HBV in HIV

Forgotten but not Gone

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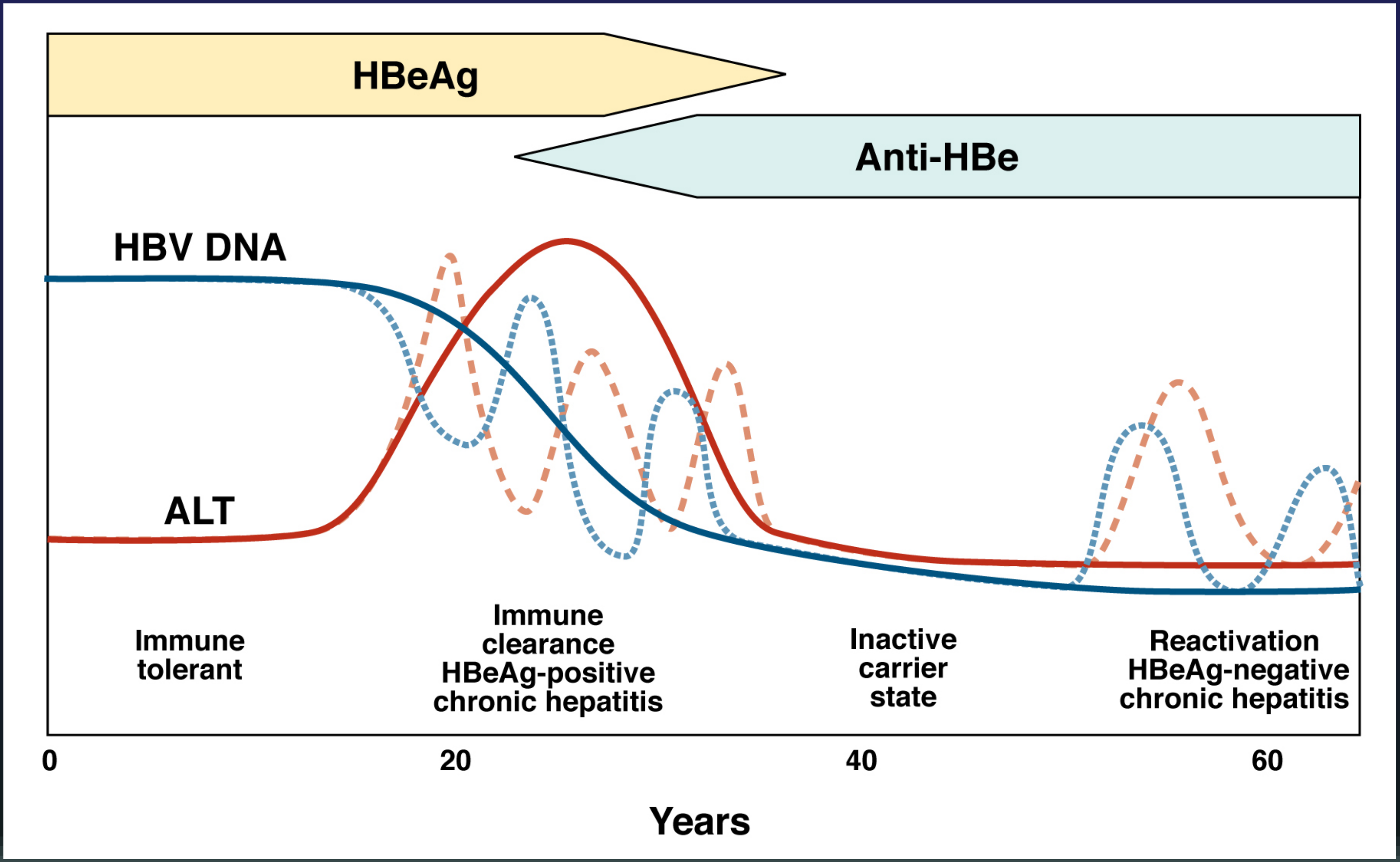
Objectives

- Natural history of HBV
- Diagnosis of HBV
  - Understanding serologies
- Definitions and terminology
- Epidemiology of HBV in HIV
  - Prevalence, presentation, natural history
- Treatment of HBV in those with HIV
  - In those who require ART and those that do not

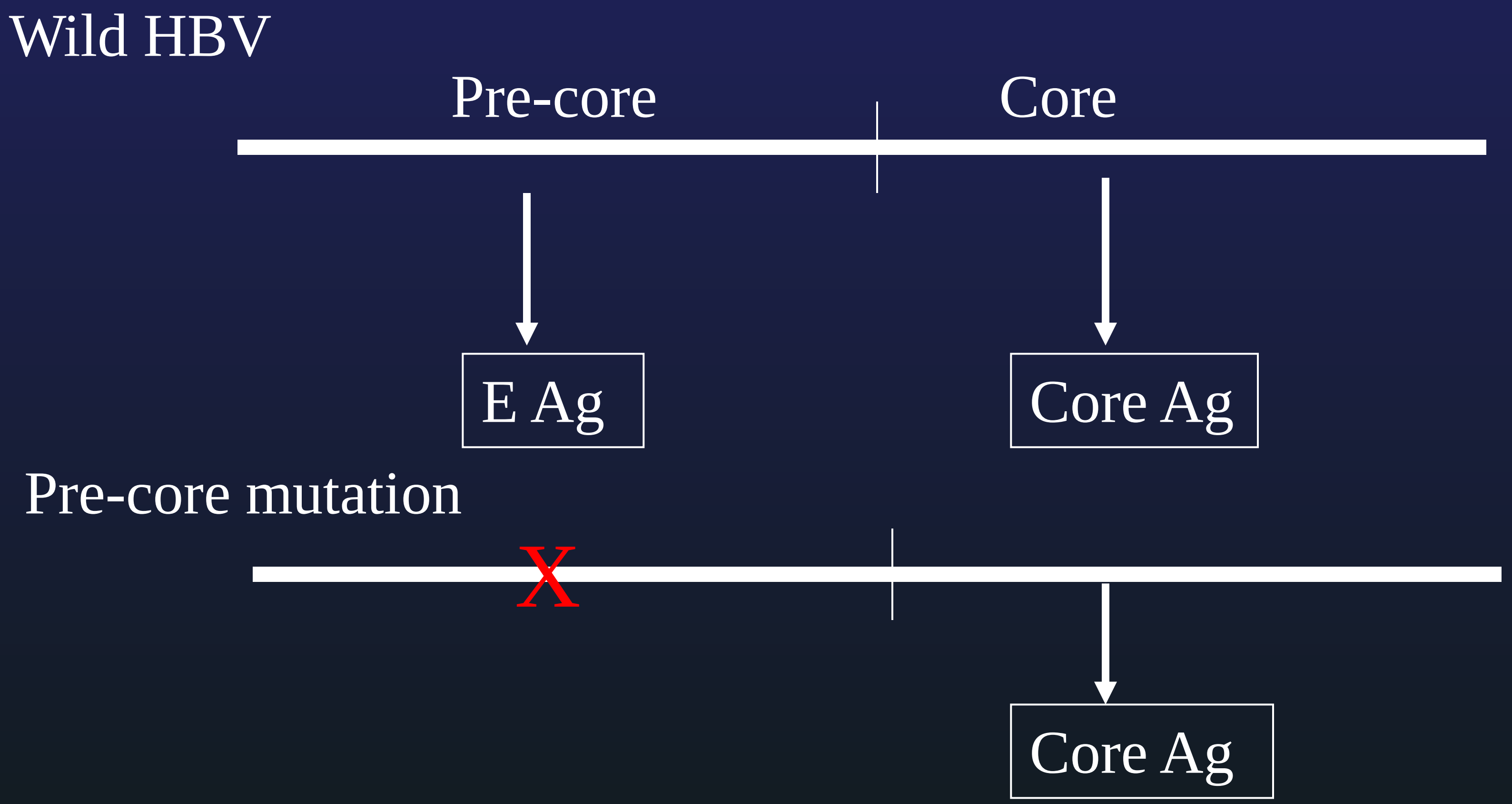
Phases of Chronic HBV Infection



Diagnosis of HBV

	Surface		Core				DNA
	Ag	Ab	IgM	IgG	E Ag	E Ab	
Acute	+	-	+	-	+	-	+
Window	-	-	+	-/+	-	+	-
Resolved	-	+	-	+	-	+	-
Chronic							
Active	+	-	-	+	+	-	+
Inactive	+	-	-	+	-	+	-
Pre-core	+	-	-	+	-	-/+	+
Vaccinated	-	+	-	-	-	-	-

HBV Pre-core Mutation



Only Core Ag needed for viral replication

Definitions

Definition	Diagnostic criteria
Chronic HBV HBeAg + / HBeAb - HBeAg - / HBeAb +/-	Surface antigen + > 6 months HBV DNA $\geq$ 2,000 IU/ml Abnormal AST/ALT Active histology
Inactive chronic HBV	Surface antigen + > 6 months HBeAg negative/ HBeAb positive HBV DNA < 2,000 IU/ml Normal AST/ALT Inactive histology (but may have advanced fibrosis)
Resolved HBV	Surface antigen negative/sAb + HBV DNA negative Normal AST/ALT

Chronic HBV: Terminology

- **Seroconversion**: Converting from HBeAg+ to HBeAg-negative and anti-HBe+ or conversion from HBsAg + to HBsAb +

- **Reversion**: Reappearance of HBeAg in carriers who were HBeAg-neg/anti-HBe+

- **Exacerbation**: Elevation of aminotransferase levels in carrier with normal levels (usually defined as 2X to 4X elevation)

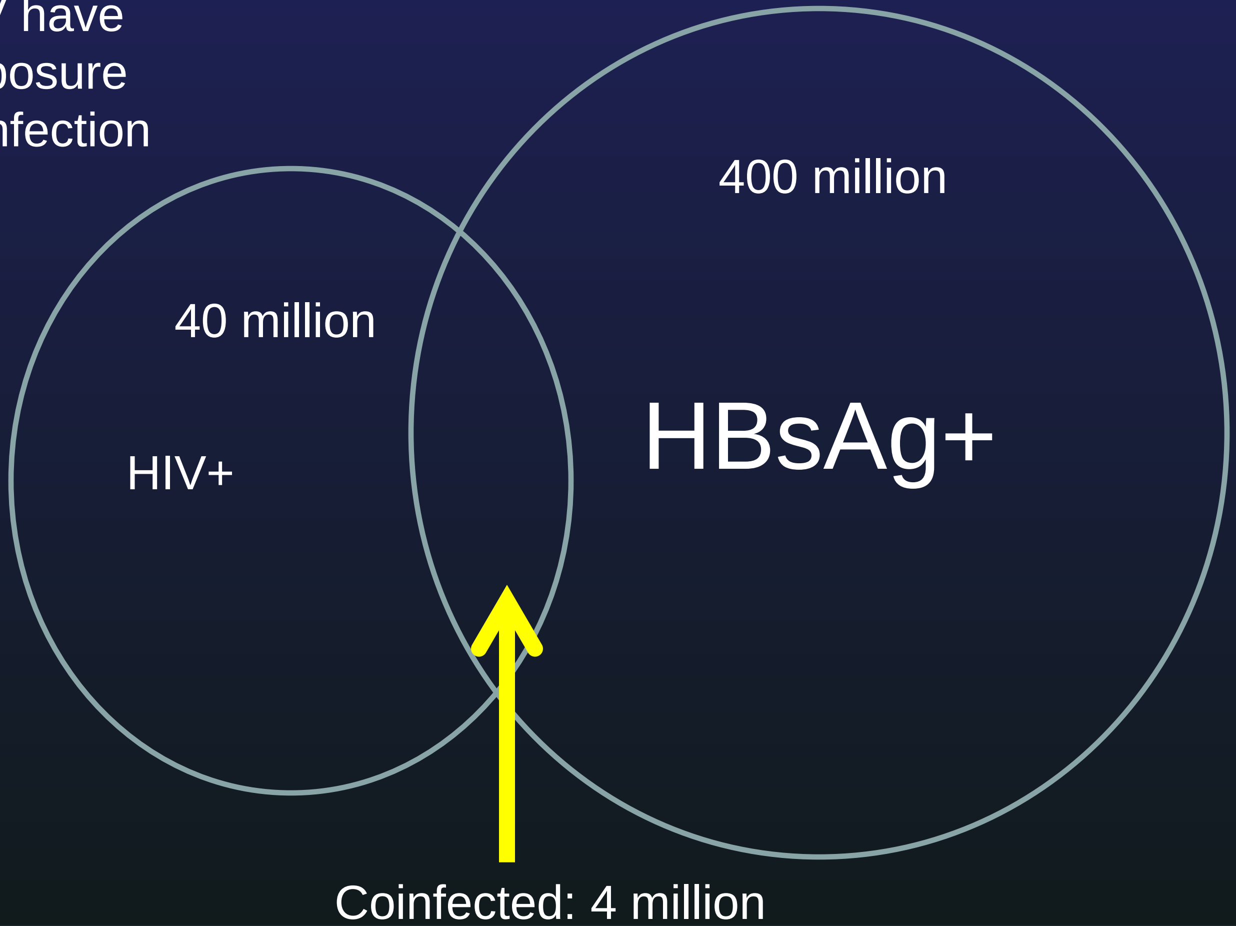
Hepatitis D

- **Coinfection**
  - More severe acute hepatitis
  - Less chronic infection

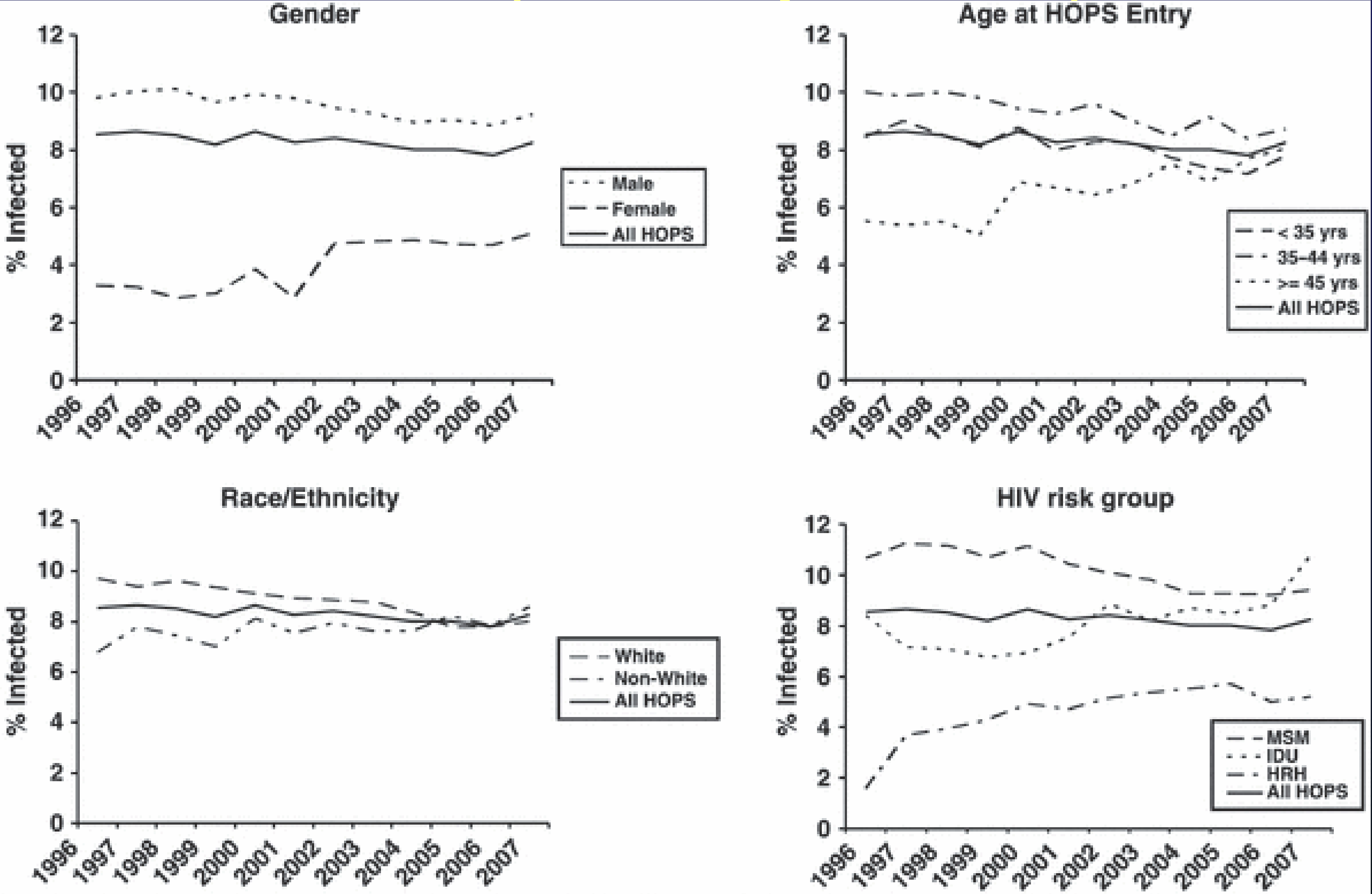
- **Superinfection**
  - Exacerbation of chronic HBV
  - Increased progression to cirrhosis
  - Increased hepatic decompensation
  - Increased risk of HCC

Prevalence of Disease

- 90% of those with HIV have
Markers of past HBV exposure
- 8-10% have chronic infection



Prevalence of chronic hepatitis B virus infection among patients in the HIV Outpatient Study, 1996–2007†



Race/Ethnicity: "Non-white" includes Hispanic ethnicity; HIV Risk Group: "HRH" = high-risk heterosexual; "IDU" = injection drug user; "MSM" = men who have sex with men. IDU + MSM were categorized IDU

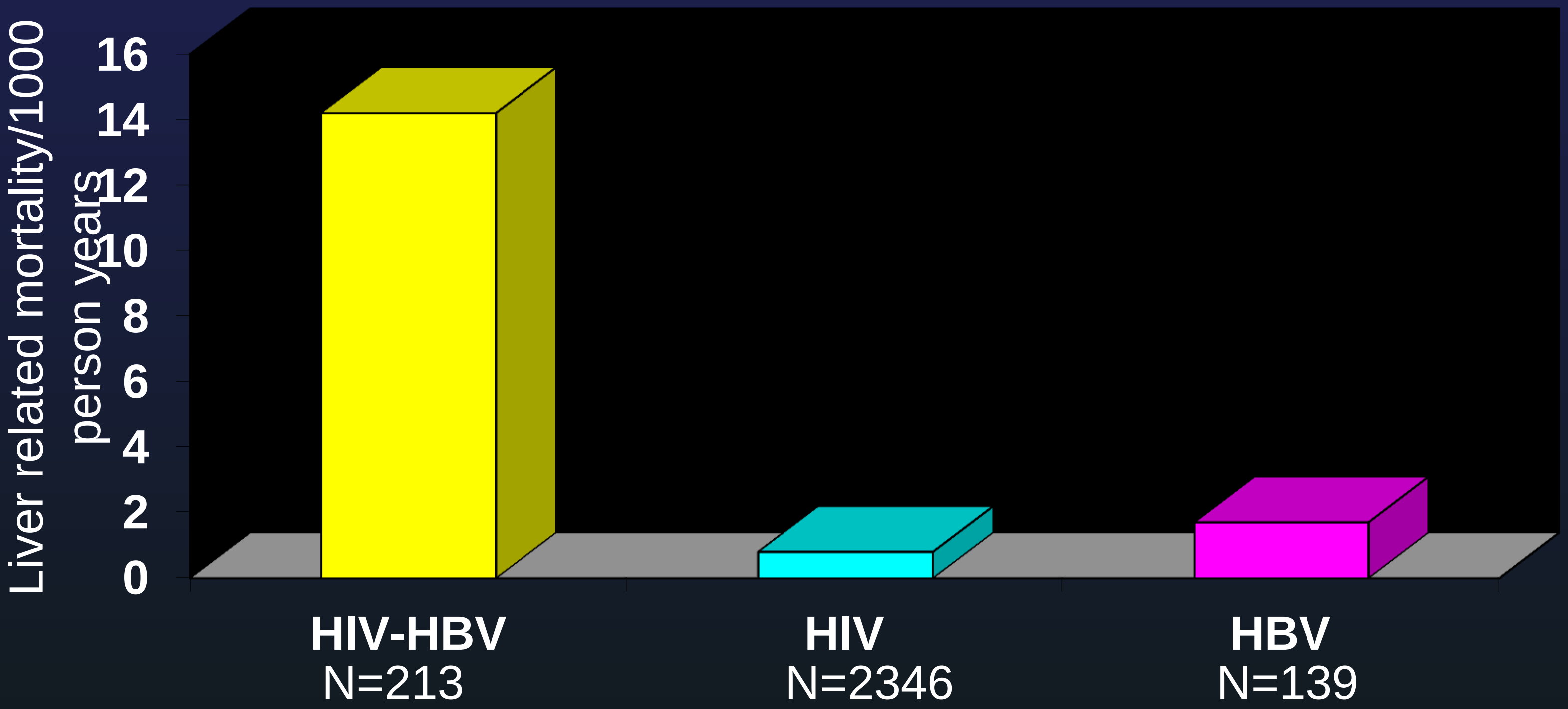
Journal of Viral Hepatitis 2010;17:879-886

Impact of HIV on HBV

- Less likely to resolve acute HBV infection
  - Bodsworth et al. JID 1991;163:1138
  - Gilson et al. AIDS 1997;11:567
- Increased chance of reactivation and flares
  - Vento et al. Lancet 1989;2:108
  - Lazizi et al. JID 1988;158:666
- Immune reconstitution syndrome
- Increased HBV DNA
  - Colin et al. Hepatology 1999;29:1306
- Increased risk of cirrhosis
  - Thio et al. Lancet 2002;360:1921
- Increased overall mortality (even with HAART)
  - Thio et al. Lancet 2002;360:1921
  - Nikolopoulos et al. CID 2009;48:1763-71
  - Hoffmann CJ et al. AIDS 2009;23:1881-1889

HIV negatively impacts on HBV
Multicenter AIDS Cohort Study

- 5293 men



Highest with lower nadir CD4
Higher after 1996 (HAART)

Thio et al. Lancet 2002

Factors associated with Death

Factor	Adjusted RR	95% CI
Age (per 5 yrs)	1.16	1.09-1.24
IVDU (MSM reference)	5.02	3.56-7.08
HTN	2.34	1.83-2.99
Diabetes	2.37	1.68-3.35
HCV	1.67	1.21-2.31
HBV	2.37	1.74-3.22
CD4 count/50 cell increase	0.82	0.79-0.85
HIV RNA >100,000 copies	1.68	1.01-2.80

D:A:D Study AIDS 2010;24:1537-1548

Liver disease outcomes

- Followed 1990-2008
- Median f/u 3 yrs (IQR 1-6)
- 64/72 (89%) on HBV-active HAART
- 7 developed cirrhosis
  - 3 died
  - 2 with HCC had negative HBV DNA and HIV RNA

N= 72	Yes (n=7)	No (n=65)	p
Baseline ALT	105	52	.002
HBV DNA negative %	57	45	0.7
HBeAg negative%	33	16	0.4
HCV+ %	28	8	0.1
CD4 nadir	80	176	0.2
ART duration (yrs)	2.8	1.7	0.2

Lee et al. HIV Clin Trials 2009

Comparison of HBV and HIV-HBV Co-infected Patients: Analysis of the HBRN Screening Log

- As of 9/17/2012, 5966 HBsAg positive adult patients (age >18) who attended clinics were screened.
- Demographic and the most recent clinical and laboratory data were collected. Although some laboratory data were current from the day of the clinic visit, many such as HBV DNA and HBV serology results were usually from the prior clinical assessment.
- Those with HIV co-infection were compared to those with HBV alone.

HepatitisB Research Network

Sterling et al
Unpublsihed

Results

- Patient characteristics of the screened patients were as follows:
  - 1491 (72%) HBeAg positive (missing 610)
  - 2469 (41%) female
  - 69.2% Asian, 17.2% White, 12.3% Black, and 1.3% other (self-reported race information missing on 246 patients)
  - median age was 47 years
  - Of the 5957 patients with information on HIV status, 149 (2.5%) were HIV positive.

Results: HIV-HBV Patients (n=149)

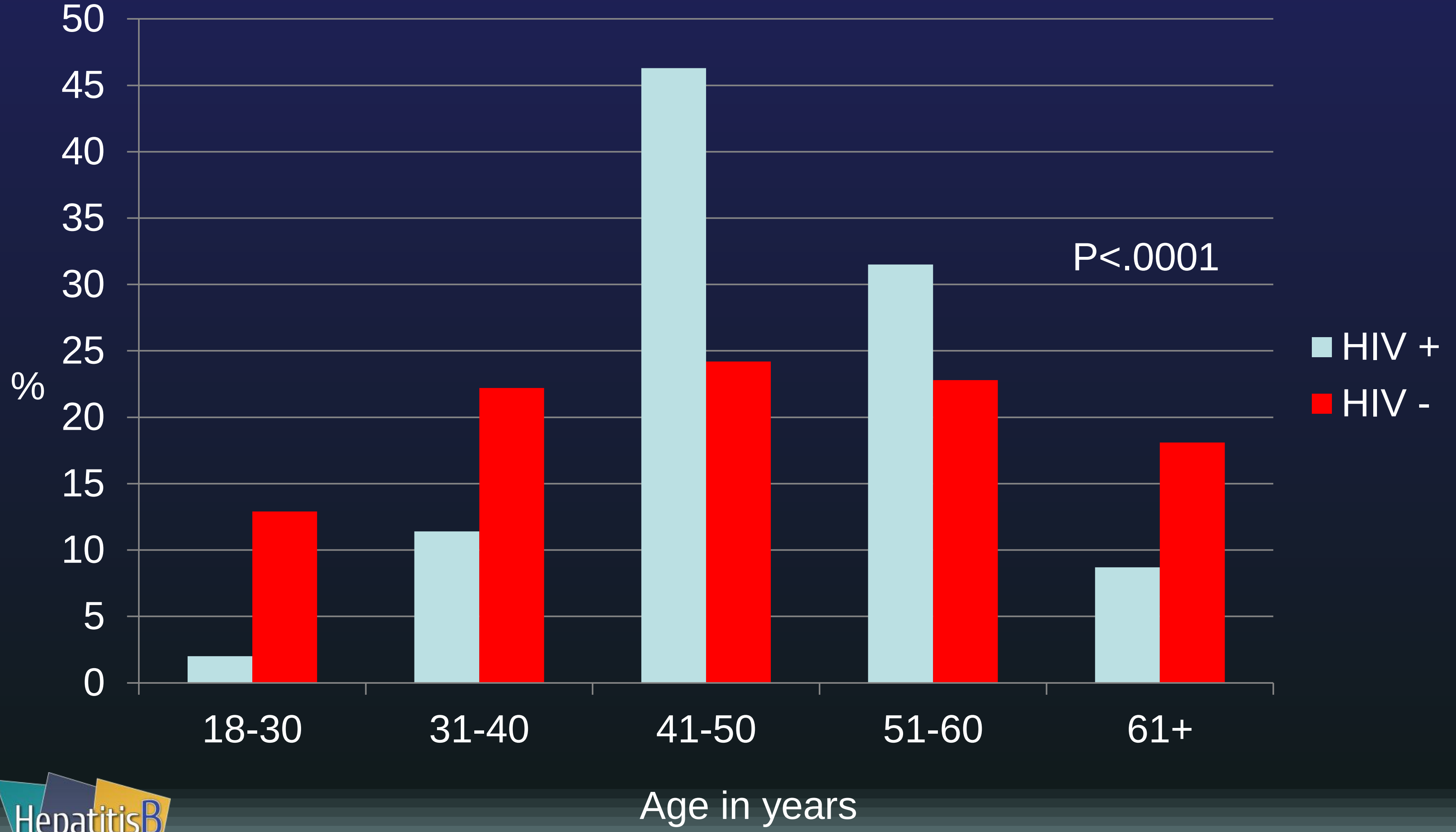
Characteristic	n	%
Sex (male/female)	135/14	90.6/9.4
Race (White/Black/Asian)	82/52/7	57.3/36.4/4.9
Age at screen (years)		
18-30	3	2.0
31-40	17	11.4
41-50	69	46.3
51-60	47	31.5
>61	13	8.7
HBeAg (+/-)	81/55	59.6/40.4

HepatitisB Research Network

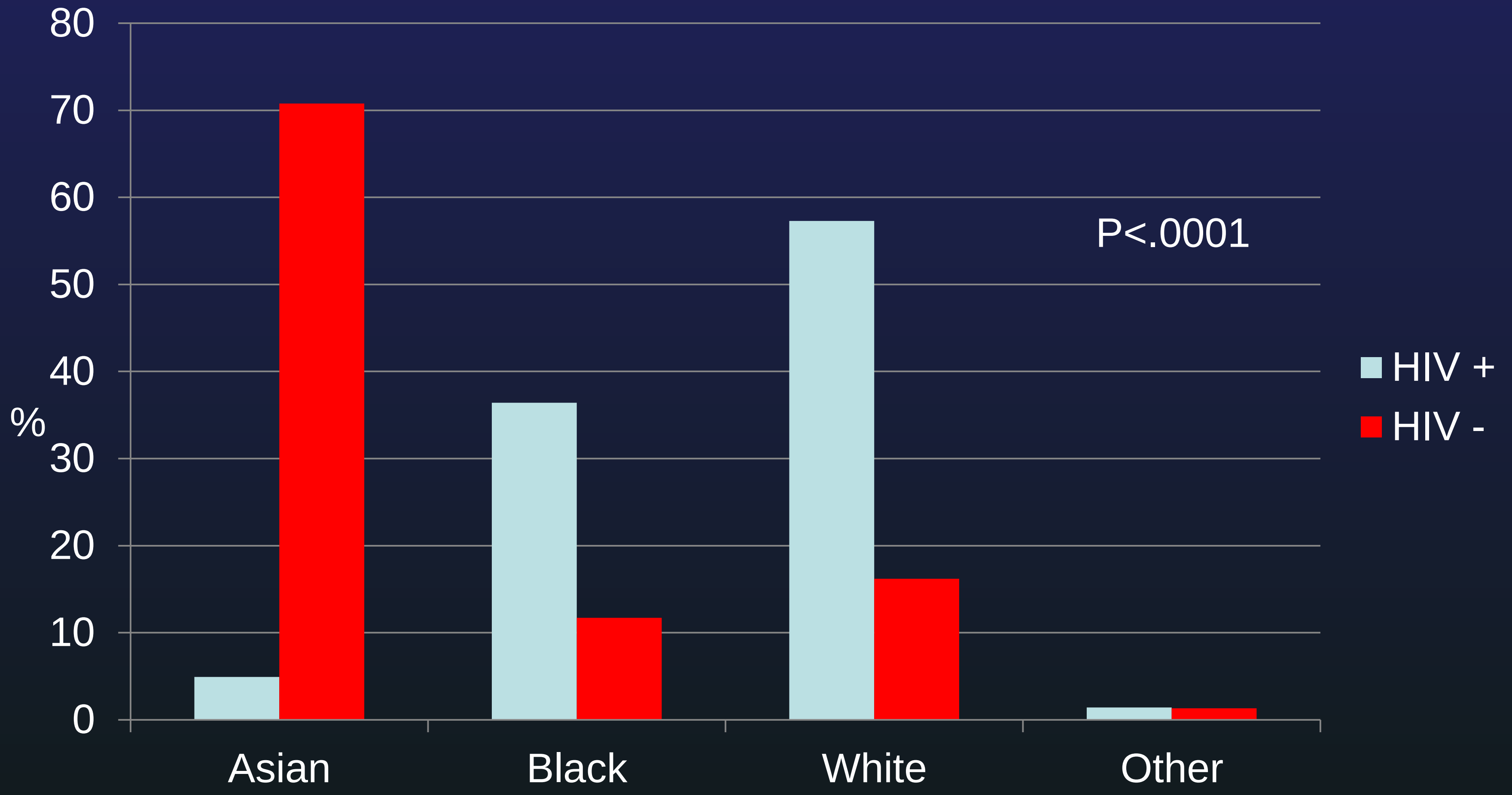
Comparing HIV+ to HIV -

Characteristics	HIV Positive (n=149)	HIV Negative (n=5808)	p
Age [years, median (25th, 75th)]	49 (44, 54)	47 (36, 57)	0.059
Male (n, %)	135 (90.6)	3358 (57.8)	<0.0001
ALT [IU/L, median (25th, 75th)]	36.5 (24.0, 61.0)	30.0 (21, 45)	0.001
HBeAg positive (n, %)	81 (59.6)	1407 (27.0)	<0.0001
HBV DNA negative (n, %)	68 (50.4)	1696 (33.4)	<0.0001
On anti-HBV Rx (n, %)	117 (78.5)	2337(40.3)	<0.0001
History of HCC (n, %)	2 (1.3)	160 (2.8)	0.44
History of decompensation (n, %)	15 (10.1)	144(2.5)	0.001
History of liver transplantation (n, %)	0 (0)	51 (0.8)	0.64

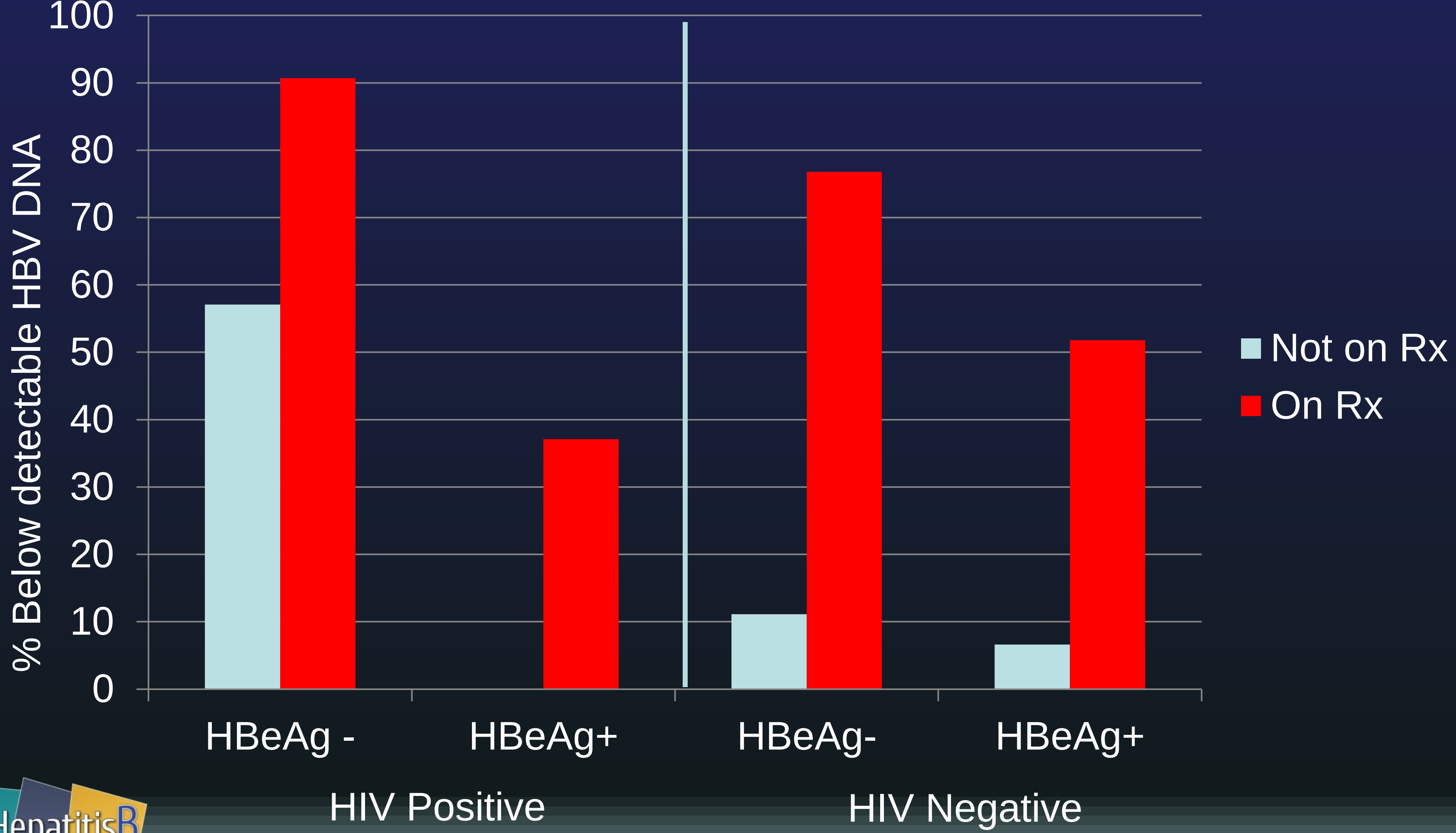
Age Distribution by HIV Status



Race Distribution by HIV Status



HBV DNA Status by HIV Status and HBV Treatment Status



Predictors of Histology

	All (n=53)	Stage 0-2 (n=22)	Stage 3-4 (n=31)	p
Age	42(10)	43(9)	41(10)	.63
Gender (% male)	96	100	90	.26
Race (%W/AA/O)	64/30/6	64/18/18	61/39/0	.03
ART (%)	66	45	81	.02
HBV Rx				.11
TDF/FTC	32	32	32	
TDF	9	0	16	
LAM	28	23	32	
HBeAg + (%)	62	59	65	.76
HDV + (%)	6	9	3	1.0
HIV Stage (% A/B/C)	57/9/34	79/0/21	43/14/43	.14
HIV RNA undetectable (%)	63	46	74	.15

HIV-HBV Research Network; EASL 2013

Predictors of Histology

	All (n=53)	Stage 0-2 (n=22)	Stage 3-4 (n=31)	p
CD4	420(288)	496(368)	389(284)	.08
AST	52(68)	47(30)	65(131)	.08
ALT	57(73)	54(48)	65(106)	.35
APRI	0.8(1.2)	0.5(.9)	1.2(1.5)	.02
FIB-4	1.8(1.5)	1.7(1.0)	1.9(2.8)	.16
HBV DNA < 1000 IU/ml	16(35)	5(23)	11(39)	.53
HBV DNA undetectable	14(30)	5(28)	9(32)	.51
HIV RNA negative	20(63)	6(46)	14(74)	.15

HIV-HBV Research Network; EASL 2013

Treatment of HBV in the setting of HIV Treatment Candidates

- Active infection (S Ag +)
  - + E Ag or HBV DNA $\geq$ 20,000 IU/ml
  - Necroinflammation / elevated ALT
  - True HBV DNA cut off not known
  - Cirrhosis (detectable HBV DNA)
- Compliant
- Need to decide which virus needs treatment: HBV, HIV, or both

Goals of therapy

- Overall goals
  - Loss of active replication
    - E Ag seroconversion
    - Loss of HBV DNA
  - Improve necroinflammation
  - Reduce liver related mortality
- Goals unique to those with HIV
  - Reduce ARV hepatotoxicity
  - No interference with HIV therapy

Treatment Options

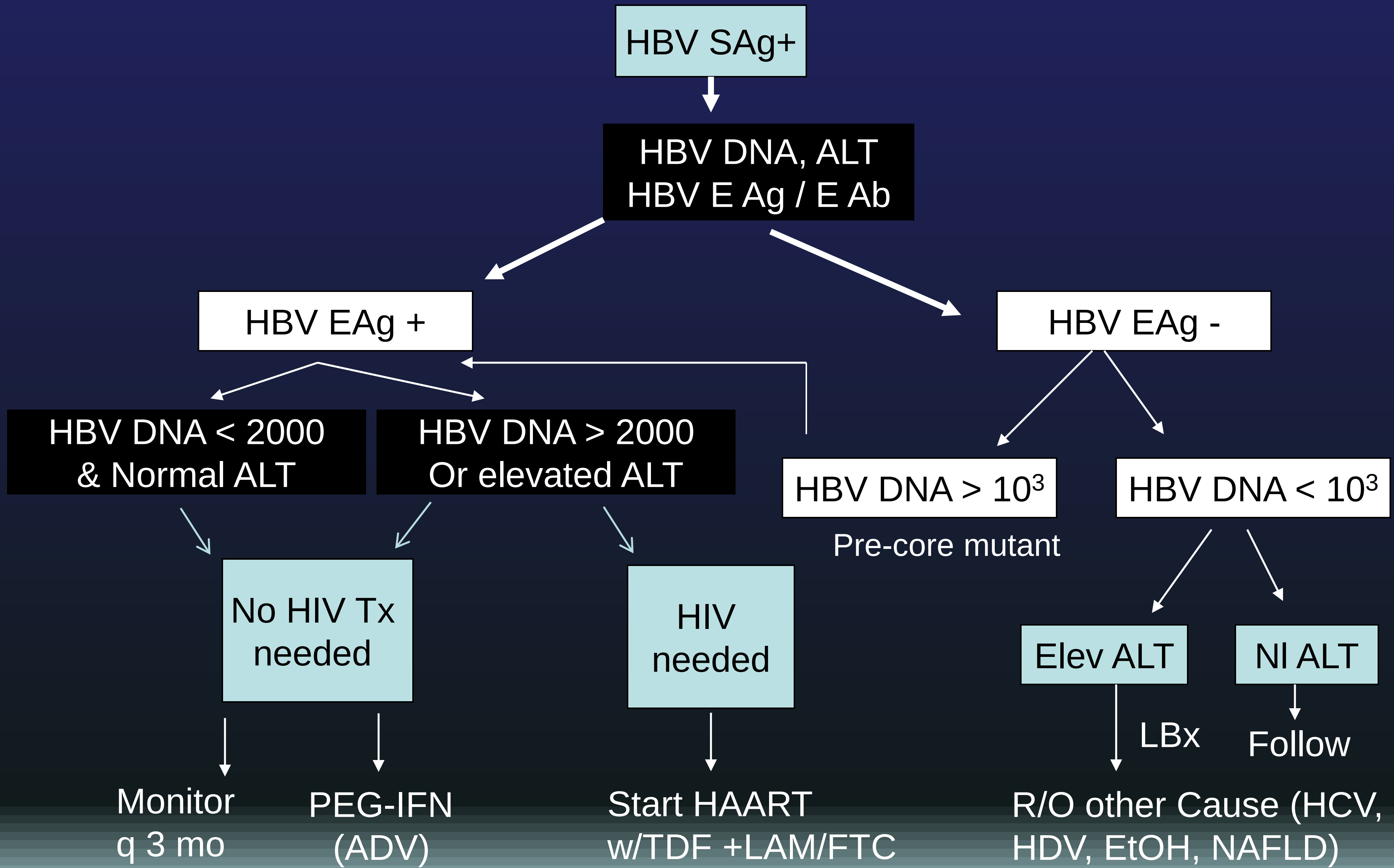
Drug	HBV	HIV
Interferon	Yes	No
Lamivudine	Yes	Yes
Tenofovir	Yes	Yes
Emtricitabine	Yes	Yes
Adefovir	Yes	No
Entectavir	Yes	No (?)

Treatment Decisions

Virus needing treatment	Preferred regimen	Drugs to avoid
HBV only	PEG-IFN Adefovir (?)	Monotherapy with LAM, FTC, TDF, Ent
HIV only	Consider reserving LAM, FTC, TDF	Use of LAM, FTC, or TDF as only anti-HBV Rx in HAART
HIV and HBV		
Naïve to LAM	TDF and FTC or LAM	Use of LAM, FTC, or TDF as only anti-HBV Rx in HAART
Prior LAM	TDF and FTC Entecavir (higher dose)	

Modified from CL Thio. Current Hepatitis Reports 2004;3:91-97

Proposed Algorithm HBV-HIV Coinfection



Proposed Algorithm HBV-HIV Coinfection

HBV
& No

NA < 10^3

Nl ALT

Follow

LBx

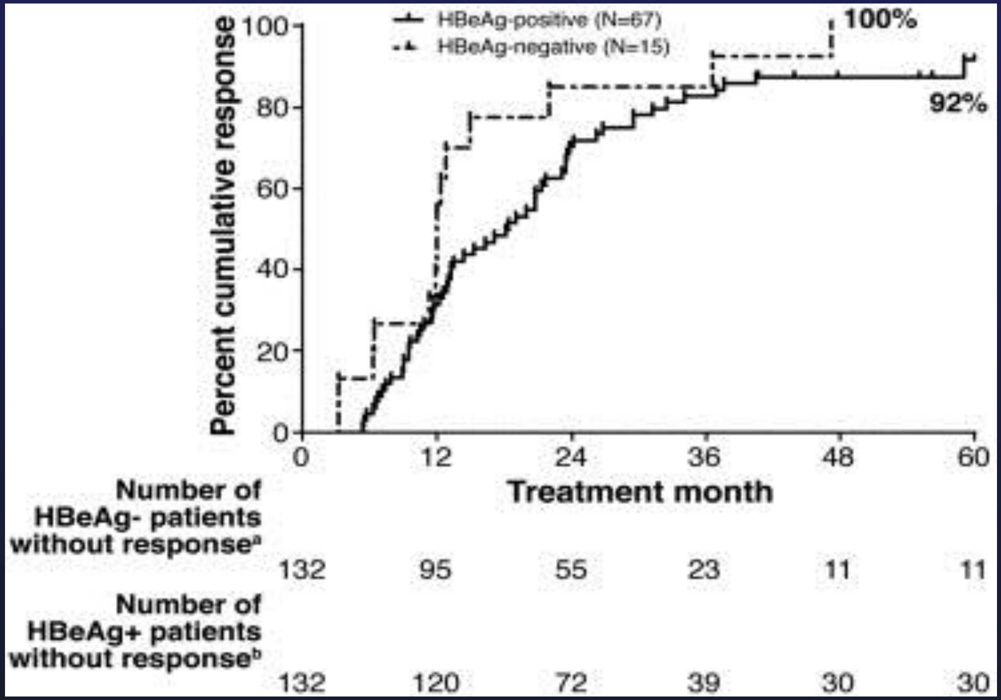
Monitor
q 3 mo

other
se (HCV, HDV)

Treat all coinfected patients with TDF + FTC/LAM based ART regardless of CD4 or HIV RNA

Long-term Therapy With Tenofovir Is Effective for Patients HIV-HBV Co-Infected based HBeAg status

82 HBV DNA+
66% Caucasian
15% cirrhosis
CD4 285
HBeAg+ 82%



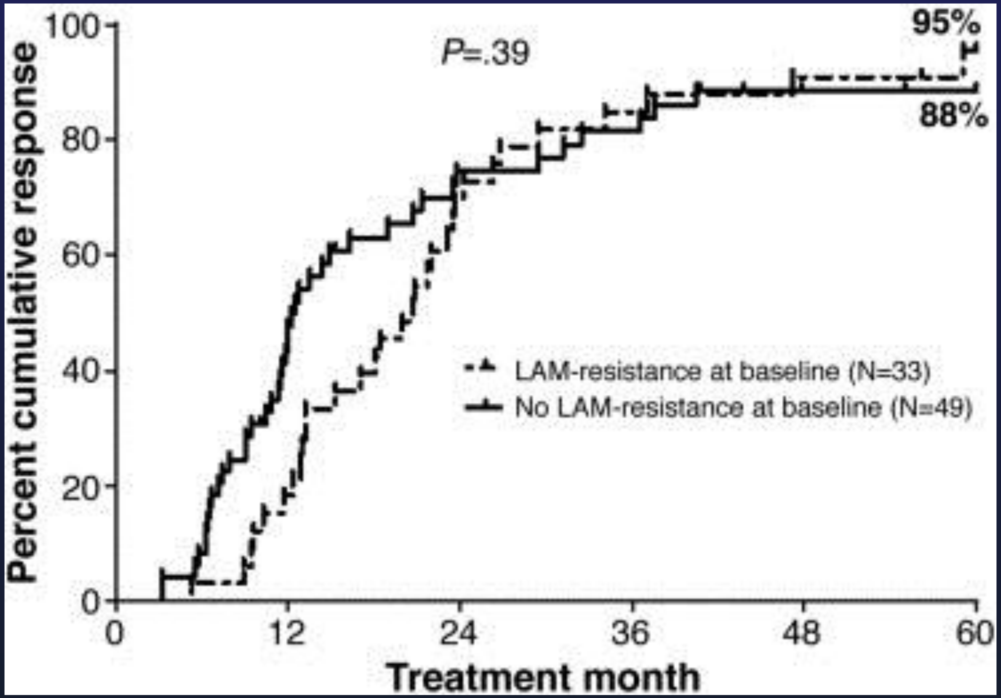
Non-response
- 13% eAg+
- 7% eAg -

Kaplan-Meier curve for the cumulative probabilities of achieving virologic response, defined as HBV-DNA levels less than 20 IU/mL, for HBeAg-positive (n = 67) and HBeAg-negative (n = 15) HIV/HBV with patients with detectable HBV DNA at baseline (n=82)

Theodora E.M.S. de Vries-Sluijs et al

Gastroenterology Volume 139, Issue 6 2010 1934 - 1941

Long-term Therapy With Tenofovir Is Effective for Patients HIV-HBV Co-Infected based LAM Resistance



Kaplan-Meier curve for the cumulative probabilities of achieving virologic response, defined as HBV-DNA levels less than 20 IU/mL, for HIV/HBV patients with detectable HBV DNA at baseline (n = 82) with (n=33) or without (n=49) lamivudine-resistant at initiation of TDF

Summary of TDF for HBV in HIV

	Lada	Miailhes	Sheng	Mathews	Piroth	De Vries	Martin-Carbonero
Year	2011	2007	2007	2009	2010	2010	2010
N	61	92	119	122	180	102	92
CD4	290-381	303	125	438	401	300	
% HCV/HDV	10/13	13/0	9/0	0/0	>12%/0	0/0	0/20
F/U (yrs)	5	5	5.2	2	3.5	4.5	3
% HBV DNA negative on Rx	82-100			30 TDF 77 TDF/FTC	87	92-100	89
%HBeAg loss					4.3/yr	10/yr	9/yr
% HBeAb seroconversion	4.4/yr	3.4/yr			0.9/yr		2.6/yr

Patient Evaluation

- History and Physical
  - Attention to signs/symptoms of advanced fibrosis
- Laboratory testing
  - Viral tests (HBV DNA, HBeAg/Ab, genotype?)
  - HCV, HDV, HAV
  - Liver chemistries, prothrombin time
  - CBC with platelets
  - In those with chronic HBV (sAg+)
    - Ultrasound +/- AFP (HCC screening)
    - Consider Liver biopsy

Recommendations to Patients

- Avoid alcohol
- Hepatitis A vaccination (if anti-HAV neg)
- Counsel on sexual transmission
- Test all household contacts
  - Vaccinate if negative
- Cover open cuts
- Clean up blood spills with bleach
- Perinatal counseling
  - HBIG and vaccinate newborn
- Avoid raw shellfish/seafood (vibrio)

Unresolved Issues in HIV-HBV

- Role of liver biopsy
- Noninvasive assessments of disease severity
- Incomplete responders
- Use of novel assays (qHBsAg)
- Isolated core antibody
- Long-term effects of TDF (renal and bone)
- Liver transplantation

Thank you for your attention

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