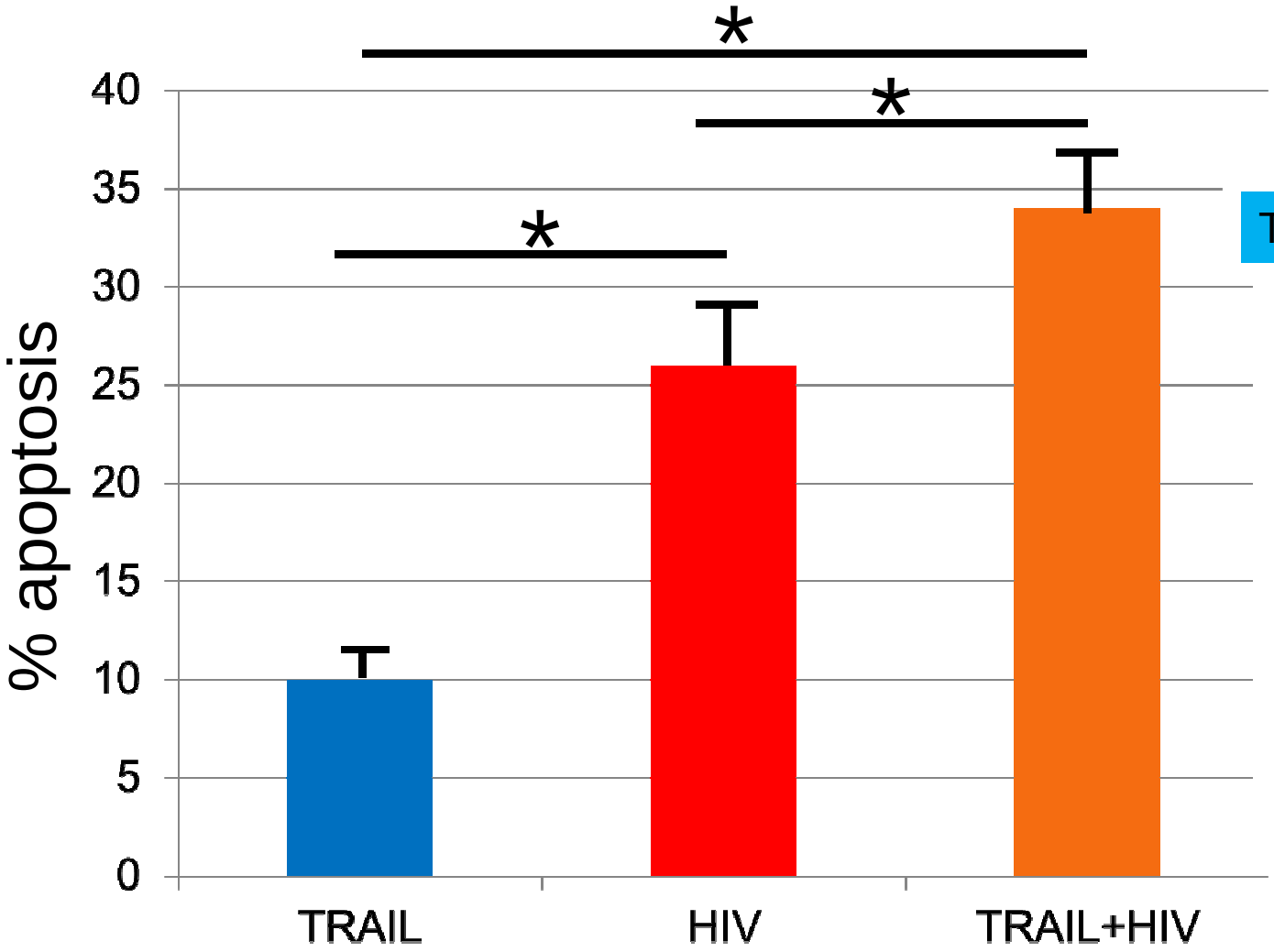
HIV infects multiple cells in the liver

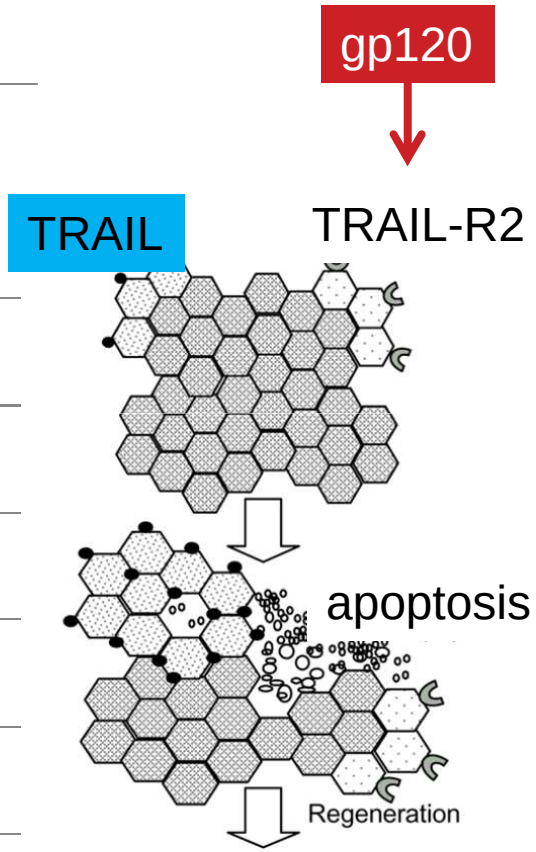
- In vitro (cell lines and primary cells)
  - Hepatocytes (HC)
  - Kupffer cells (KC)
  - Stellate cells (HSC)
  - Endothelial cells (LSEC)
- In vivo
  - Hepatocytes
  - Kupffer cells



Housset C., *Res Virol* 1990; 141: 153; Cao Y., *AIDS* 1992; 6: 65; Housset C., *J Hepatol* 1993; 19: 252; Schmitt M., *Res Virol* 1990; 141: 143; Steffan A., *Proc Natl Acad Sci* 1992; 89: 1582; Cao Y., *J Virol* 1990; 64: 2553; Banerjee R., *AIDS* 1992; 6: 1127; Vlahakis S., *J Infect Dis* 2003; 188: 1455; Iser et al., J Virol 2010 84:5860-7; Kong L., Virol J. 2012 Aug 9;9(1):157

HIV infection of hepatocytes increases apoptosis



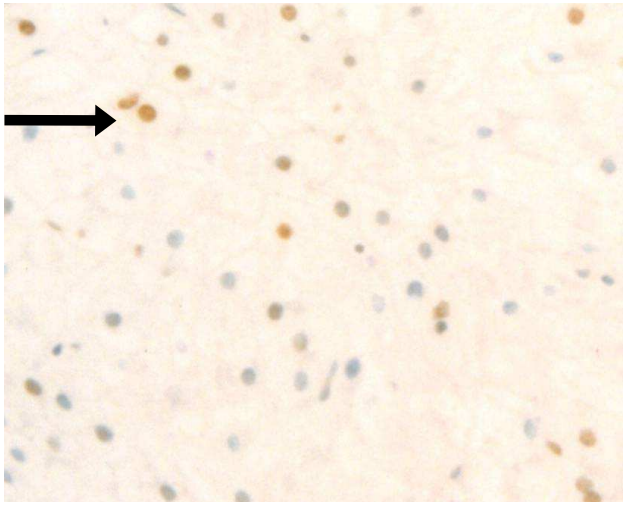


Huh7 cell line

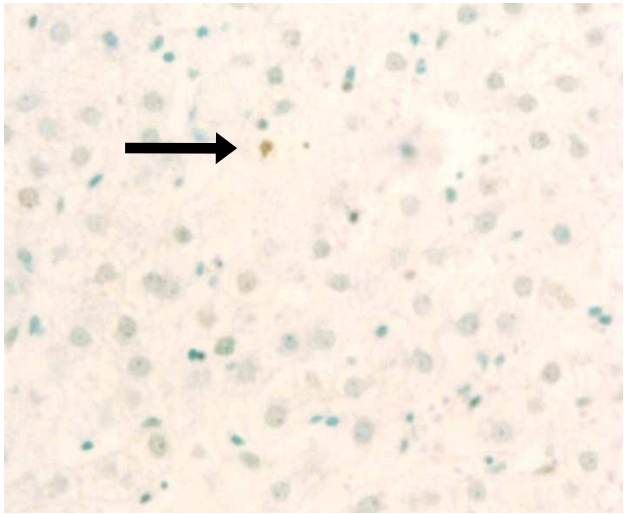
Babu et al., Plos ONE 2009

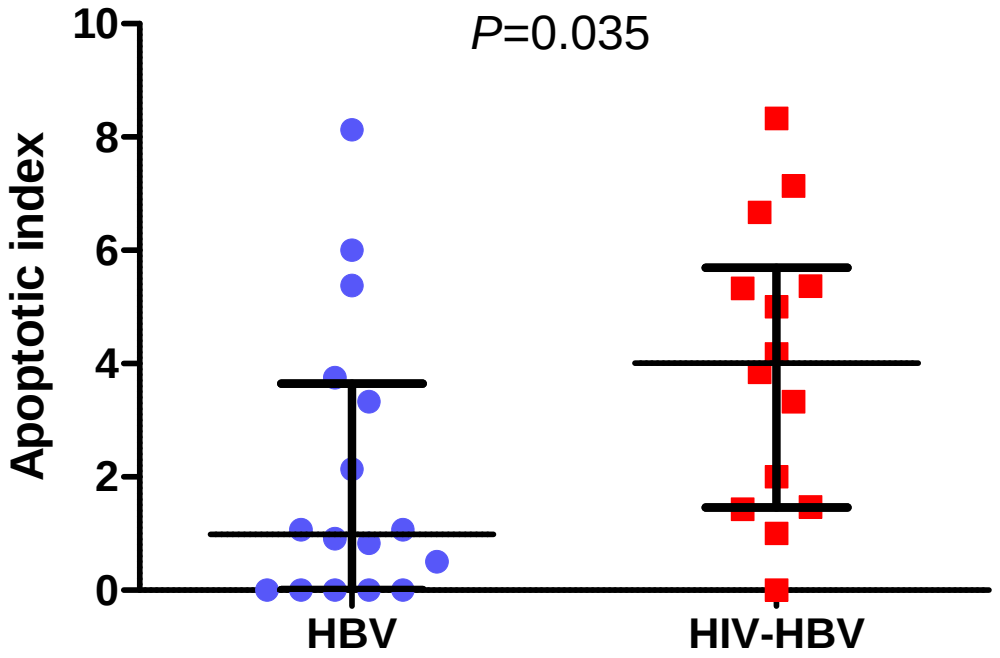
Increased hepatic apoptosis in HIV-HBV co-infection

HIV/HBV



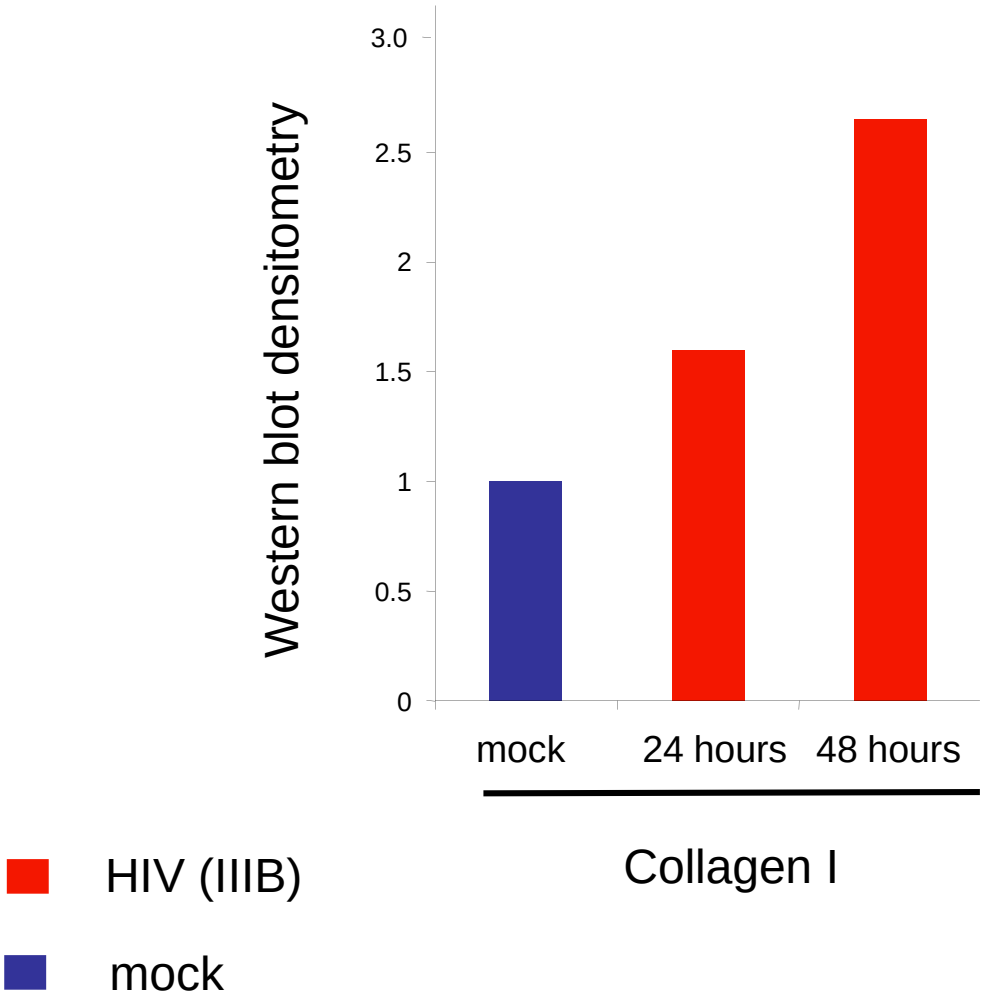
HBV





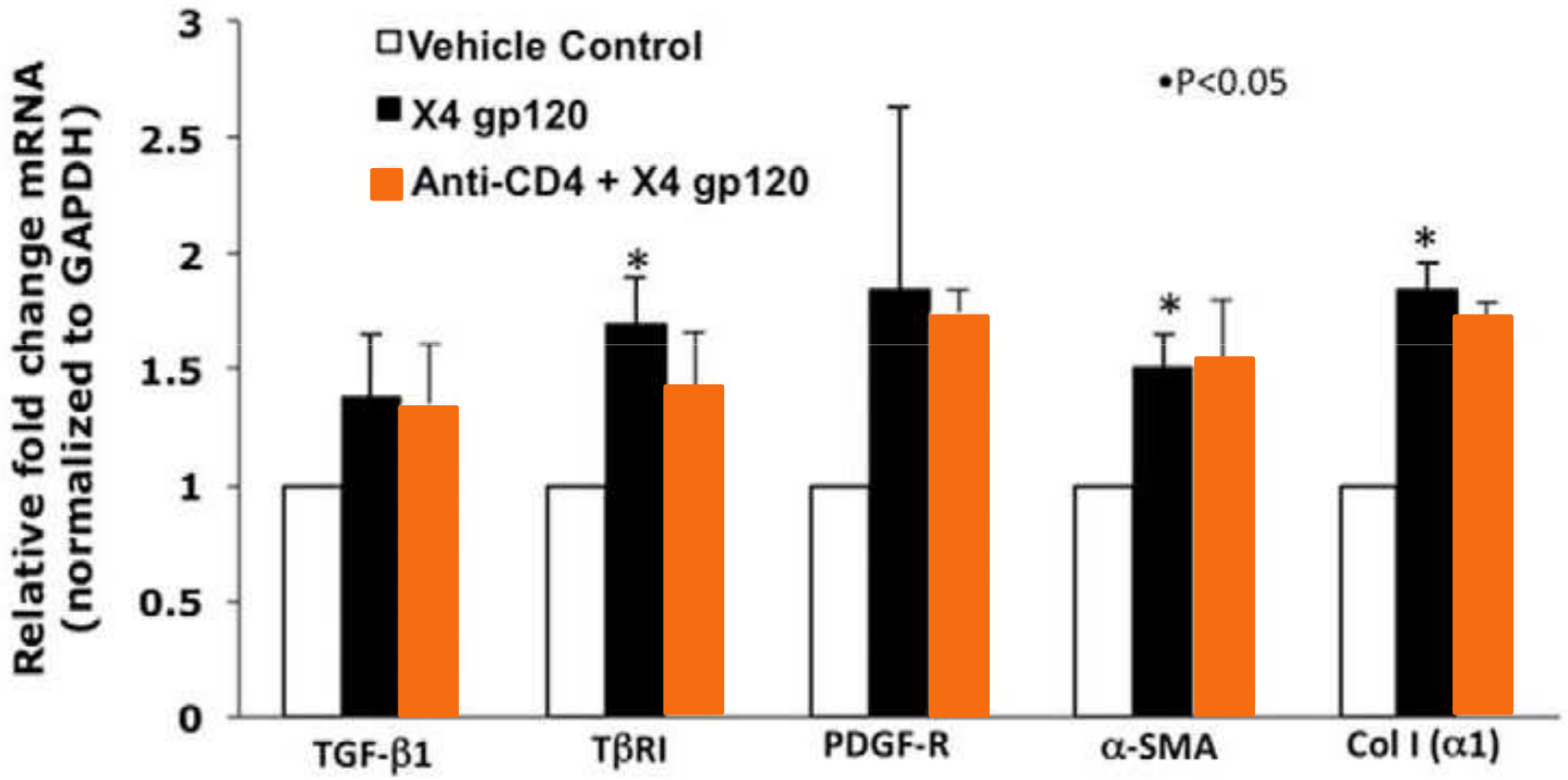
Iser et al AIDS 2011; 25(2):197-205

HIV infection increases stellate cell activation



Tuyama et al *Hepatology* 2010

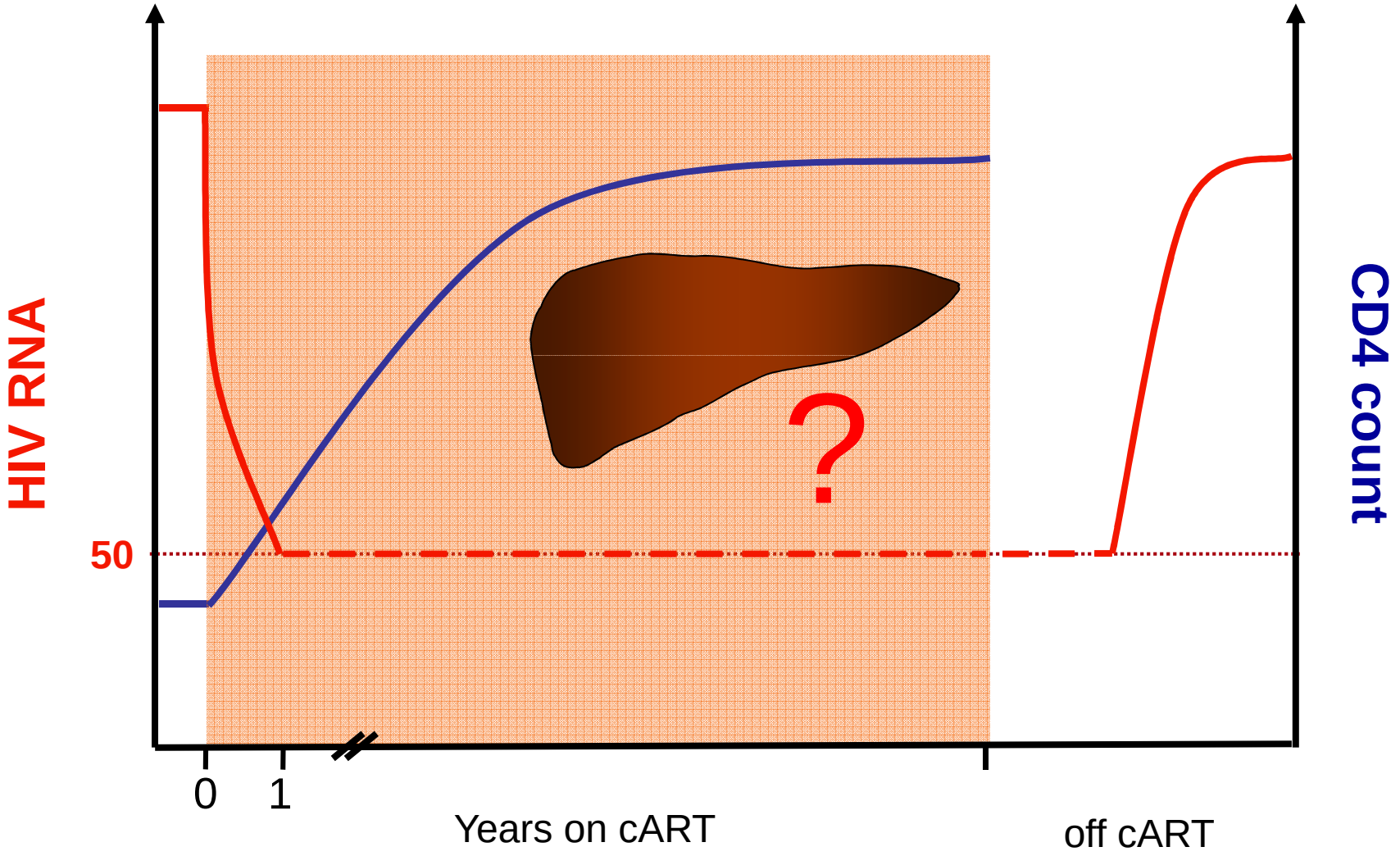
Gp120 + CXCR4 (and CCR5) mediate stellate cell activation



LX-2 cell line; changes in collagen confirmed in primary HSCs

Hong et al., Plos One 2012; e33659

Does HIV persist in the liver in patients on cART?



RT-SHIV model demonstrates liver has persistent virus on suppressive cART

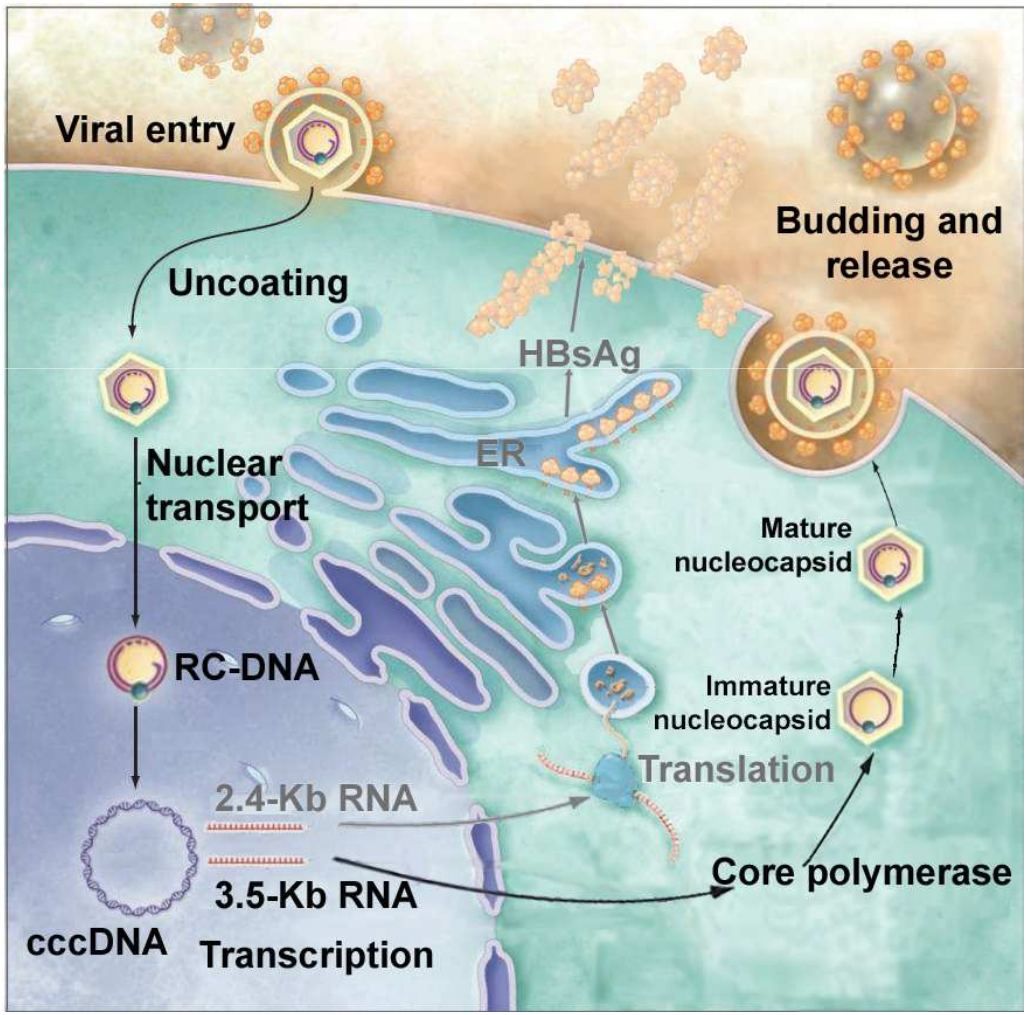
	1 VL=17 CSF VL<50	2 VL=11 CSF VL<50	3 VL=28 CSF VL<50	4 VL=20 CSF VL<50	5 VL=17 CSF VL<50

RT-SHIV infection; Tenofovir / emtricitabine / efavirenz 26 weeks
++++ - >1000; +++ - 100-1000; ++ - 10-100; + - 1-10; neg - <1 copies/million cells

North TW et al., J Virol 2010; 84:2913

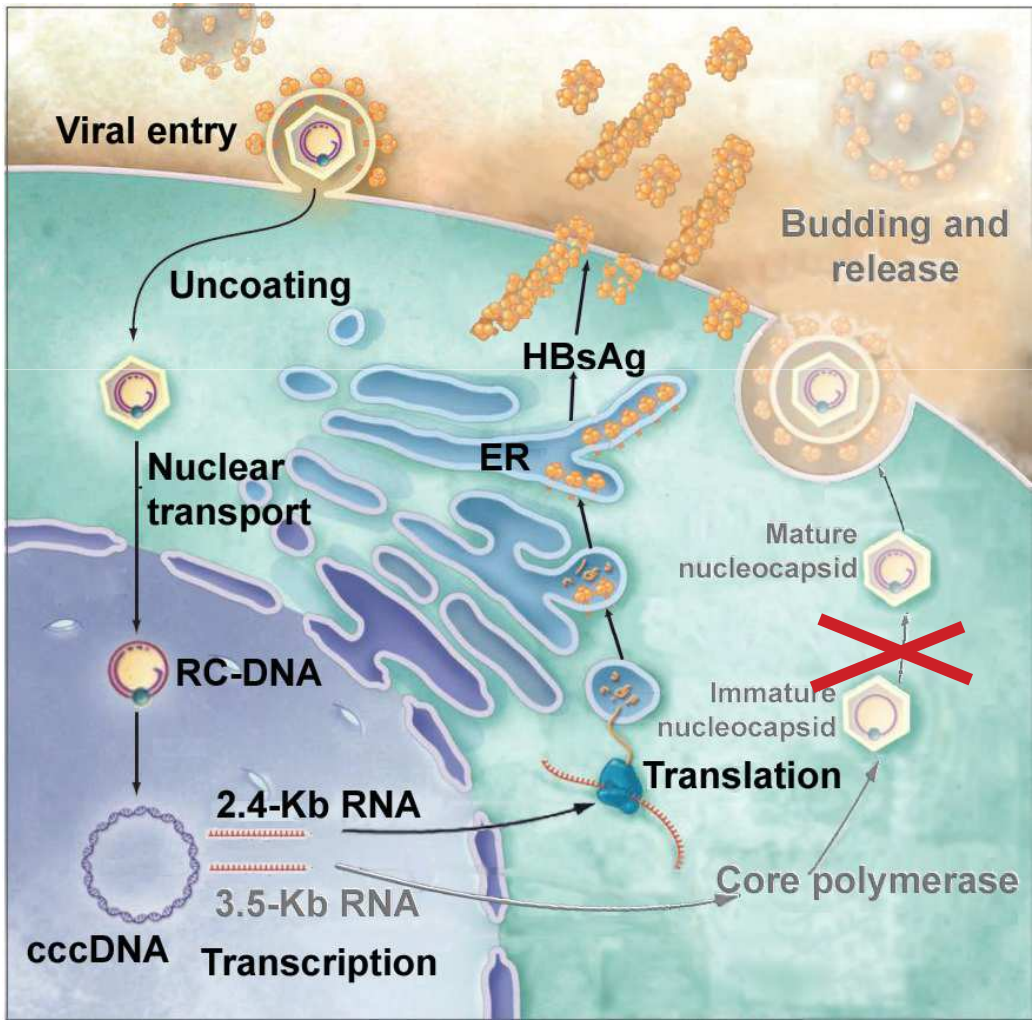
viral factors: HIV and HBV interactions

HBV Replication: HBV DNA Pathway



Adapted from: Diestag, N Engl J Med, 2008

HBV Replication: HBsAg (Envelope) Pathway



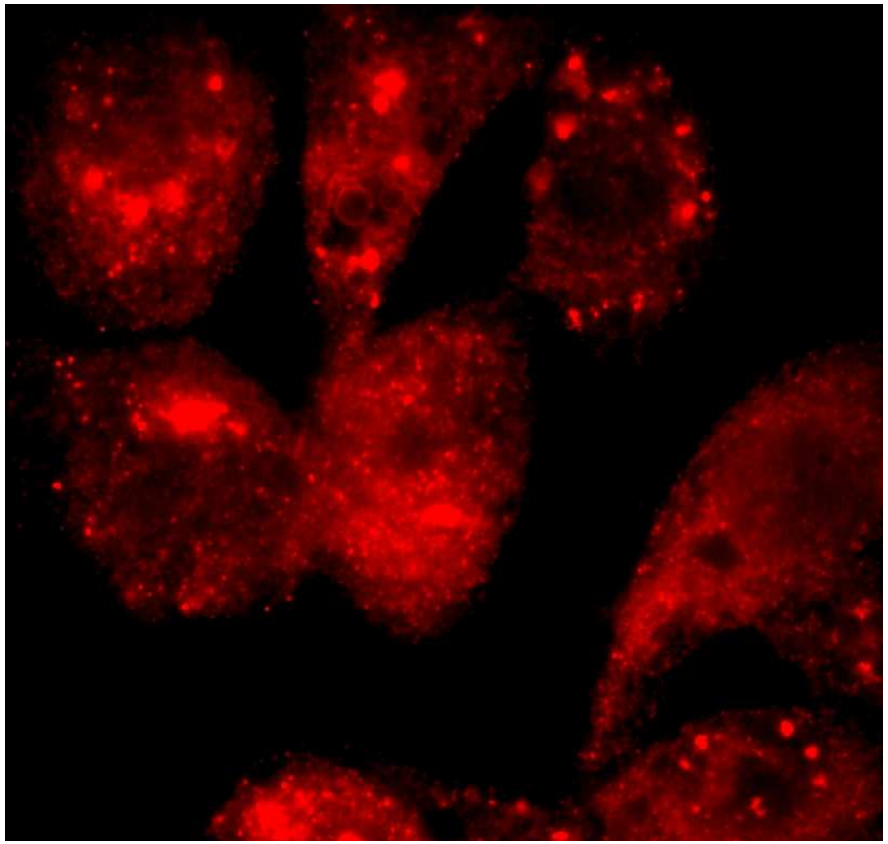
HBsAg

- Clearance is immune mediated
- Intrahepatic accumulation can drive apoptosis
- Quantitation of HBsAg can predict HBsAg loss
- Not inhibited by RT inhibitors

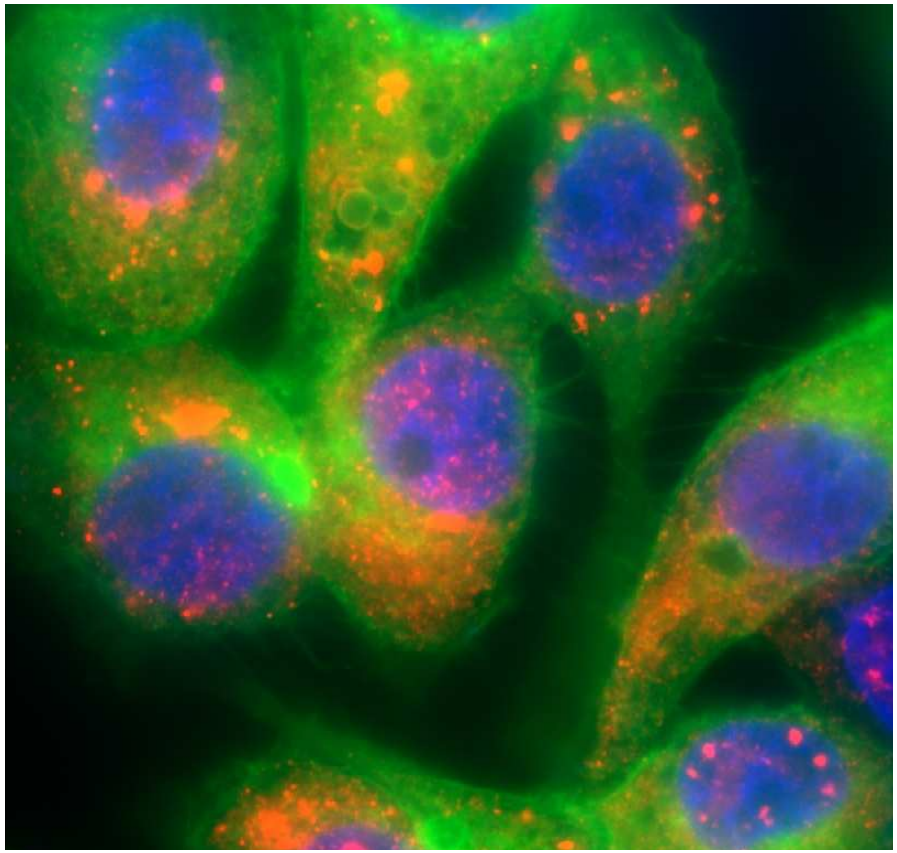
Adapted from: Diestag, N Engl J Med, 2008

HIV increases intrahepatic HBsAg

AD38 cells – express HBsAg, HBcAg, HBeAg, HBV DNA

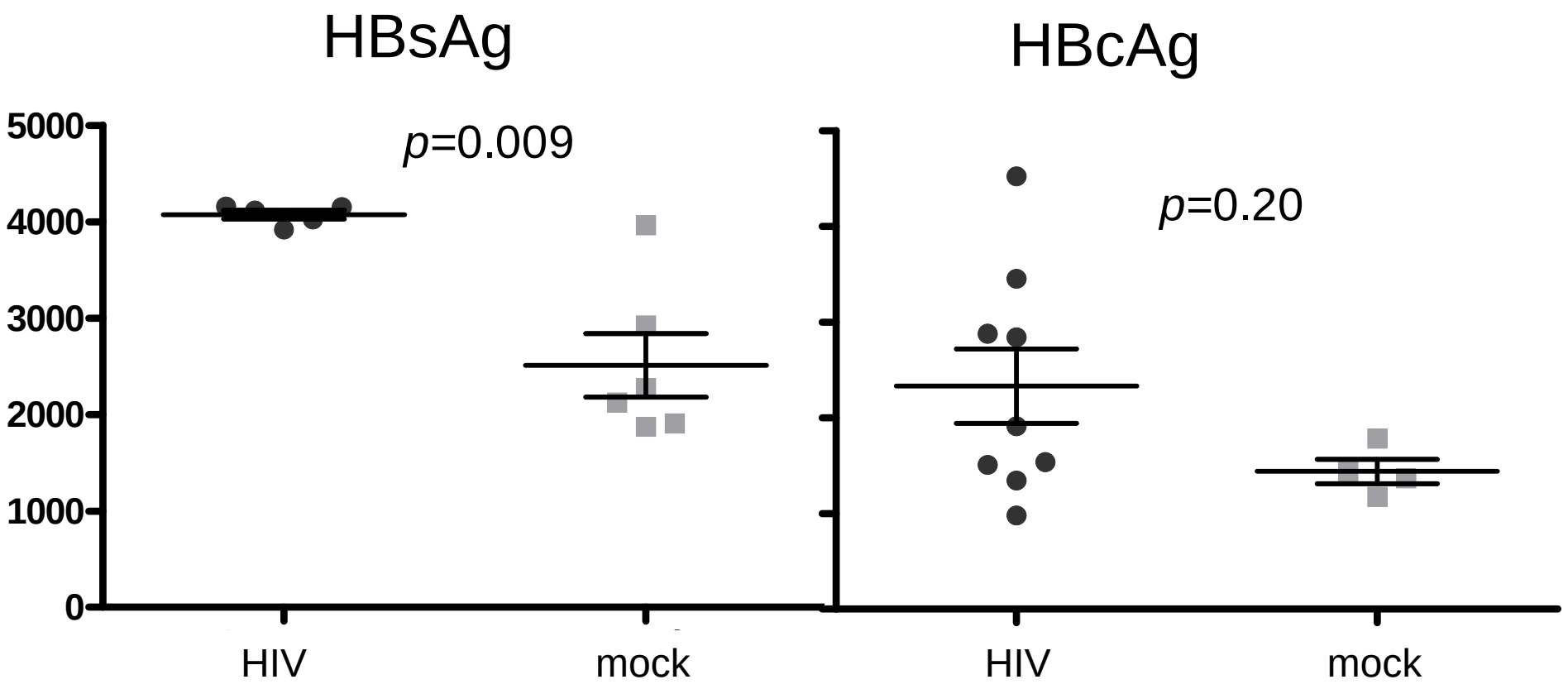


HBcAg
(red)



HIV
(green)

HIV increases intrahepatic HBsAg

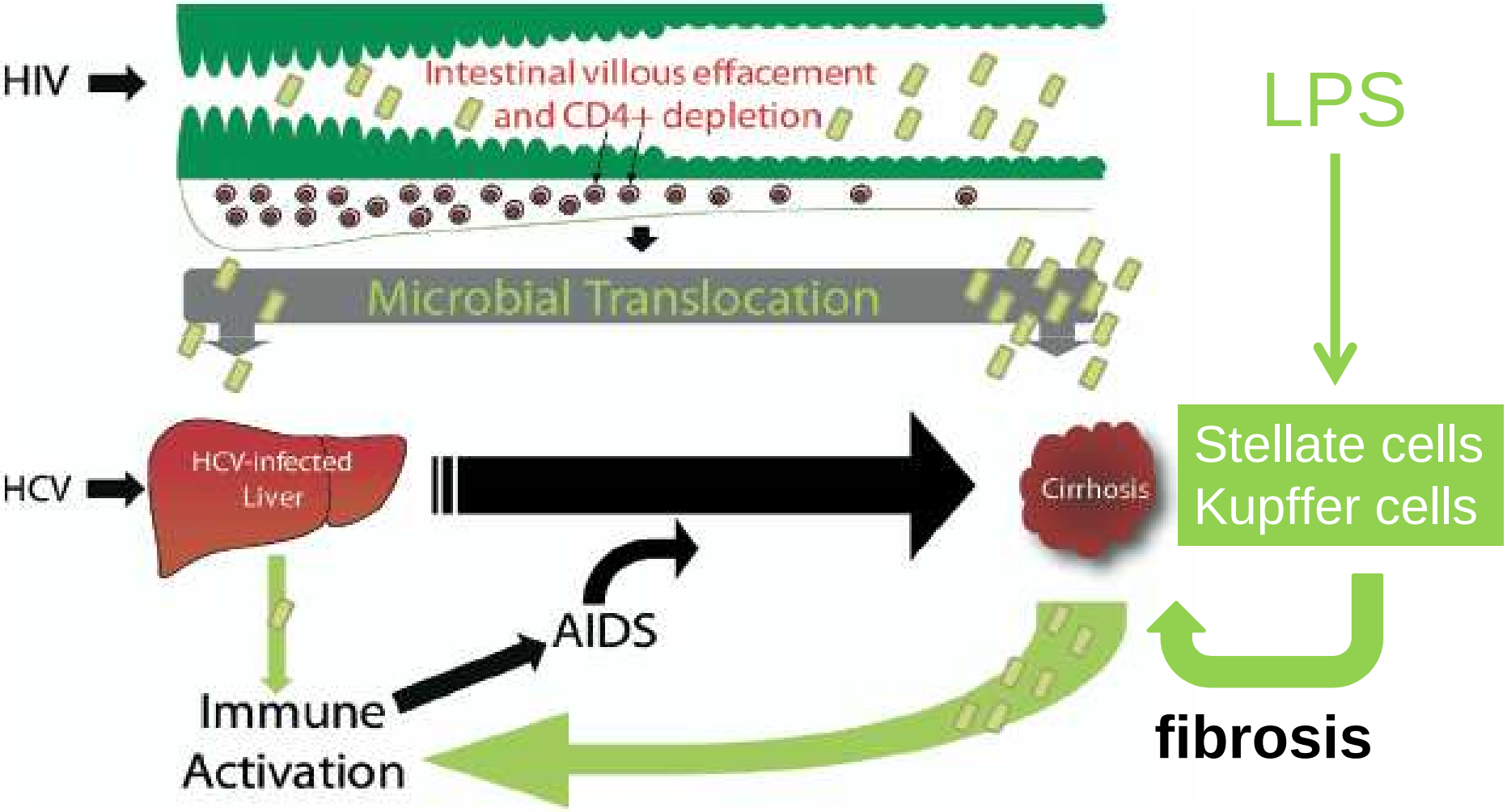


No significant difference in HBV DNA following HIV infection

Iser et al., *J Virol* 2010 84:5860-7

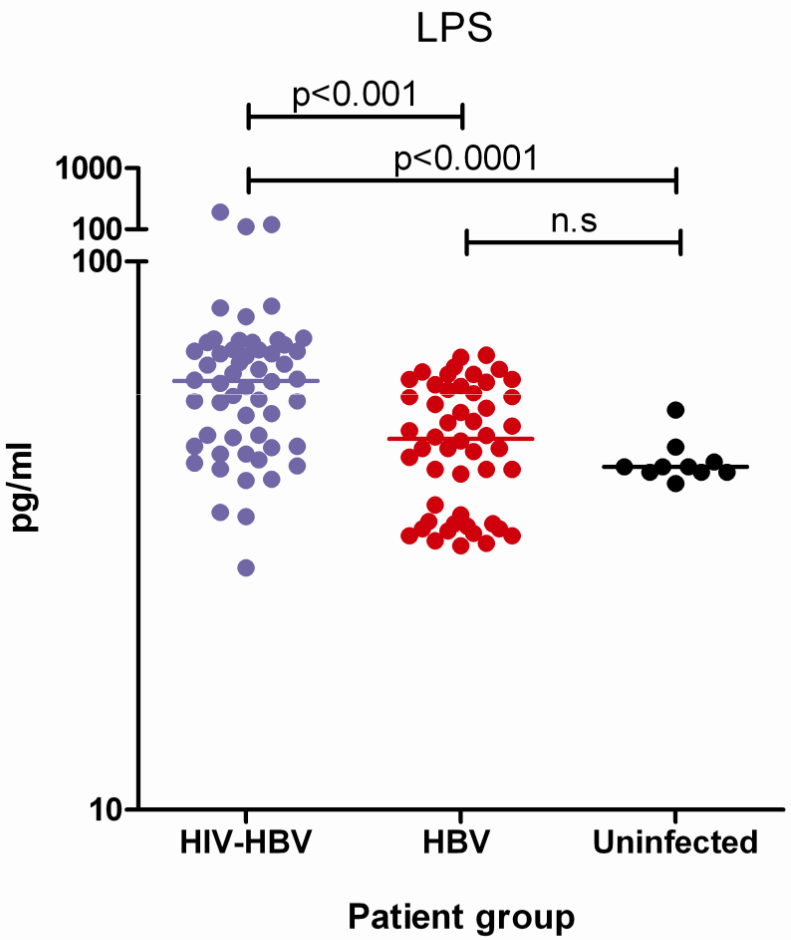
host factors: immune activation

Microbial translocation associated with liver disease in HIV-HCV



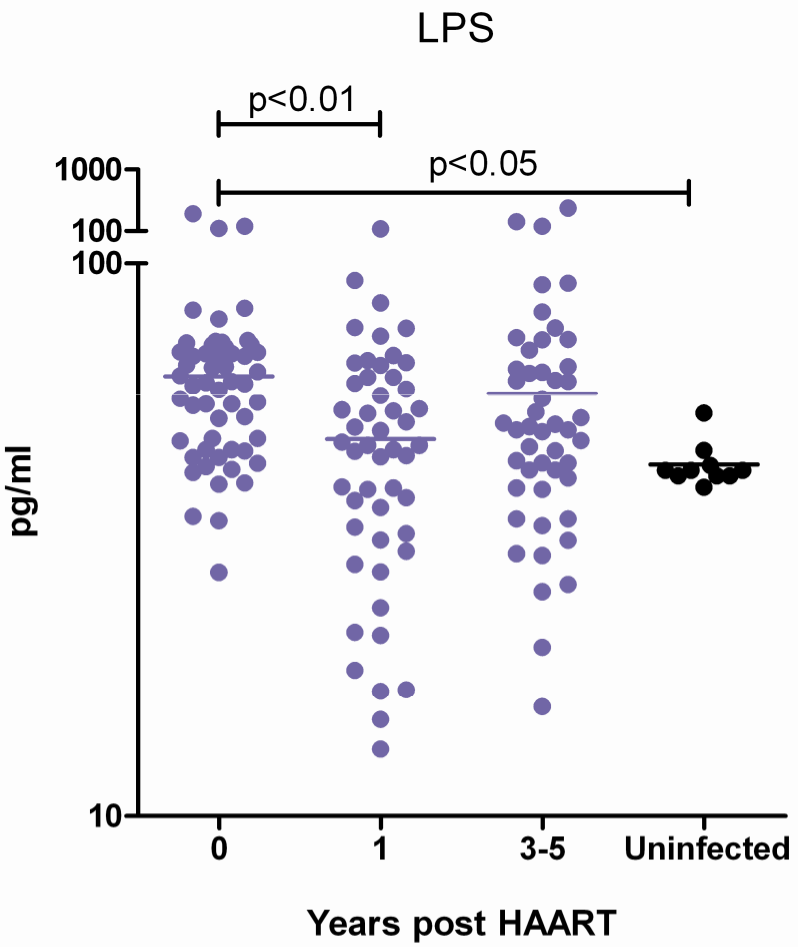
Mathurin et al., Hepatology 2000; 32:1008-1017; Paik et al., Hepatology 2003; 37:1043-1055;
Balagopal et al., Gastroenterology 2008; 135:226-233..

LPS and sCD14 and markers of immune activation are all elevated in HIV-HBV



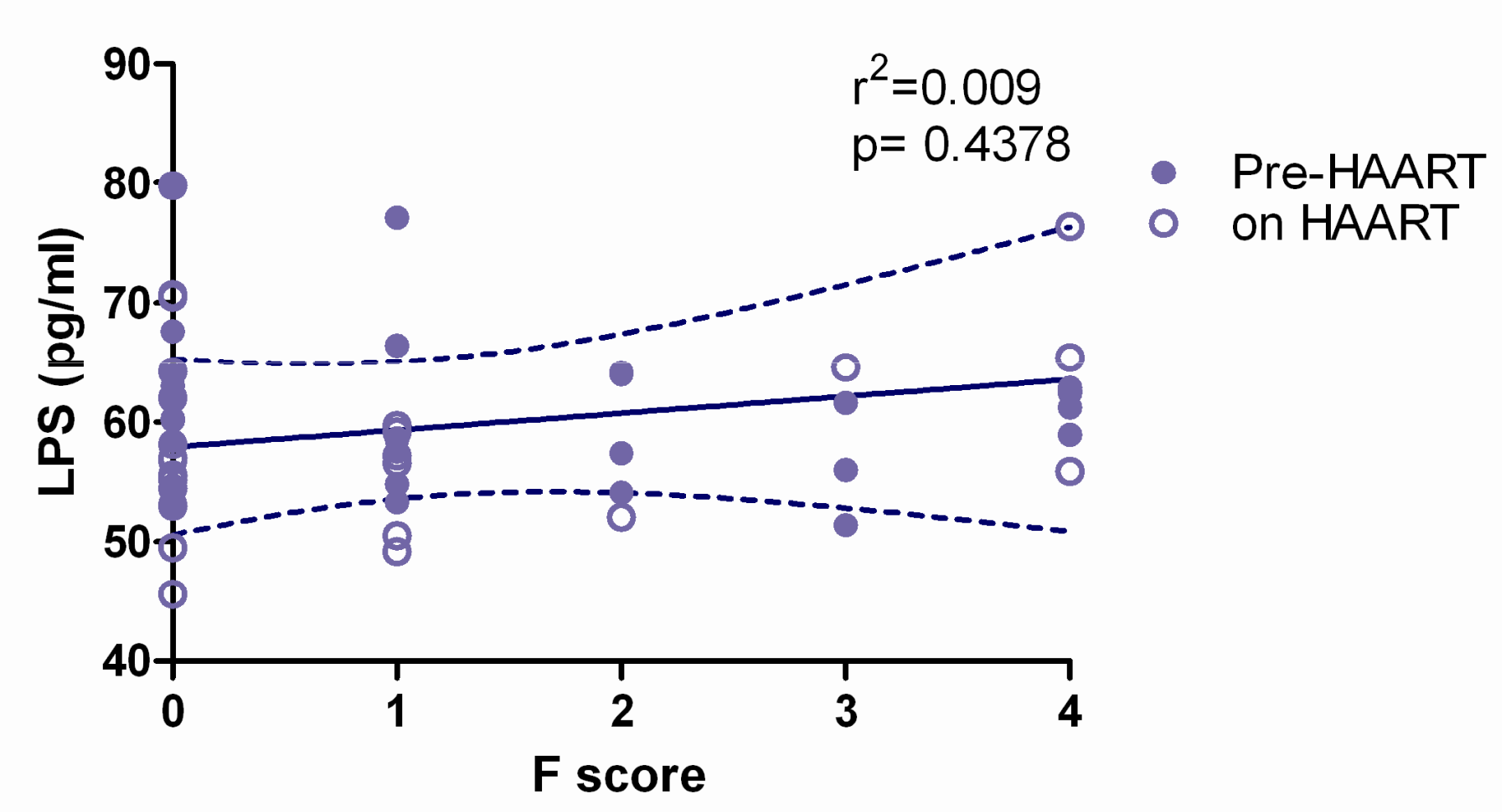
CXCL10, CCL2, TNF-α, IL-6 were all significantly elevated in HIV-HBV co-infection

LPS and sCD14 significantly decline on HBV-active HAART



Thai cohort, n=55; genotype C and B; median (IQR) CD4: 48 (20-204) baseline,;223 (172-367) year 1 and 340 (235-475) year 5-7

No relationship between LPS and fibrosis in HIV-HBV co-infection



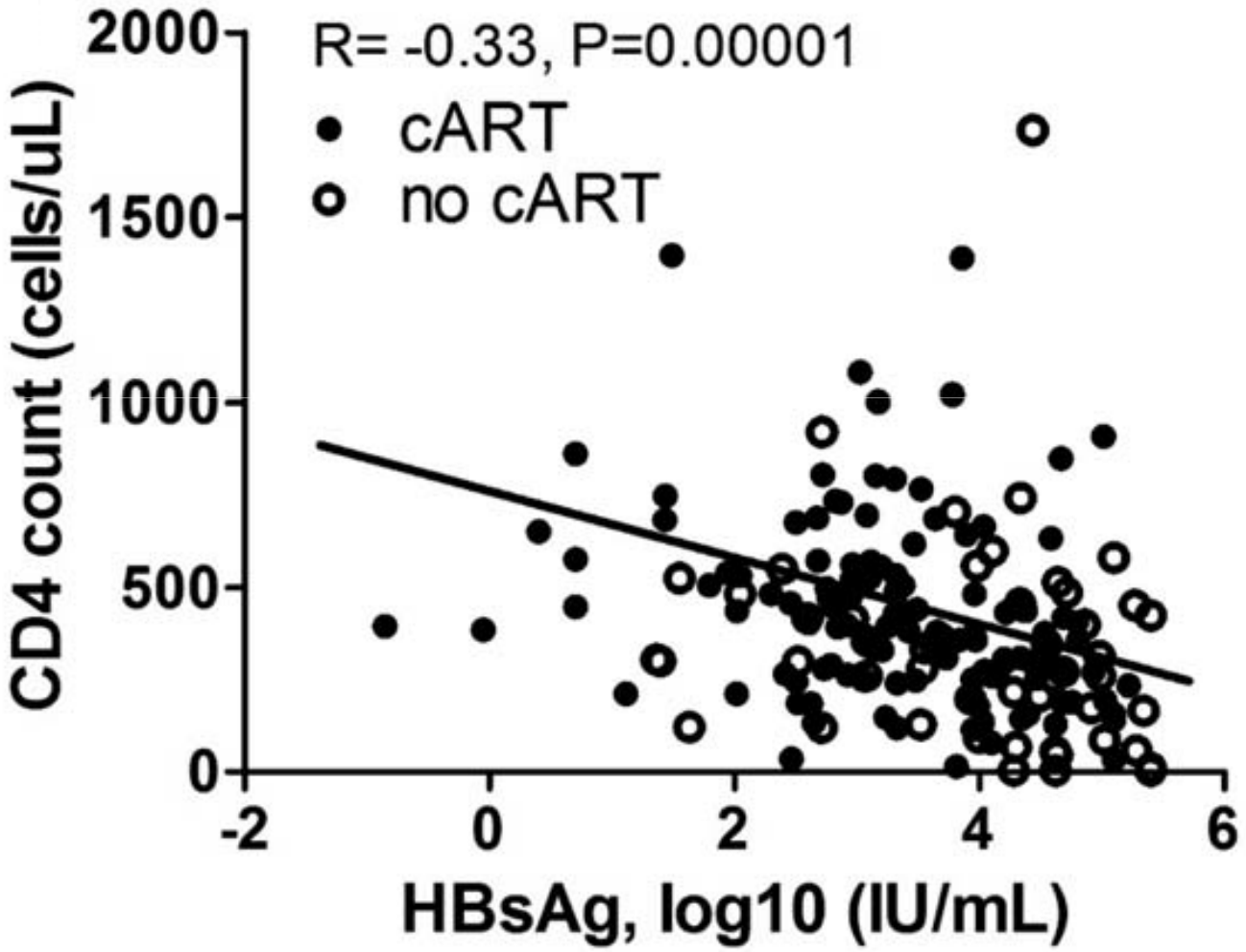
n=31; baseline, n=19 ; year one cART, n=9; year 5-7 cART, n=3

Immune activation associated with AST elevation on cART

	Outcome		
	Liver disease	Abnormal liver function (>x2ULN)	
Predictor	F score >/=3	AST>74 IU/ml (M) AST>82 IU/ml (F)	ALT>80 IU/ml (M) ALT>62 IU/ml (F)

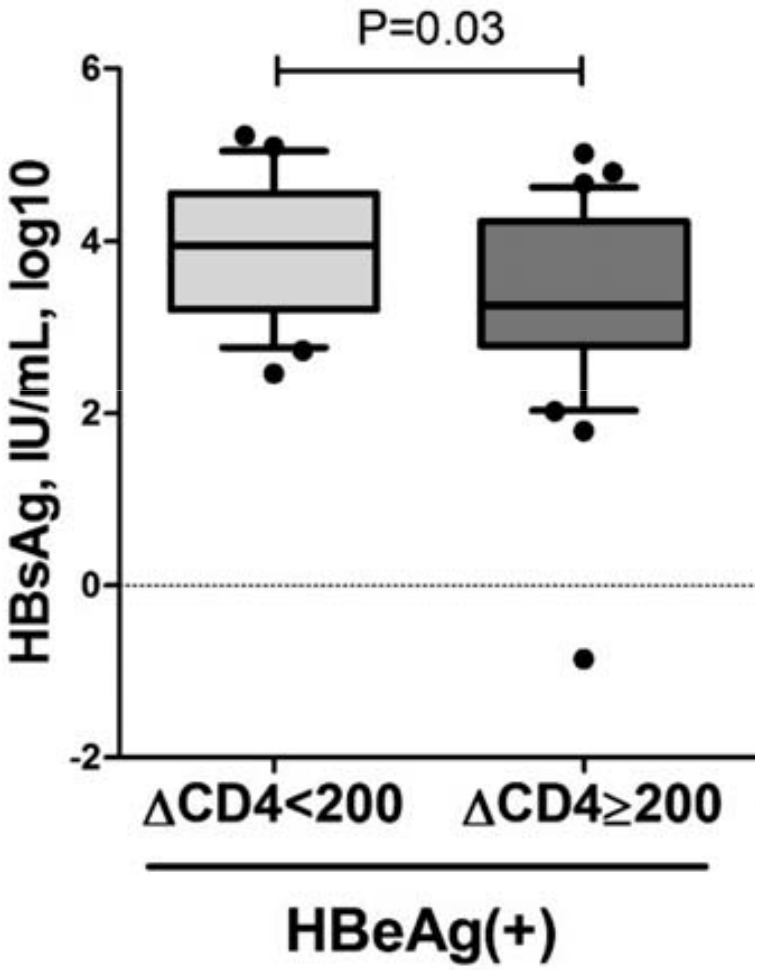
host factors: immune recovery

qHBsAg inversely correlated with CD4 T-cell counts



Jaroszewicz J et al., Plos One 2012; 7(8):e43143

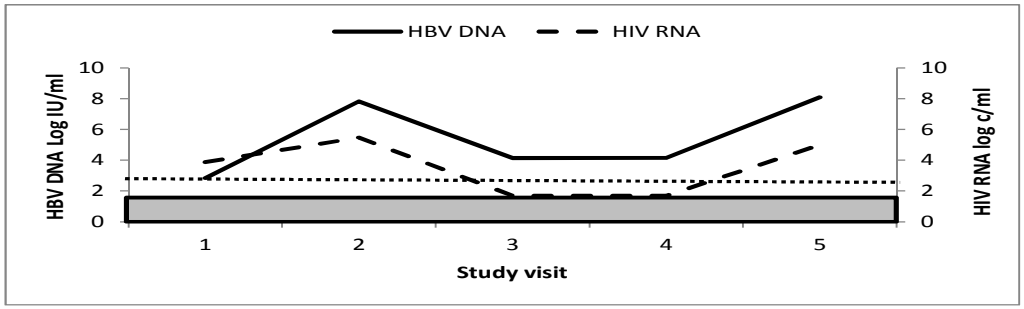
Immune recovery determines qHBsAg levels



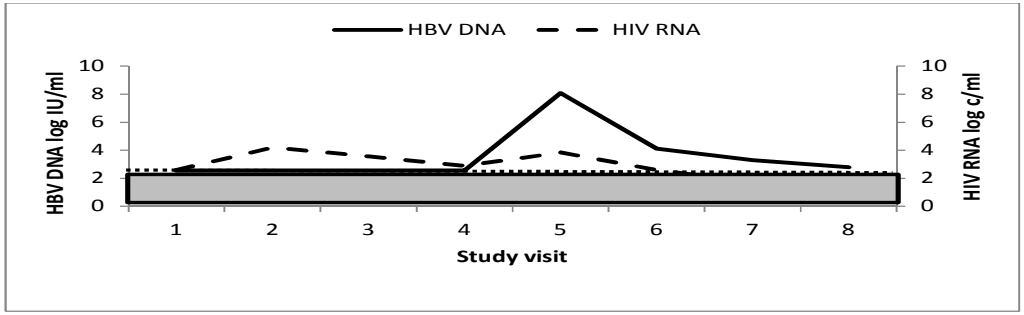
Jaroszewicz J et al., Plos One 2012; 7(8):e43143

Patterns of HBV DNA viremia on HBV-active HAART

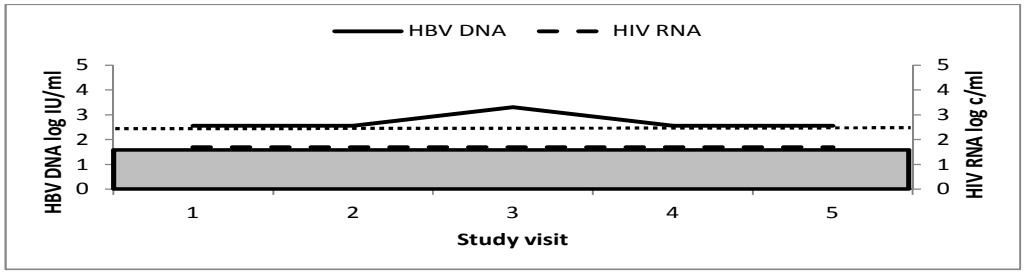
Clinic based prospective cohort; n=170; Australia, Thailand and US; median follow up = 5 years



Persistent viraemia (n=25)

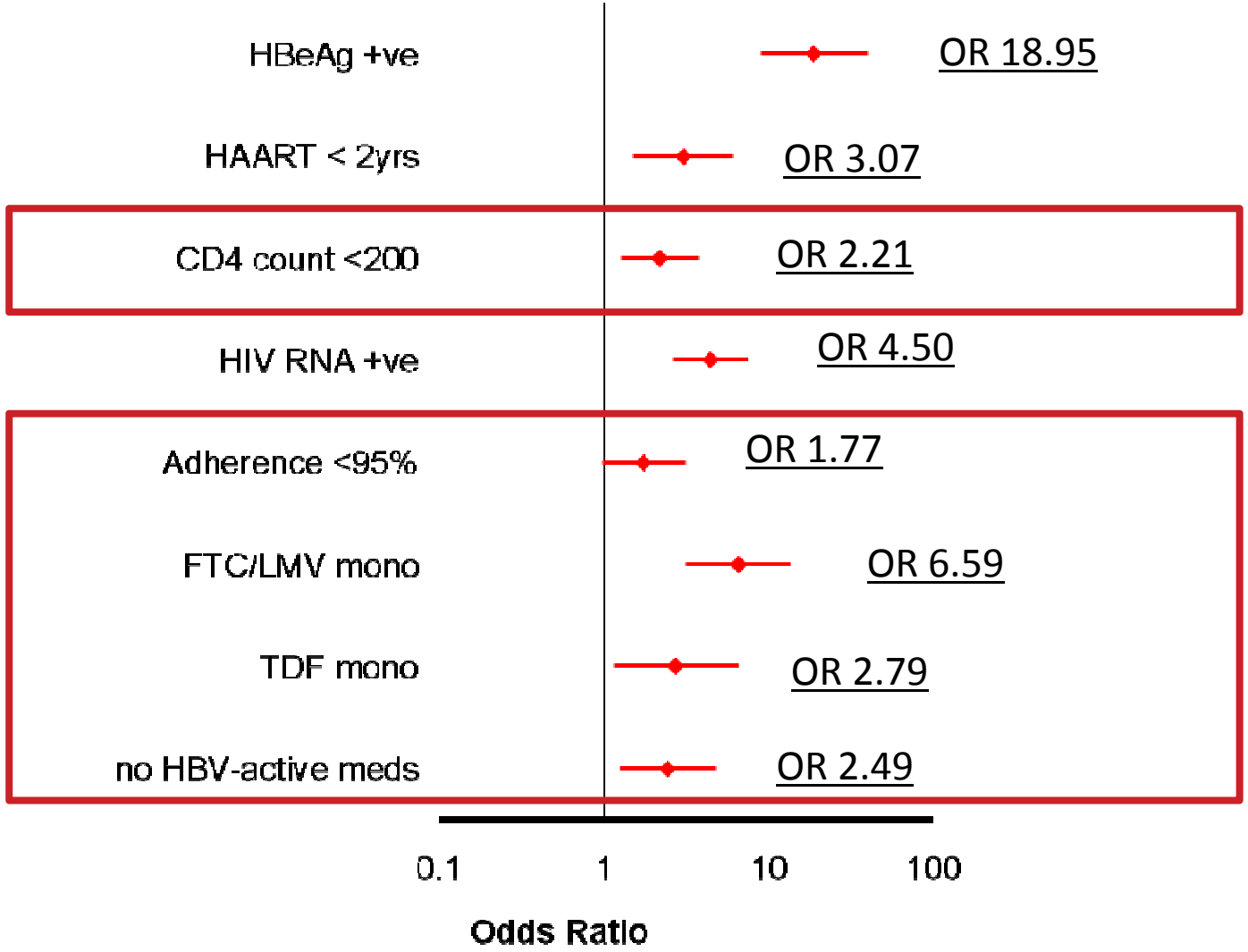


Viral rebound (n=13)



Blipper (n=24)

Factors associated with detectable HBV DNA



Summary

- Long term control of HBV excellent with TDF-based cART
- Liver related and total mortality has significantly reduced but remains elevated in HIV-HBV co-infected patients in the setting of HBV-active HAART
- HIV infects multiple cells in the liver including HSC and hepatocytes → apoptosis and activation
- Persistent immune activation following HBV-active cART associated with inflammation not fibrosis. Unclear if LPS plays a role
- Immune recovery important for treatment success: reduction in HBsAg and HBV DNA control

Emerging research issues

- Long term follow up of TDF treated patients
- Natural history of HIV-HBV co-infection in low income countries: different genotypes, vertical acquisition, women, pregnancy
- Is the liver a reservoir of HIV on cART?
- Can immune modulation have an effect on liver disease progression?
- Impact of early cART on natural history of HIV-HBV co-infection – virological control, HBsAg loss and liver disease progression

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