Impact of antiretroviral therapy on HBV-related liver disease

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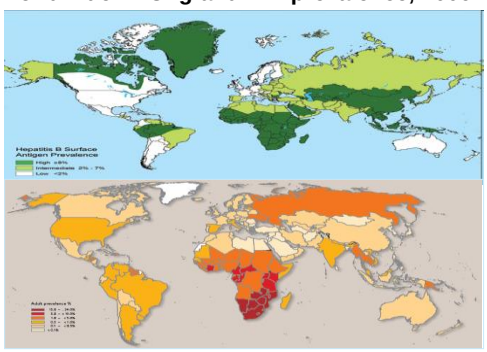
Outline

- Background-Liver disease prior to ART
- ART and HBV virological outcomes
- ART and HBV liver disease outcomes
- Can we cure HBV?
- Summary

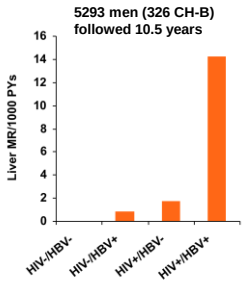
Worldwide HBsAg and HIV prevalence, 2006



UNAIDS 2006

HIV increases liver mortality from CHB prior to HAART

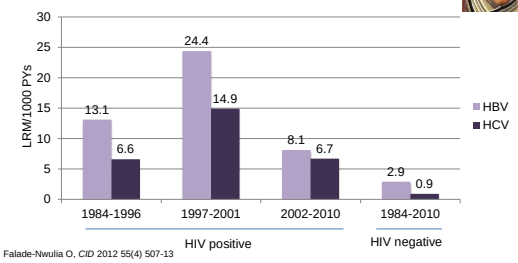
- 5293 men (326 HBsAg+ baseline) followed 10.5 years
- RR of liver death 17.7 in coinfected vs. only HBsAg+



Thio et al, *The Lancet* 2002

Liver-related mortality is higher from HBV than from HCV in the MACS

•337 men with CHB and 343 with CHC at study entry in MACS
•Outcome: liver-related mortality (LRM) expressed as rate/1000 PYs



Falade-Nwulia O, *CID* 2012 55(4) 507-13

Multivariate analysis of LRM in HIV-coinfected

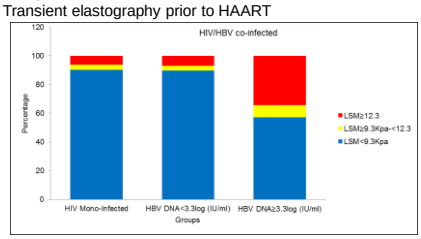
	IRR	95% CI	P
Hepatitis status (HCV ref)			
HBV	2.0	1.0-1.9	0.047
Age/10 year increase	1.6	1.1-2.3	0.009
Most recent CD4 count (>350 ref)			
200-350	7.1	2.4-20.1	<0.001
<200	16.3	6.2-42.8	<0.001
HAART	0.7	0.3-1.5	NS

Also adjusted for alcohol, recruitment period, race

Falade-Nwulia O, *CID* 2012 55(4) 507-13

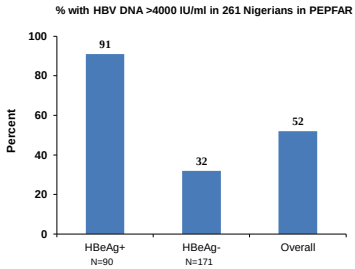
Liver fibrosis advanced in HIV-HBV co-infection with higher HBV DNA in Nigeria

- Cross sectional study of 232 HIV+ and 93 HIV-HBV patients in Nigeria
- Transient elastography prior to HAART



Hawkins et al, *CID* 2013 57(12): e189-92

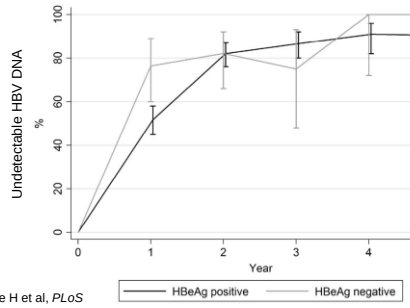
HBV DNA >4000 IU/ml in HIV-HBV co-infected Nigerian subjects prior to HIV therapy



Idoko et al *CID* 200949(8): 1268

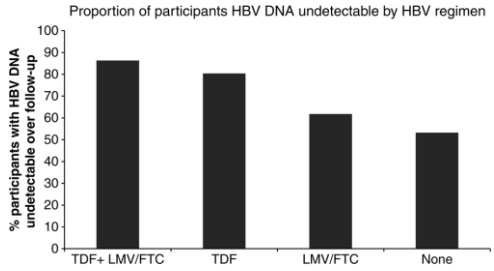
ART AND HBV VIROLOGICAL OUTCOMES

Meta-analysis of TDF response in 550 HIV-HBV co-infected subjects



Price H et al, *PLoS One* 2013 Jul

Treatment response in 165 HIV-HBV co-infected subjects with median 2.8 yrs treatment



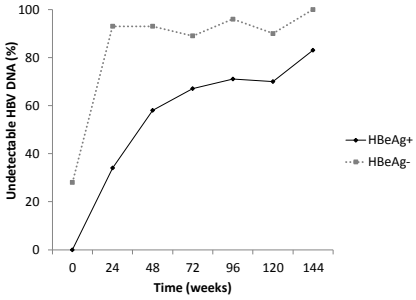
Matthews et al *CID* 2013 56(9):e87-94

Factors associated with detectable HBV DNA in those with HIV RNA < 400 cp/ml

	OR	95% CI	P
Age (per 10 yrs)	0.90	0.48, 1.69	0.74
HBeAg pos	12.06	3.73, 38.98	<0.0001
<95% adherent	2.52	1.16, 5.48	0.02
HAART <2 yrs	2.64	1.06, 6.54	0.04
CD4 < 200 cells/mm^3	2.47	1.06, 5.73	0.04

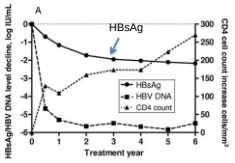
Matthews et al *CID* 2013 56(9):e87-94

Response to TDF in multinational ACTG studies: 5175 and 5208

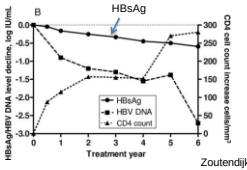


HBsAg kinetics in 104 HIV-HBV subjects on TDF-based ART

66 HBeAg+
- Baseline sAg 4.6 log IU/ml
- 2.2 log decline yr 6
- 5 HBsAg loss



38 HBeAg-
- Baseline sAg 2.8 log IU/ml
- 0.6 log decline yr 6
- 3 HBsAg loss



Zoutendijk et al *JID* 2012;206:974–80

ART AND HBV LIVER DISEASE

Incidence of cirrhosis in HIV-HBV on TDF-based HAART is low

- 508 Spanish HIV-hepatitis non-cirrhotic patients
- Two TEs 2.6 ± 1.0 yrs apart
- 54 (10.6%) developed cirrhosis
- 1/24 (4.2%) with HBV

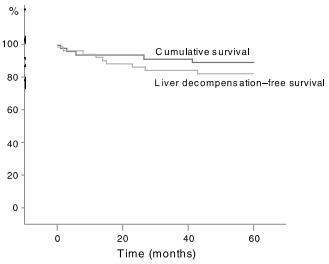
Multivariable analysis for risk of developing cirrhosis adjusted for baseline factors including TE

	OR	*P*
HIV-HCV with SVR	1	
HIV-HCV	3.73	0.04
HIV-HBV	0.69	0.81

Tuma et al, *AVT* 2010 15:881-6

Liver decompensation-free survival in 79 HIV-HBV co-infected subjects

- 97% on HBV-active ART
- 45.7% HBeAg+
- Median f/u 35 months
- 11 (15%) cirrhosis baseline
- 8 (10%) with liver decompensation
  - 7 cirrhosis baseline



Martin-Carbonero et al, *AIDS* 2011; 25:73-79

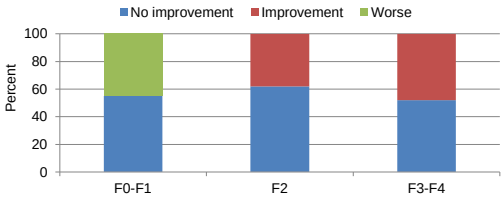
Liver disease progression by TE

- 71/79 with two TE over median time of 40.1 mos
- Median TE scores stable
- Proportion with no or mild fibrosis increased from 47.8% to 64.7%
- 6 (8.4%) with increase in fibrosis stage
- Limitation: no control group

Martin-Carbonero et al, *AIDS* 2011; 25:73-79

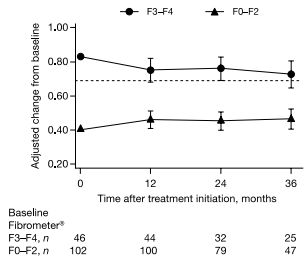
Fibrosis progression in 184 French HIV-HBV patients on TDF

- Fibrosis measured by Fibrometer every 12 mos
- Median f/u 29.5 mos
- 115 (63%) <F4 prior to TDF
- 12 (10.4%) with incident F4 (4.5/100 PYs) after median of 11.2 months



Boyd et al, *AVT* 2010 15:963

Change in mean Fibrometer® during TDF treatment



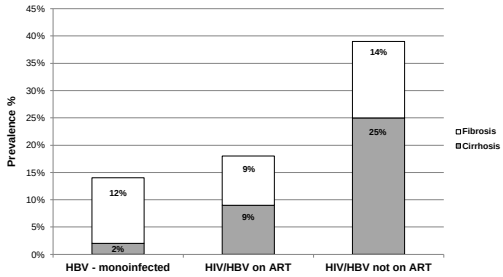
Boyd et al, *AVT* 2010 15:963

Factors associated with increase in Fibrometer to F3-F4

Factor	HR	95% CI
HCV serology positive	3.6	1.3-9.8
Age >40.6 yrs	2.3	1.0-5.1
>4 glasses alcohol/day	3.1	1.4-6.9
AIDS defining event	2.5	1.1-5.6
GGT flare >50 IU/ml	2.6	1.2-5.7
CD4 >350 cells/mm^3	0.3	0.2-0.7

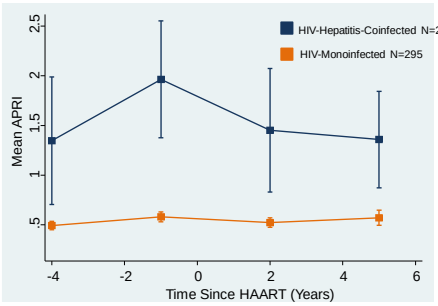
Boyd et al, *AVT* 2010 15:963

Prevalence of elastography-defined liver fibrosis (>9.3 kPa) and cirrhosis (≥12.3 kPa) among Ugandans



Jjingo et al, manuscript submitted

APRI improves with HAART in HIV-hepatitis co-infected



Price et al, manuscript in preparation

CXCL10 elevated in HIV-HBV co-infected patients on ART

- Thai HIV-HBV co-infected subjects vs HBV monoinfected or uninfected
- Prior to ART: LPS, sCD14, CXCL10, CCL2 higher in co-infected
- With ART: CXCL10 declined but remained elevated
- In vitro, LPS and IFN-γ synergistically increased CXCL10
- In other studies, CXCL10 associated with hepatic flares. (Crane et al, *JID* 2009; 199:974–81)

Crane et al, *JID* epub March 2014

CAN WE CURE HBV?

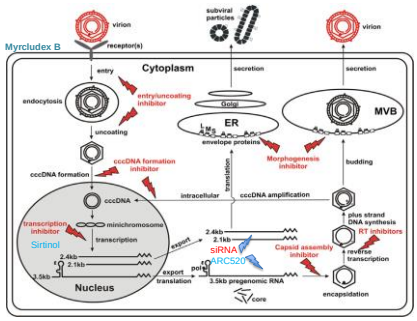
Types of HBV cure

- Functional cure (akin to SVR in HCV)
  - Maintain undetectable HBV DNA off therapy
  - Ideally anti-HBs+
- Eradication (complete) cure
  - Eliminate cccDNA

Barriers to cure

- cccDNA
  - Stable intranuclear form that is transcription template
  - Not substantially affected by current anti-virals (1 log reduction)
  - Difficult to eradicate even with natural recovery
- Functional cure is possible
  - anti-HBs in 5% on long-term anti-virals

Drug targets in HBV replication cycle

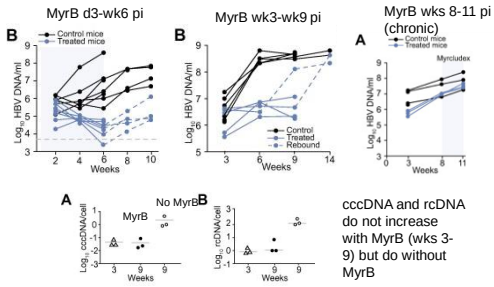


Block et al, *Antiviral Res* 2013 98:27

Virological approaches

- Block entry-Myrcludex B
- Silence cccDNA
- Endonucleases to cleave cccDNA
- HBV capsid inhibitor- destabilizes capsid assembly
- siRNA targeted to viral mRNA (Li et al Cell Biochem Biophys 2014 Feb epub; Wooddell et al Mol Ther 2013 21:973)
- RNase H inhibitors
- Sirtuin 1 inhibitors

Myrcludex B inhibits HBV replication in early but not chronic HBV in humanized mice



Volz et al, *Journal of Hepatology*, 2013; 58(5):861

Immunological approaches

- TLR7 agonist
  - Leads to development of anti-HBs in woodchuck model (Menne et al, *J Hepatol* 2011)
  - In chimps, prolonged suppression of HBV DNA (Lanford et al, *Gastro* 2013[144: 1508)
- PD-1 blockade
- Therapeutic vaccine
- Adoptive transfer of genetically modified T cells that express receptor directed against HBV surface proteins (Krebs et al, *Gastro* 2013 145:466)
- Nanoparticles with HBV-CpG induce IFN-α thru TLR9 dependent pathway
- LTβR agonist (Lucifora *Science* 2014 Feb)

Summary

- Virological response from ART
  - HBV DNA
  - HBsAg
  - High level of adherence
- Decreased fibrosis progression
  - Not universal
- Substantial progress but risk is not zero. Need cure
  - Several potential virological or immunological approaches
  - Data on immune response during recovery from natural infection needed

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