HBV Diagnosis and Treatment

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Outline

- Diagnosis of HBV
  - HBV markers: old and new
- Treatment
  - Efficacy and limitations of available therapies
  - Indications: when to start
  - Which drug
  - When to stop

Serological Markers of HBV Infection

HBsAg	Acute/chronic infection
Anti-HBc IgM	Recent infection
HBeAg	High infectivity
Anti-HBe	Low infectivity
Anti-HBs	Immunity
Anti-HBc IgG + HBsAg	Chronic infection
Anti-HBc IgG + anti-HBs	Resolved infection

Screening for HBV infection: HBsAg and anti-HBs +/- anti-HBc IgG

Interpretation of HBV Serology

HBsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	Interpretation
–	–	–	–	Not been exposed
+	+	–	–	Chronic infection
+	+	+	–	Acute Infection
–	+	–	+	Immunity from past infection
–	–	–	+	Immunity after vaccination
–	+	–	–	Occult / past HBV infection

Concurrent HBsAg and Anti-HBs

- **Prevalence**
  - **5%-60%**
  - **6.6% in NIH-funded Hepatitis B Research Network (HBRN)**
- **Clinical characteristics**
  - **No differences in country of birth, modes of transmission, AST, ALT, HBeAg, HBV DNA, HBV genotype; but lower HBsAg level**
  - **Anti-HBs not neutralizing, management as for other chronic HBV patients who are anti-HBs-**

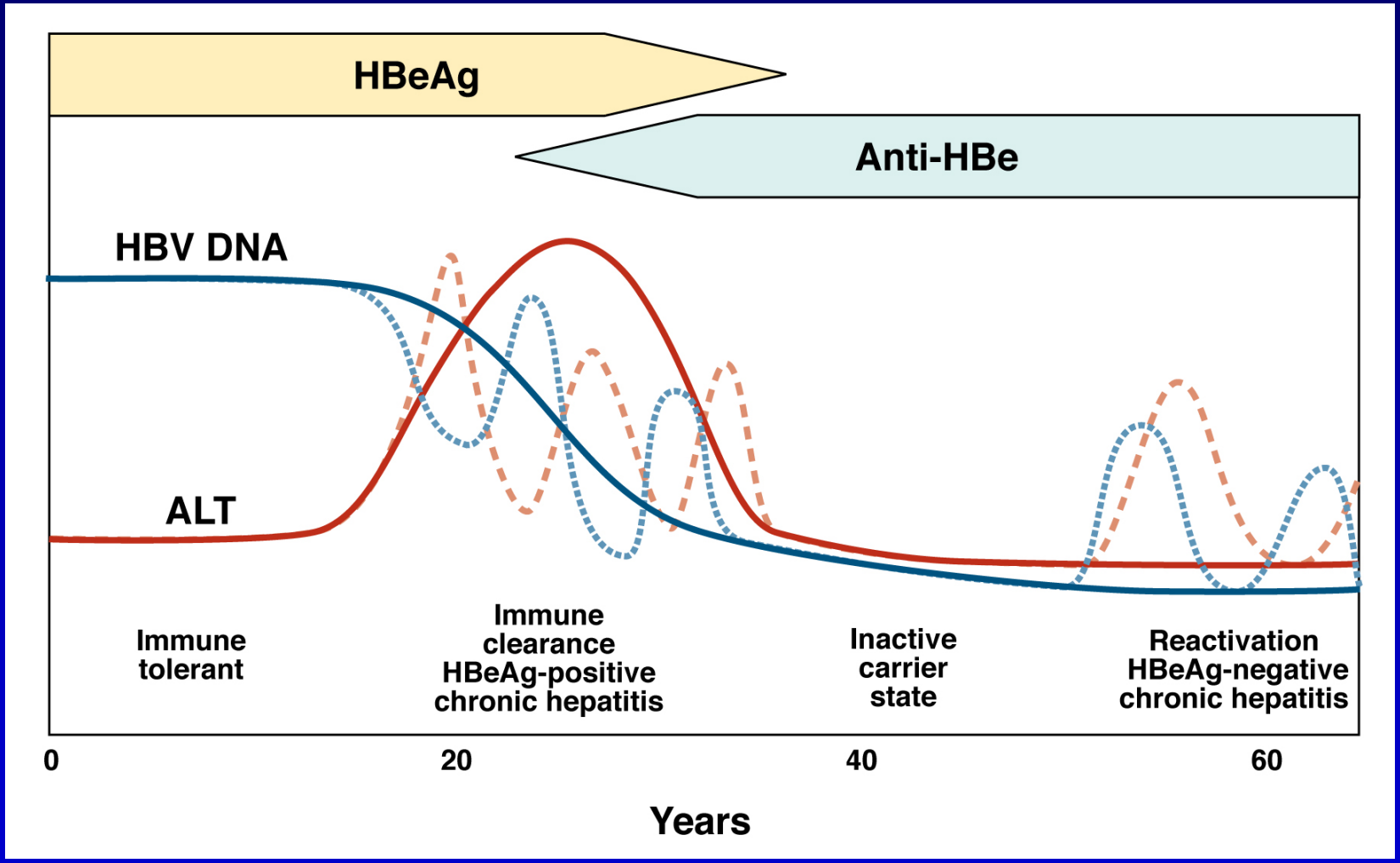
Isolated Anti-HBc+ (HBsAg-, anti-HBs-)

- Most common scenario: past HBV with spontaneous loss of HBsAg, particularly in
  - Persons from endemic areas
  - Persons with risk factors for HBV
    - Risk behaviors
    - HCV or HIV infection
- HBV DNA
  - Usually not detected in serum except for those who are HIV+
  - Often detected in liver

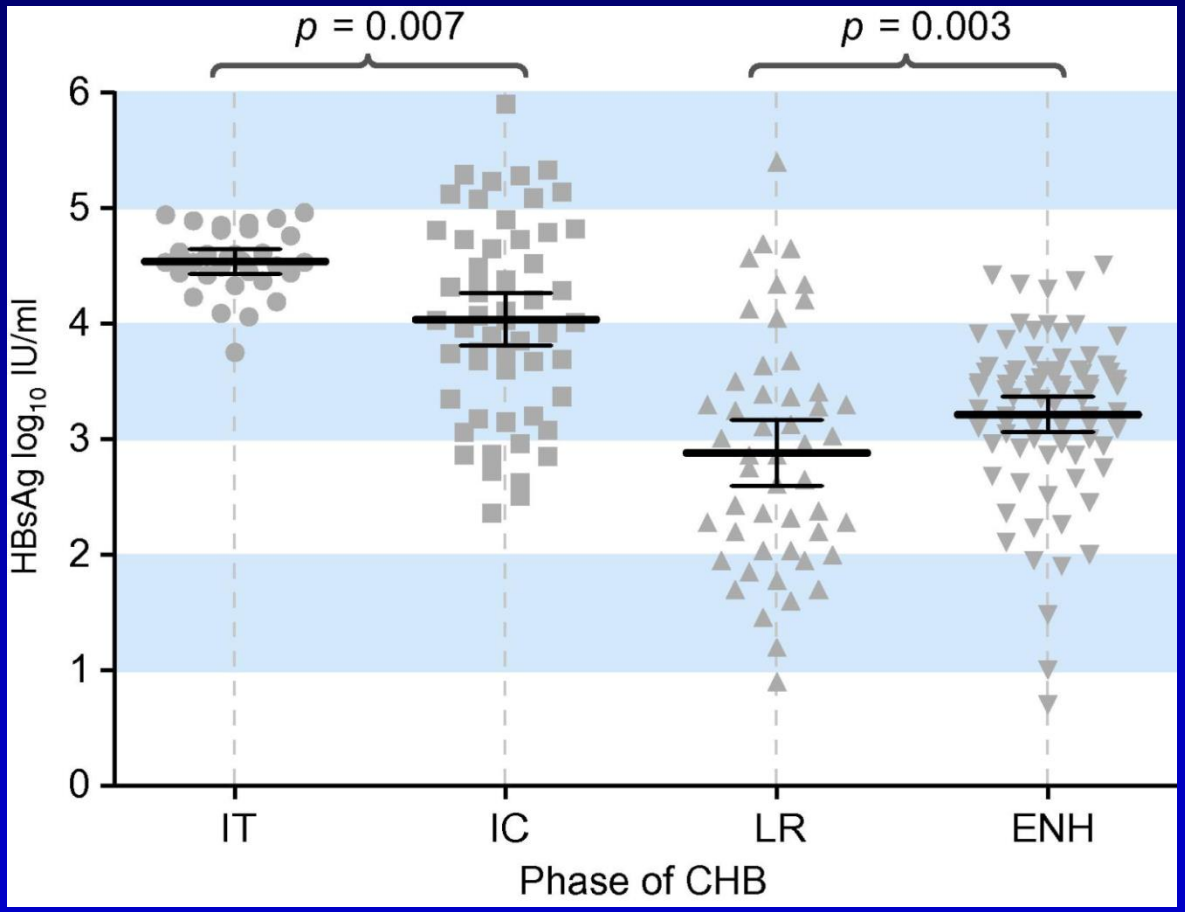
Isolated Anti-HBc+ / Occult HBV

- Potential clinical implications
  - Antiviral treatment not indicated
  - HBV vaccine not necessary
  - Underlying liver damage may be present if chronically infected for decades before HBsAg loss
  - Risk of hepatocellular carcinoma may be increased compared to anti-HBc- persons
  - HBV reactivation with reappearance of HBsAg may occur during potent immunosuppressive therapy

Phases of Chronic HBV Infection



HBsAg Levels during Different Phases of Chronic HBV Infection



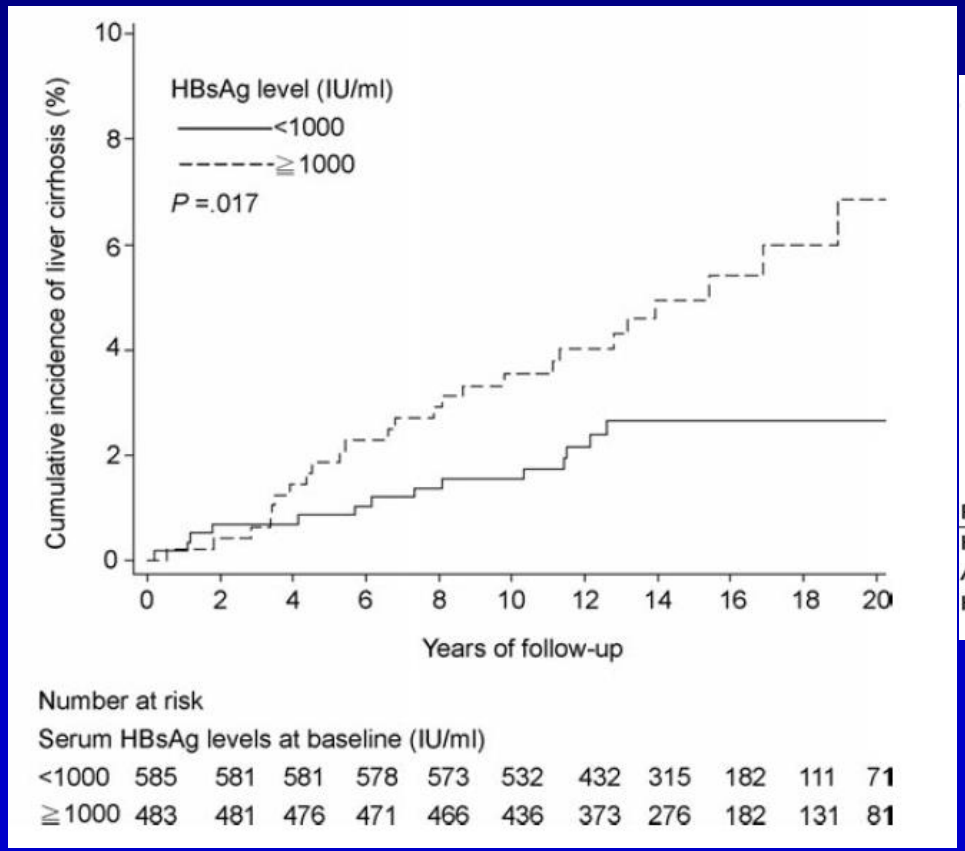
- HBV produces excess S proteins; subviral particles outnumber complete virions >1000:1
- HBsAg levels lowest in inactive carriers, correlate with cccDNA and immune control of HBV

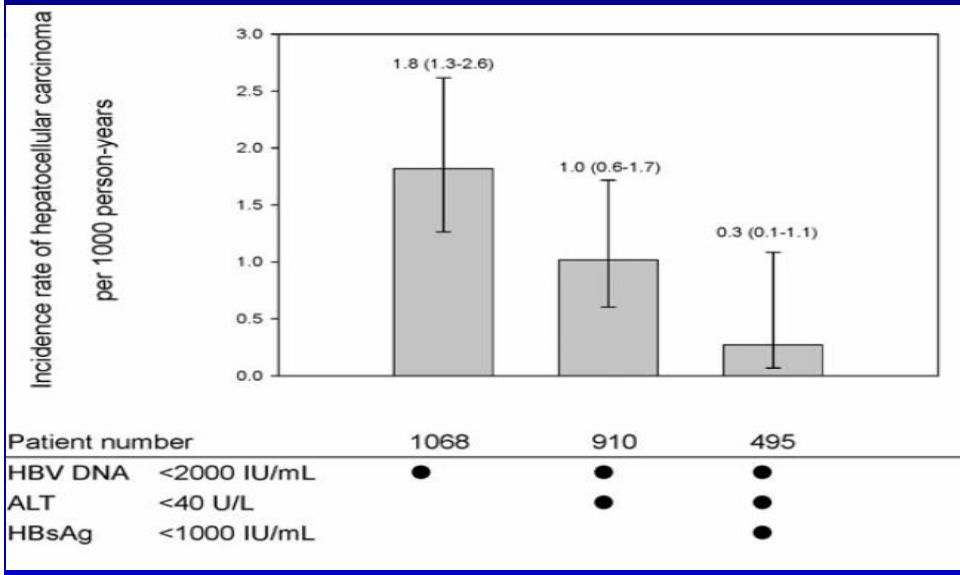
220 patients
IT = immune tolerance, IC = immune clearance
LR = inactive carrier, ENH = HBeAg- chronic hepatitis

Nguyen T, J Hepatol 2010; 52: 508

HBsAg Levels Predict Disease Progression in HBeAg- Patients with Low HBV-DNA Levels

1068 Taiwanese HBeAg- persons with HBV DNA <2000 IU/mL followed for a mean of 13.0 years





Tseng T, Hepatology 2013;57:441

HBV Genotypes

- A-J, difference in geographical distribution
- B/C most common in the US followed by A, D, & E
- Genotype C associated with delayed spontaneous HBeAg seroconversion
- Genotype C (F) associated with increased risk of HCC
- Genotype A associated with highest rate of interferon-related HBeAg and HBsAg loss
- No impact on response to nucleos(t)ide analogue therapy
- Testing not clinically indicated except for patients in whom treatment is indicated and are potential candidates for interferon therapy

HBV Precore and Core Promoter Variants

- Abolish or decrease HBeAg production, but HBV replication and HBcAg expression not affected
- Present in most patients with HBeAg- chronic hepatitis
- Geographical distribution related to HBV genotype
- Precore variant most common in genotypes D, B, C, rarely A
- Core promoter variant less genotype-specific, most common in genotype C
- Testing not indicated in most clinical settings

AASLD Guidelines for HCC Surveillance

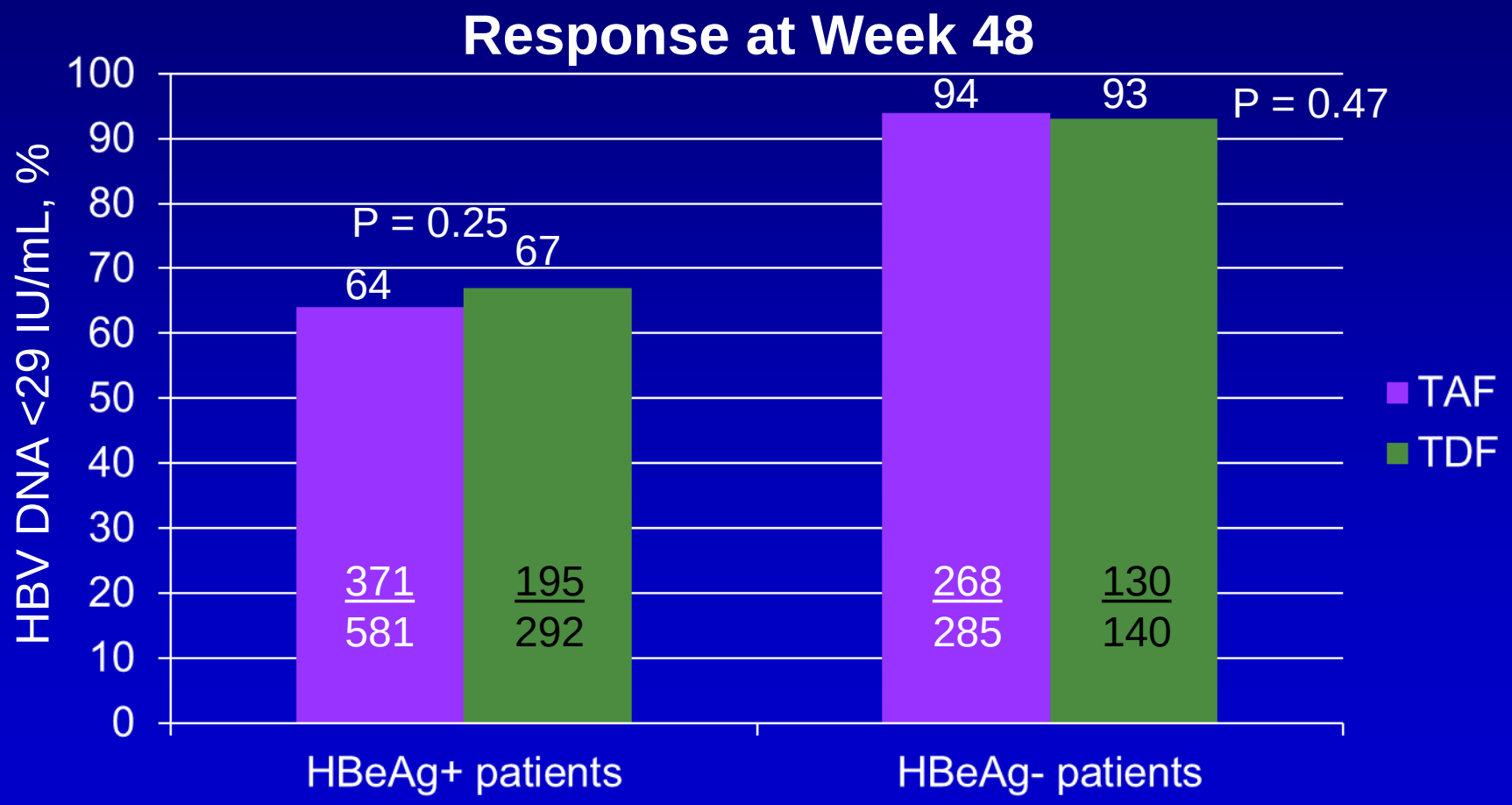
- **2017 guidelines**
  - **Who: adults with cirrhosis but not Child C unless on liver transplant waiting list**
  - **How: Ultrasound ± alpha-fetoprotein (AFP) q 6 months**
- **2005 guidelines for HBsAg+ patients**
  - **Who**
    - **Asian males ≥40, Asian females ≥50, Africans >20**
    - **All patients with cirrhosis**
    - **For noncirrhotics, consider screening if high HBV DNA and ongoing hepatic necroinflammation**
    - **Family history of HCC**
  - **How (2011 update)**
    - **US q 6 months**

Heimbach J, Hepatology 2017 (in press), Bruix J, Hepatology 2005; 42:1208; 2011; 53: 1020

Approved HBV Treatments

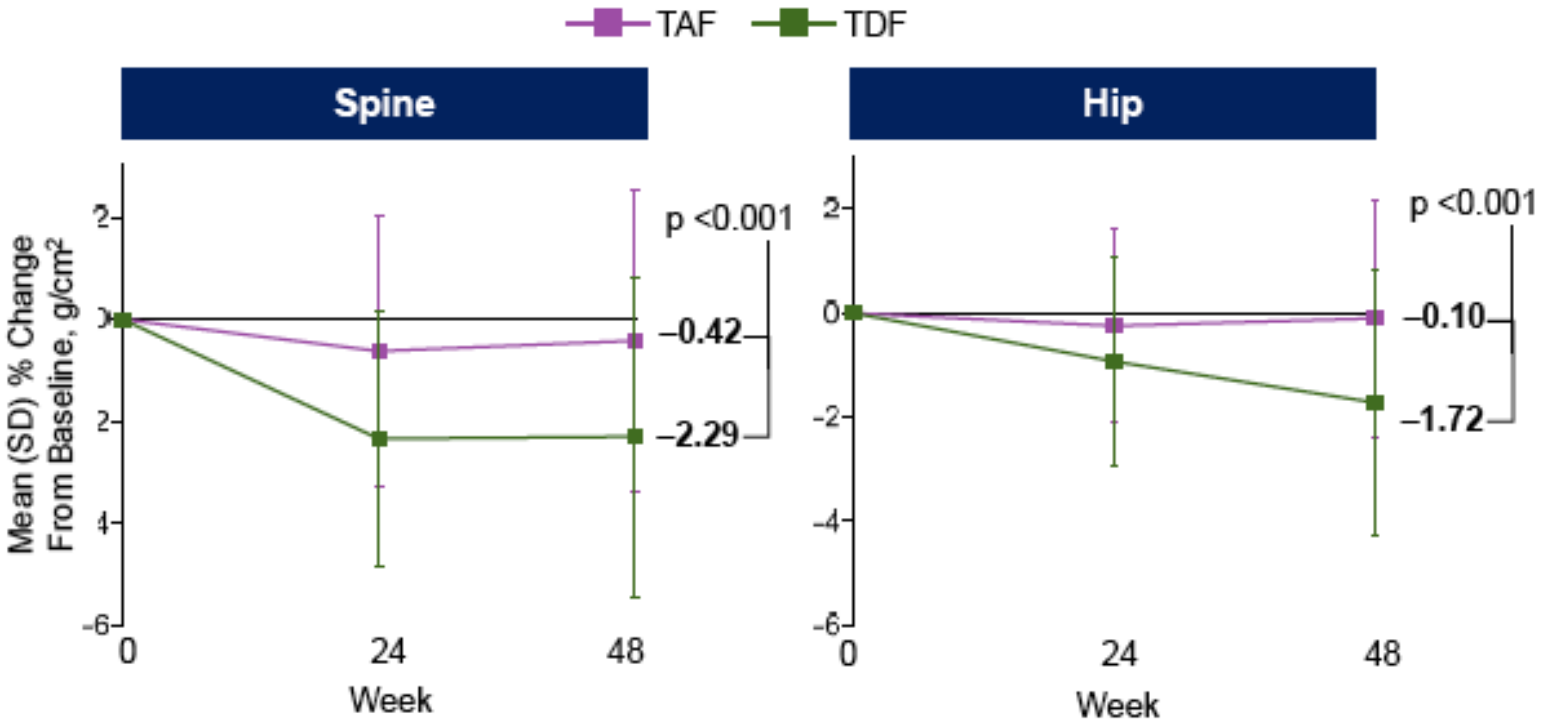
- Interferons (IFN)
  - Standard IFN alfa - 1992
  - Pegylated IFN alfa - 2005
- Nucleos(t)ide analogues
  - Lamivudine - 1998
  - Adefovir - 2002
  - Entecavir - 2005
  - Telbivudine - 2006
  - Tenofovir disoproxil fumarate - 2008
  - Tenofovir alafenamide - 2016

Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF) in HBeAg+ and in HBeAg- Patients



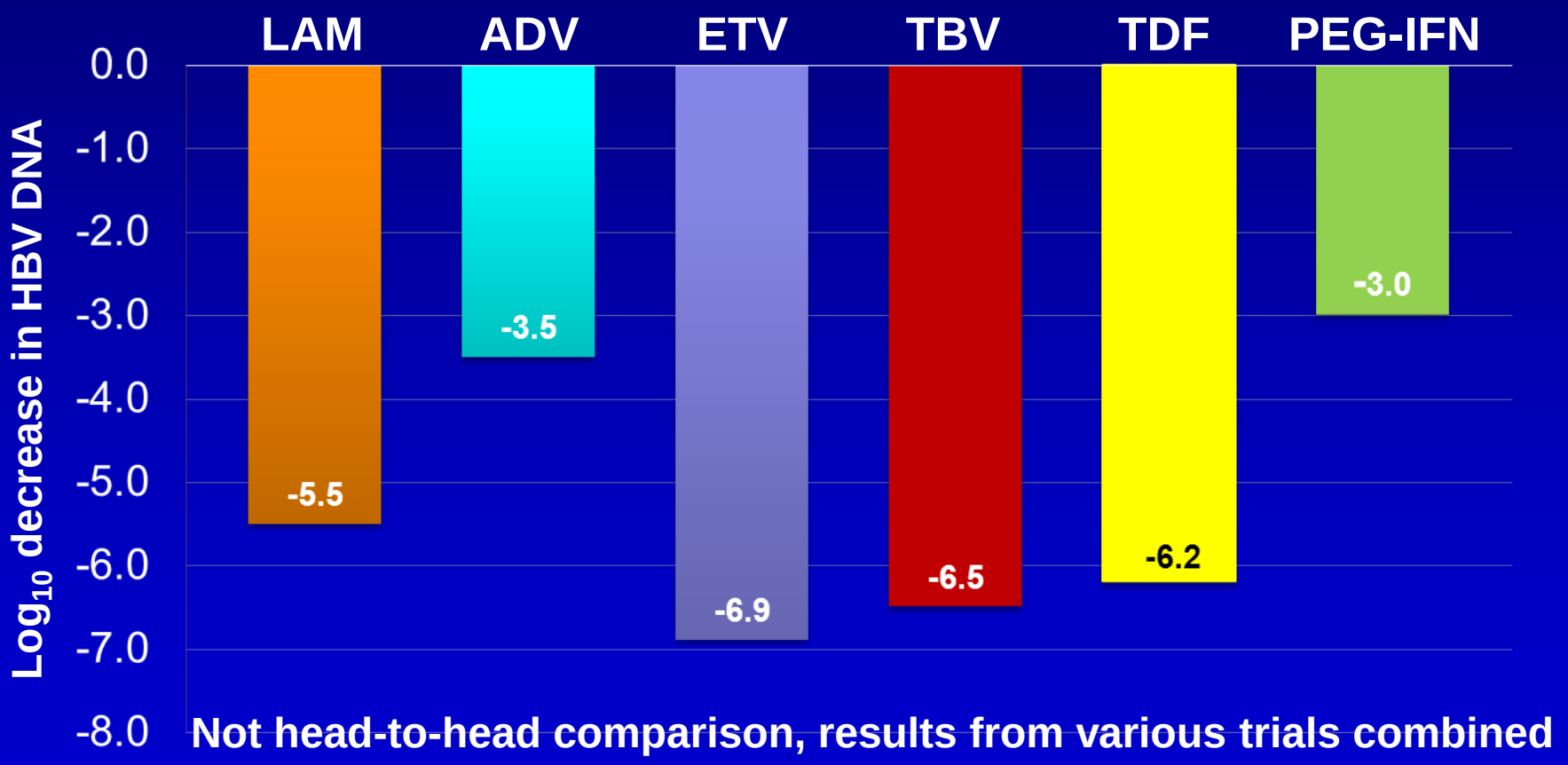
Chan H, Lancet Gastroenterol Hepatol 2016; 1: 185; Buti M, Lancet Gastrotnerol Hepatol 2016; 1: 196

TAF Associated with Less Decrease in Spine and Hip Bone Mineral Density Than TDF



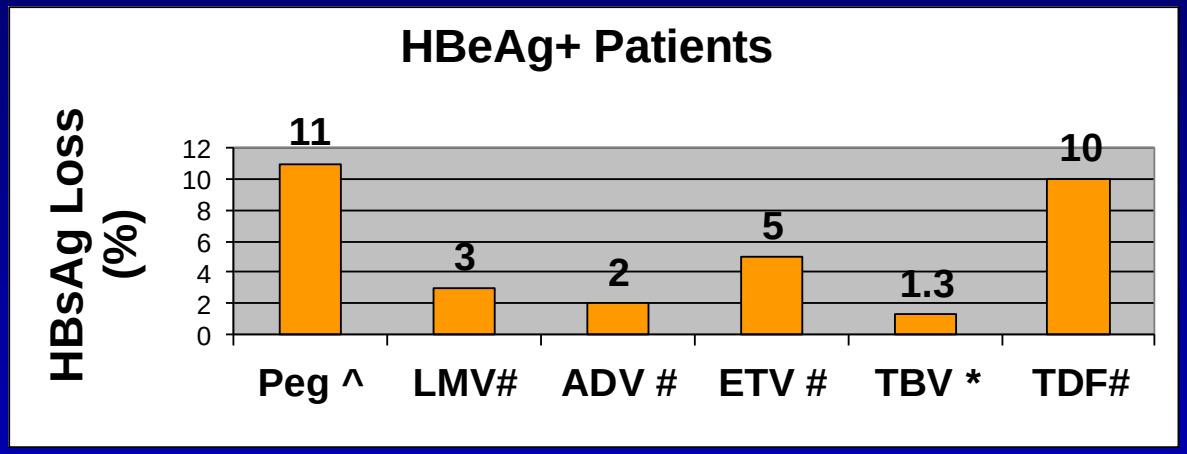
- Fewer TAF patients had >3% decreases in BMD at Week 48
  - Spine: 18% TAF; 38% TDF (p <0.001)
  - Hip: 8% TAF; 24% TDF (p <0.001)

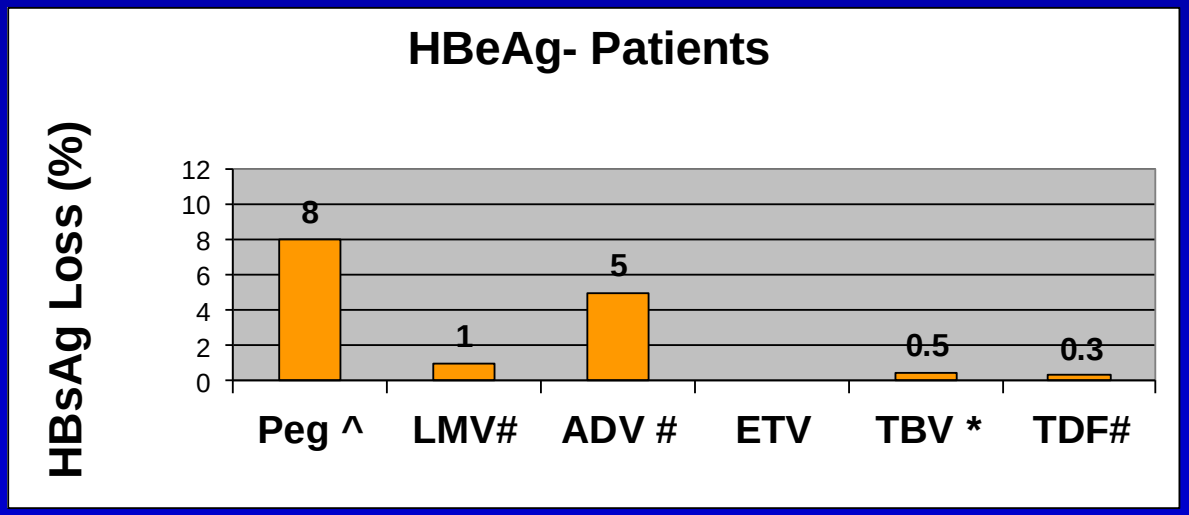
Decrease in Serum HBV DNA after 1 Year of Treatment



LAM=lamivudine, ADV=adefovir, ETV=entecavir, TBV=telbivudine, TDF=tenofovir, PEG-IFN=peginterferon

HBsAg Loss after 2-5 Years of Treatment



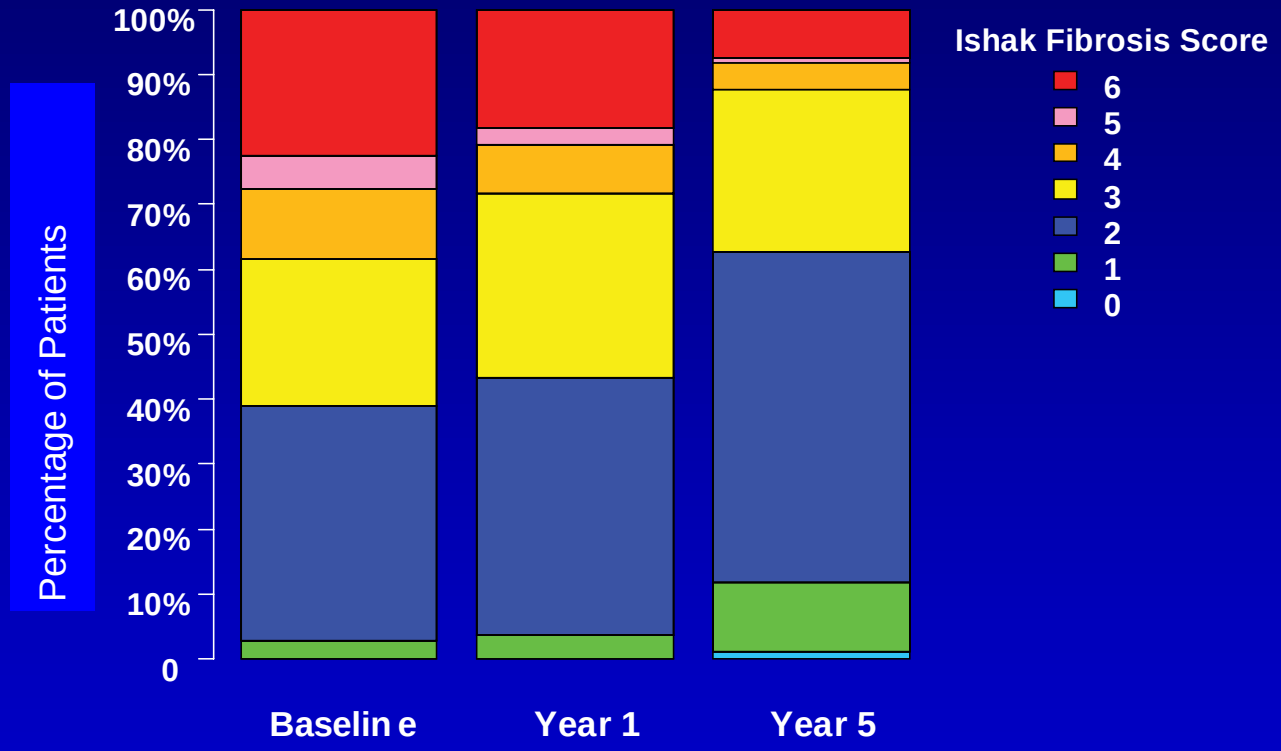


Peg = peginterferon
LMV = lamivudine
ADV = adefovir
ETV = entecavir
TBV = telbivudine
TDF = tenofovir

^ 3 years off Rx
# 4-5 years on Rx
* 2 years on Rx

Reversal of Fibrosis and Cirrhosis

Tenofovir Phase III Trial: Biopsies at Years 0, 1, 5

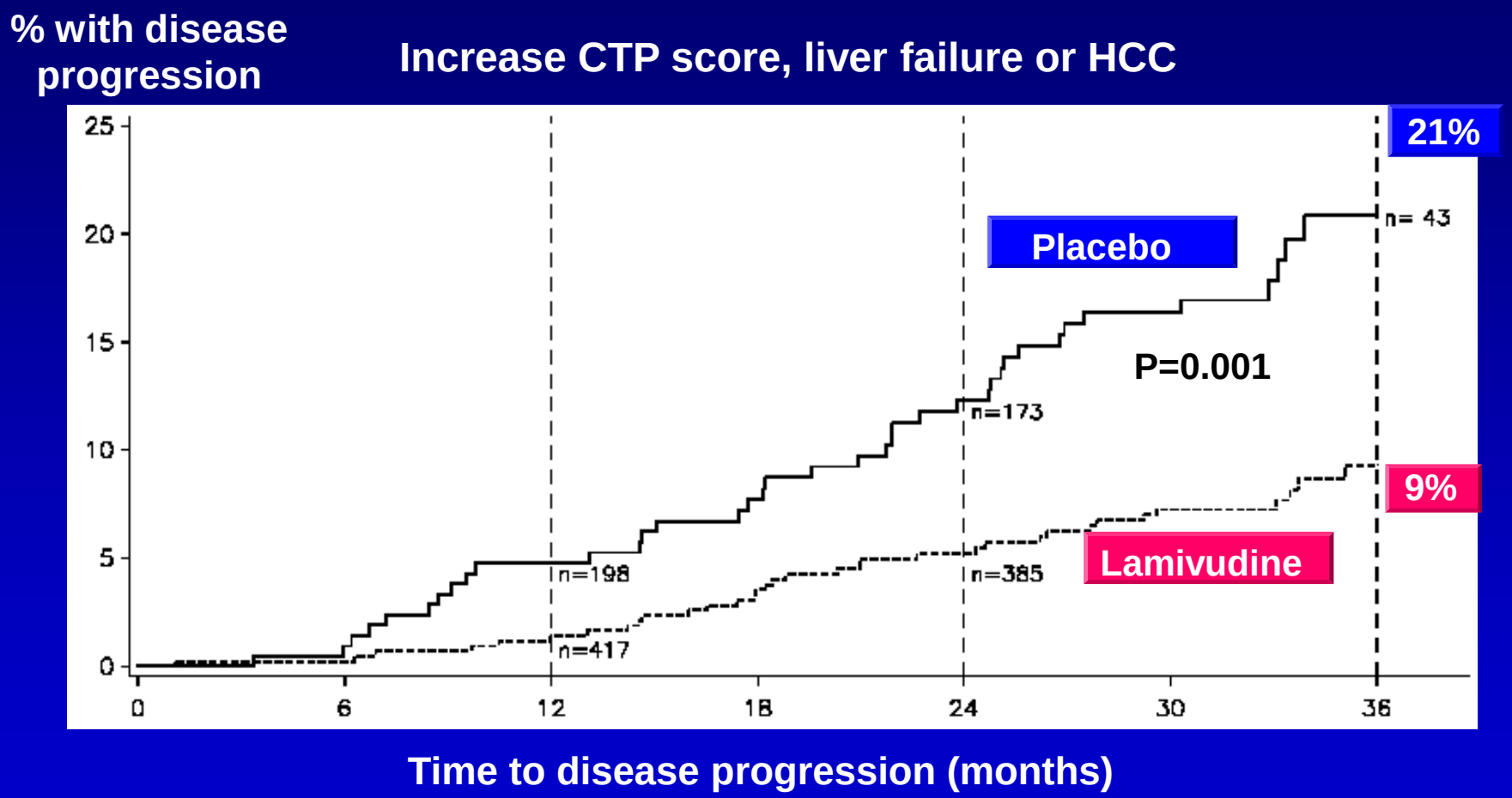


- **348/641 (54%) had liver biopsy at baseline and Year 5**
- **71/96 (74%) with cirrhosis (Ishak Score ≥5) at baseline no longer had cirrhosis at Year 5**

Marcellin, P, Lancet 2013; 381: 468

Antiviral Therapy Prevents Disease Progression

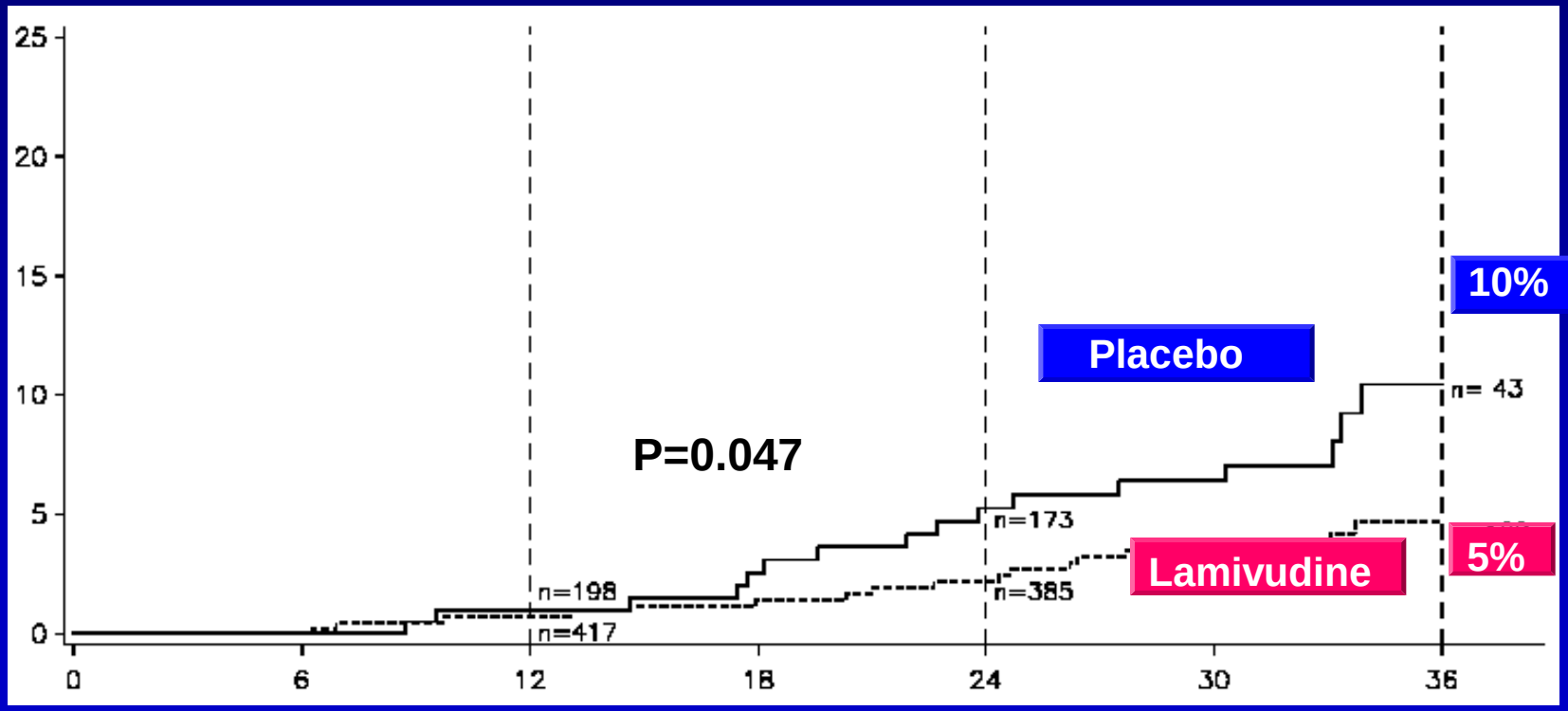
Bridging fibrosis or cirrhosis, HBeAg+ / HBV DNA >700,000 GEq/ml



Liaw YF, NEJM 2004; 351:1521

Antiviral Therapy Decreases Incidence of HCC

651 pts, bridging fibrosis or cirrhosis, HBeAg+ and/or HBV DNA >140,000 IU/mL



Time to diagnosis (months)

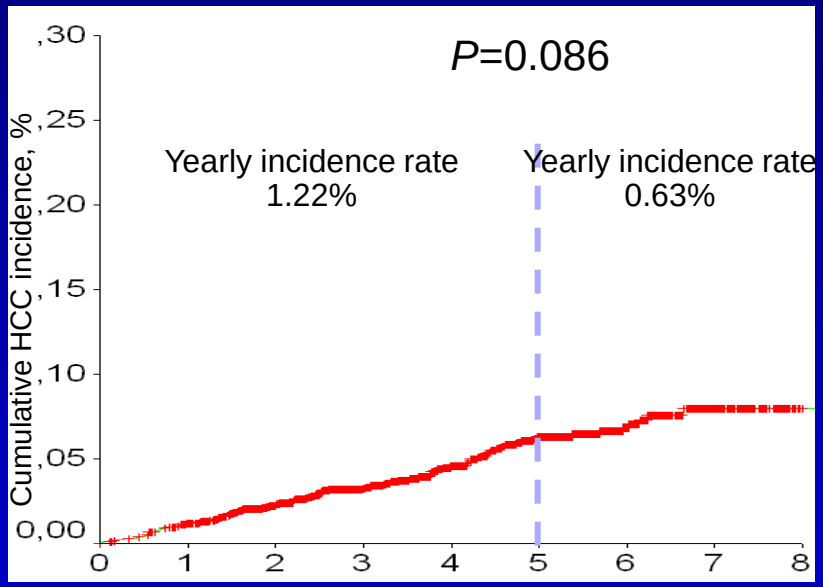
After exclusion of cases in yr 1: HR = 0.47; P = 0.052

Liaw YF, NEJM 2004; 351:1521

Risk of HCC Remains after Five Years of ETV or TDF Therapy in Caucasian CHB Patients

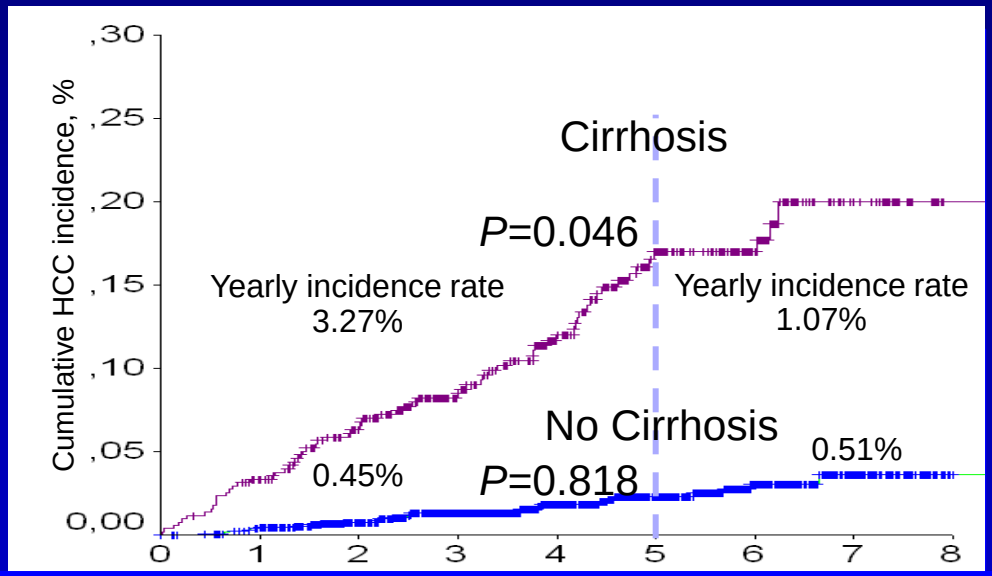
794 adult Caucasian CHB patients

Cumulative HCC Incidence



# pts at risk							
	1946	1670	1088	794	498	169	56

Cumulative HCC Incidence in Relation to Presence of Cirrhosis



No Cir	1346	1156	734	329	127	45
Cir	518	444	304	145	34	6

HCC risk seems to be decreasing after the first 5 years of ETV/TDF therapy in CHB patients, especially in those with compensated cirrhosis at baseline. Older age (≥55 yrs) at treatment initiation appears to represent the main risk factor associated with late HCC development

Papatheodoridis G, AASLD 2015, abs 2012

Efficacy of Currently Available HBV Therapies

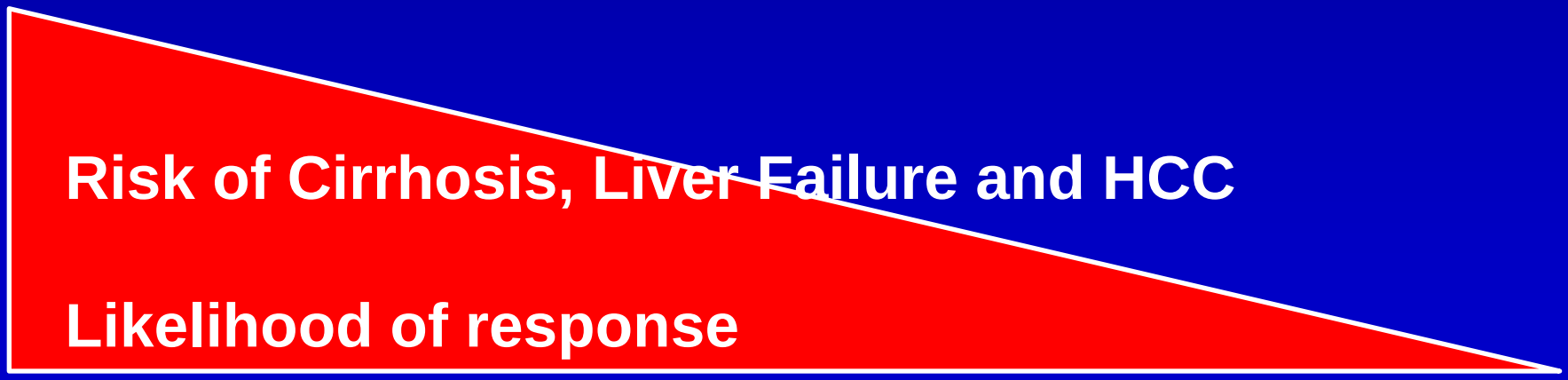
- Potent viral suppression
- Reverse hepatic fibrosis / cirrhosis
- Prevent progression to liver failure

BUT

- Low rate of HBsAg loss
- Decrease but not eliminate incidence of HCC

HBV Treatment: for Whom and When?

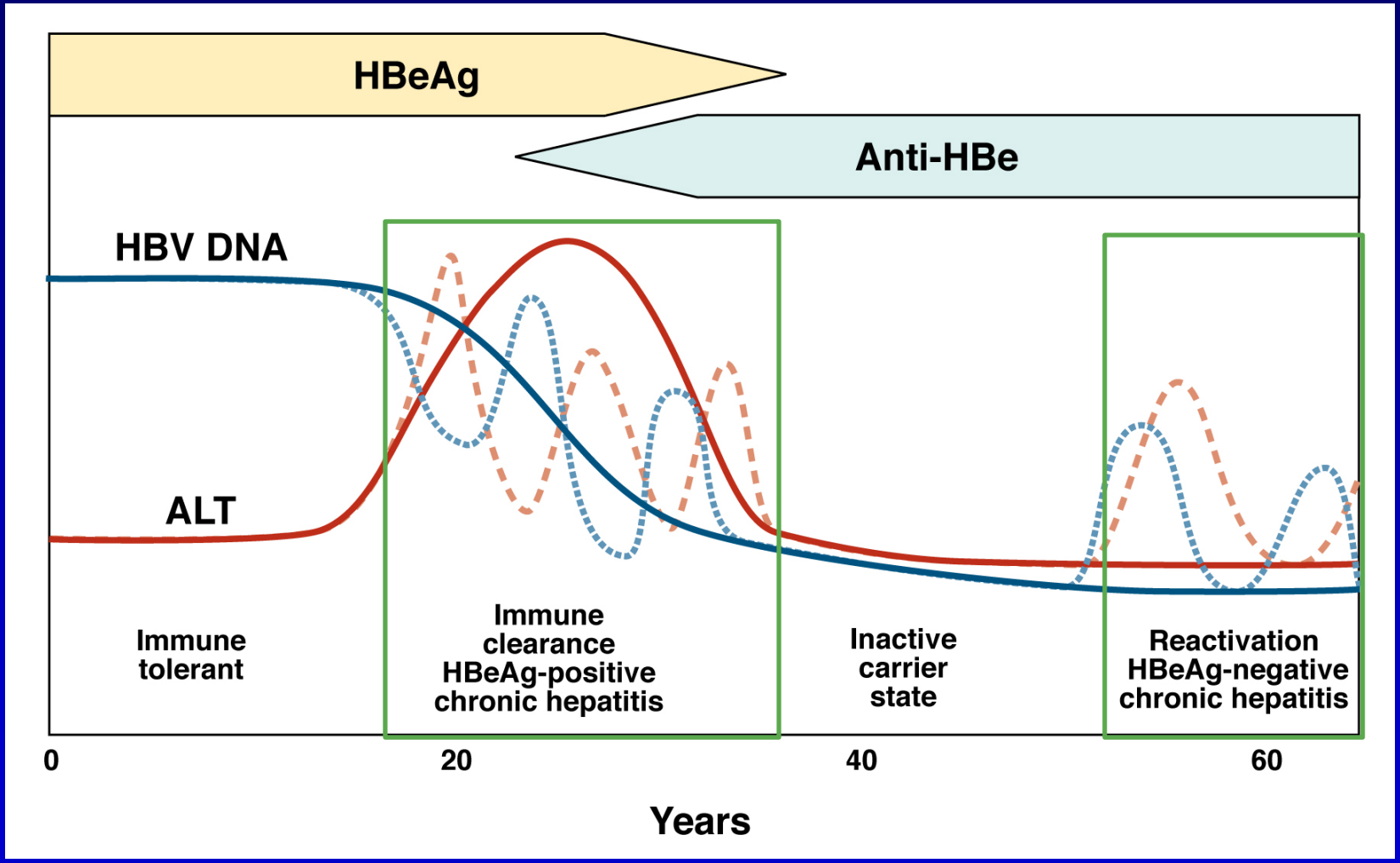
TREAT NOW	TREAT NOW OR MONITOR?	MONITOR & DEFER TREATMENT UNTIL INDICATED



Clear-Cut Cases in Which Treatment Should Be Initiated Now

- Life-threatening liver disease (regardless of HBV DNA and ALT level)
  - Fulminant hepatitis B
  - Severe exacerbations of chronic hepatitis B
  - Decompensated HBV cirrhosis
- High risk of liver failure/HCC in the near future
  - Compensated cirrhosis (any HBV DNA level?)
- HBsAg+ patients who will be starting immunosuppressive therapy
- HBsAg+ pregnant women with HBV DNA >200,000 IU/mL
- Noncirrhotics at high risk of progressive liver disease

When to Initiate Treatment in Noncirrhotics?



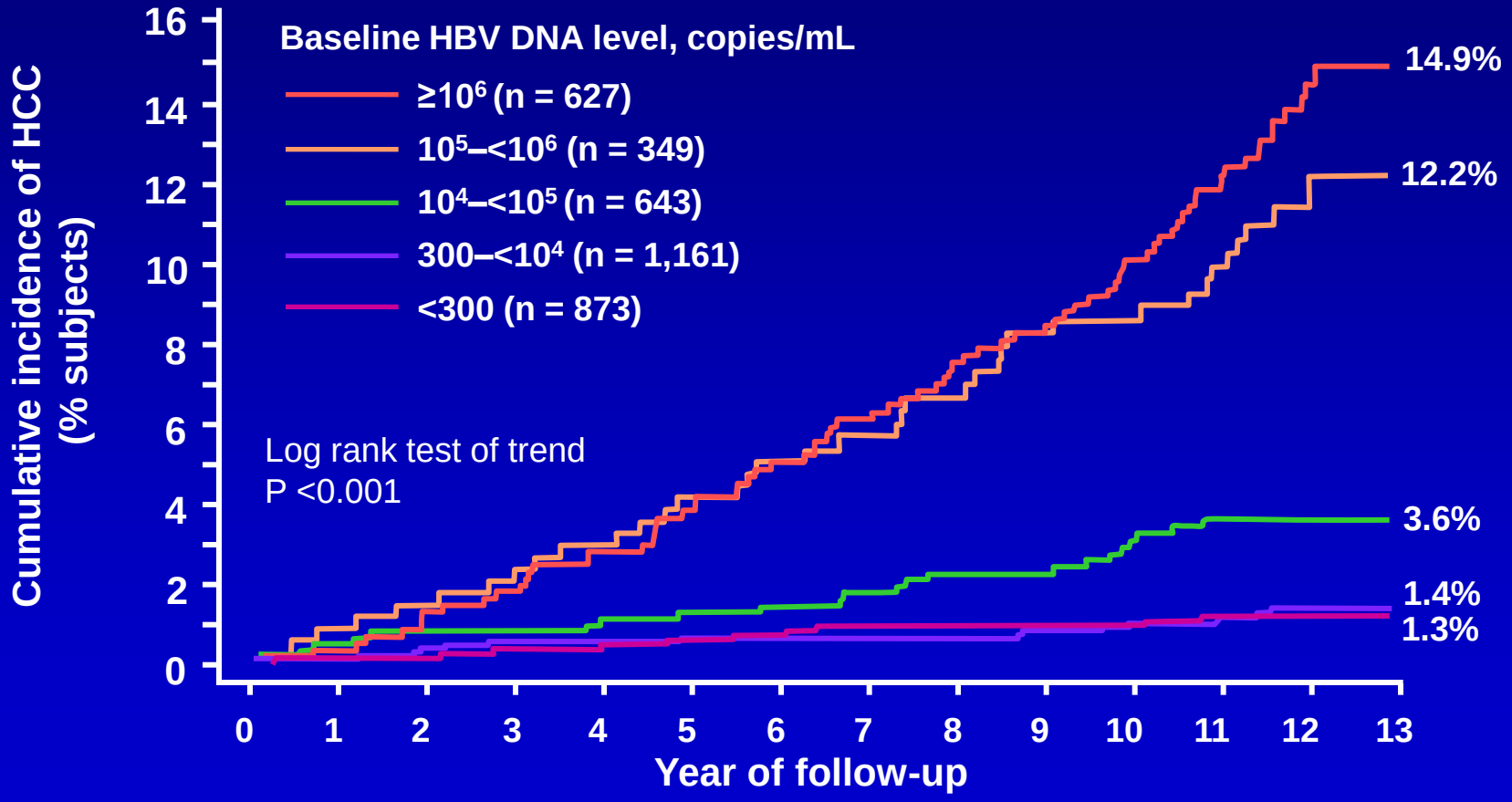
AASLD Guideline Recommendations Regarding When to Start Treatment

	AASLD 2015
HBeAg+	
Immune tolerant	**No treatment except age >40, 3rd trimester pregnancy**
Immune active	**Treat, HBV DNA >20,000 IU/mL, ALT elevated, moderate-severe inflammation / fibrosis**
HBeAg-	
Inactive	**No treatment if truly inactive**
Immune active	**Treat, HBV DNA >2,000 IU/mL, ALT elevated, moderate-severe inflammation / fibrosis**
Cirrhosis	
Compensated	**Treat regardless of ALT, especially if HBV DNA >2000 IU/mL**
Decompensated	**Treat regardless of ALT and HBV DNA**

Terrault N, Hepatology 2016; 63: 261

High Viral Load is Associated with Increased Incidence of HCC

REVEAL Study (n = 3,653), mean age 43



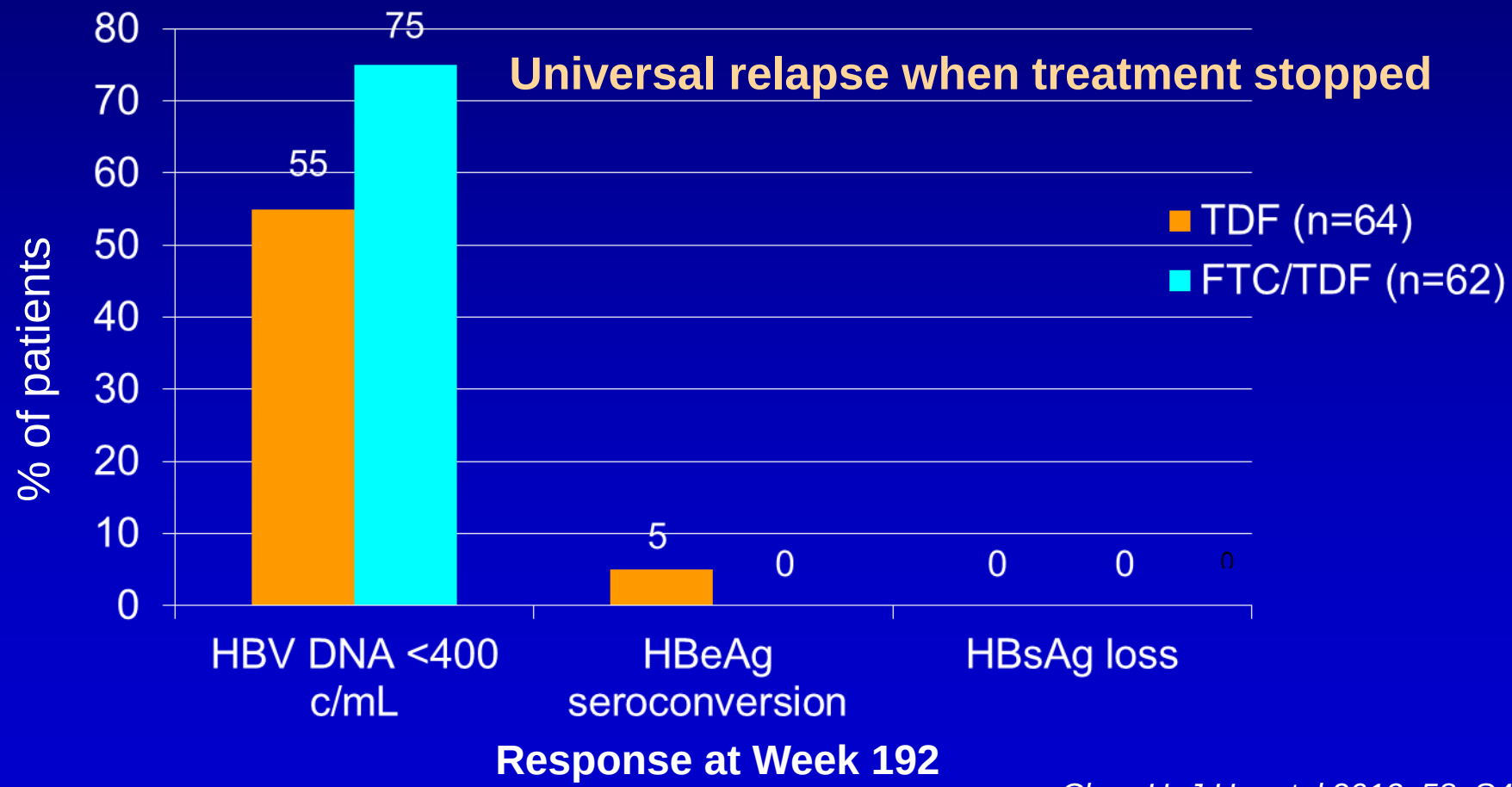
Chen CJ, et al. JAMA. 2006; 295:65

Outcome of Patients in the Immune-tolerant Phase is Favorable after 10-Year Follow-up

- 240 patients (130 M: 110 F), mean age 27.6 yr
- Mean FU 10.5 yr (3-20)
- Spontaneous HBeAg seroconversion: 85%
- Reactivation of hepatitis after HBeAg seroconversion: 2.2%/yr
- Cirrhosis: ~1.5% after 10 yr
- HCC: none

Chu CM, Am J Med 2004; 116: 829

Tenofovir vs Emtricitabine + Tenofovir x 4 Years
Immune Tolerance Phase
HBeAg+, HBV DNA ≥8 $\log_{10}$ c/mL, ALT ≤ULN

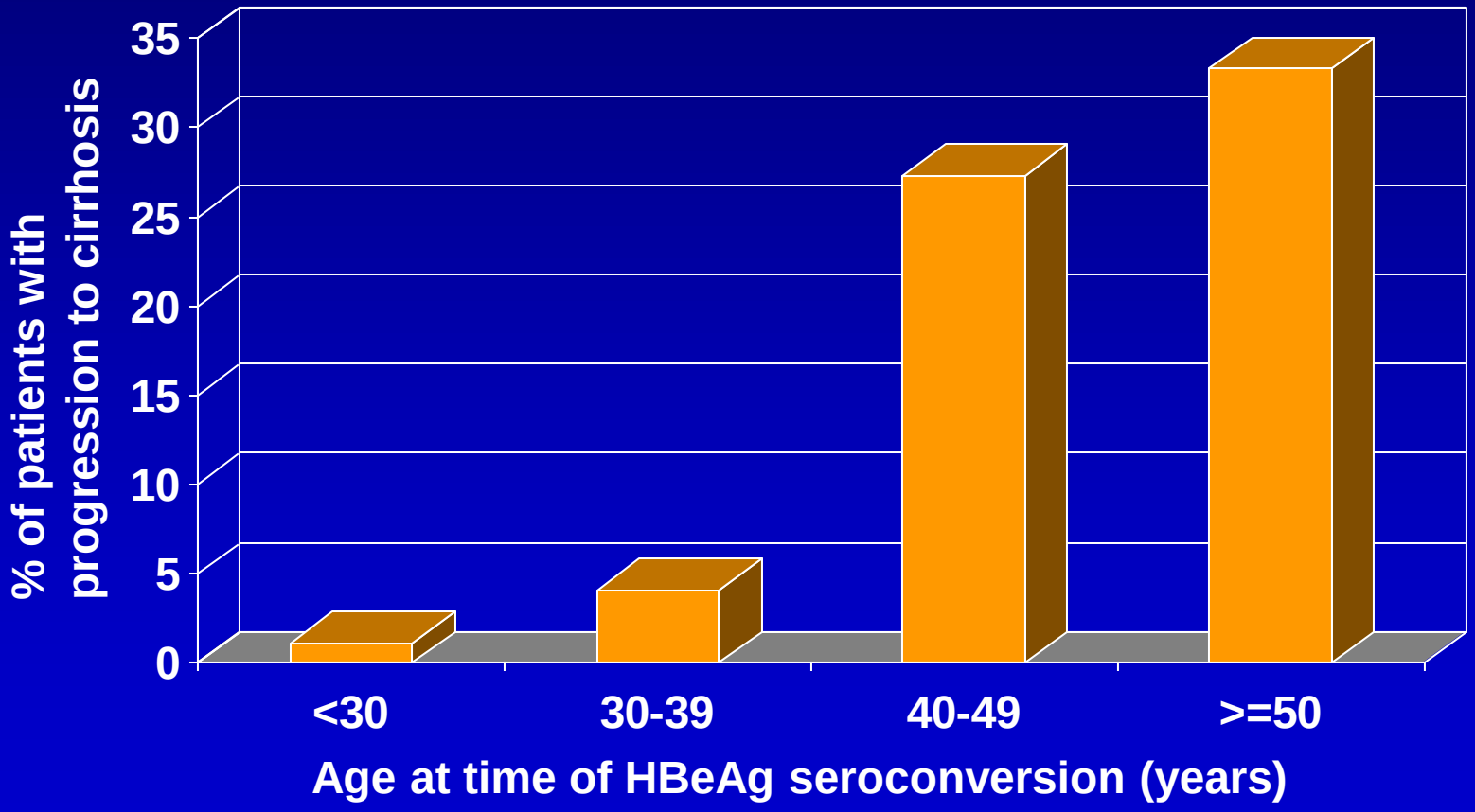


Chan H, J Hepatol 2013; 58: S45

Can HBeAg+ Patients in Immune Tolerance Phase Wait?

- Minimal inflammation / fibrosis
- No to low risk of cirrhosis and HCC during 10-year follow-up
- Possibility of spontaneous HBeAg seroconversion and durable remission
- Response to both IFN and nucleos(t)ide analogue poor

Persistence of HBeAg after Age 40 Associated with Increased Risk of Cirrhosis



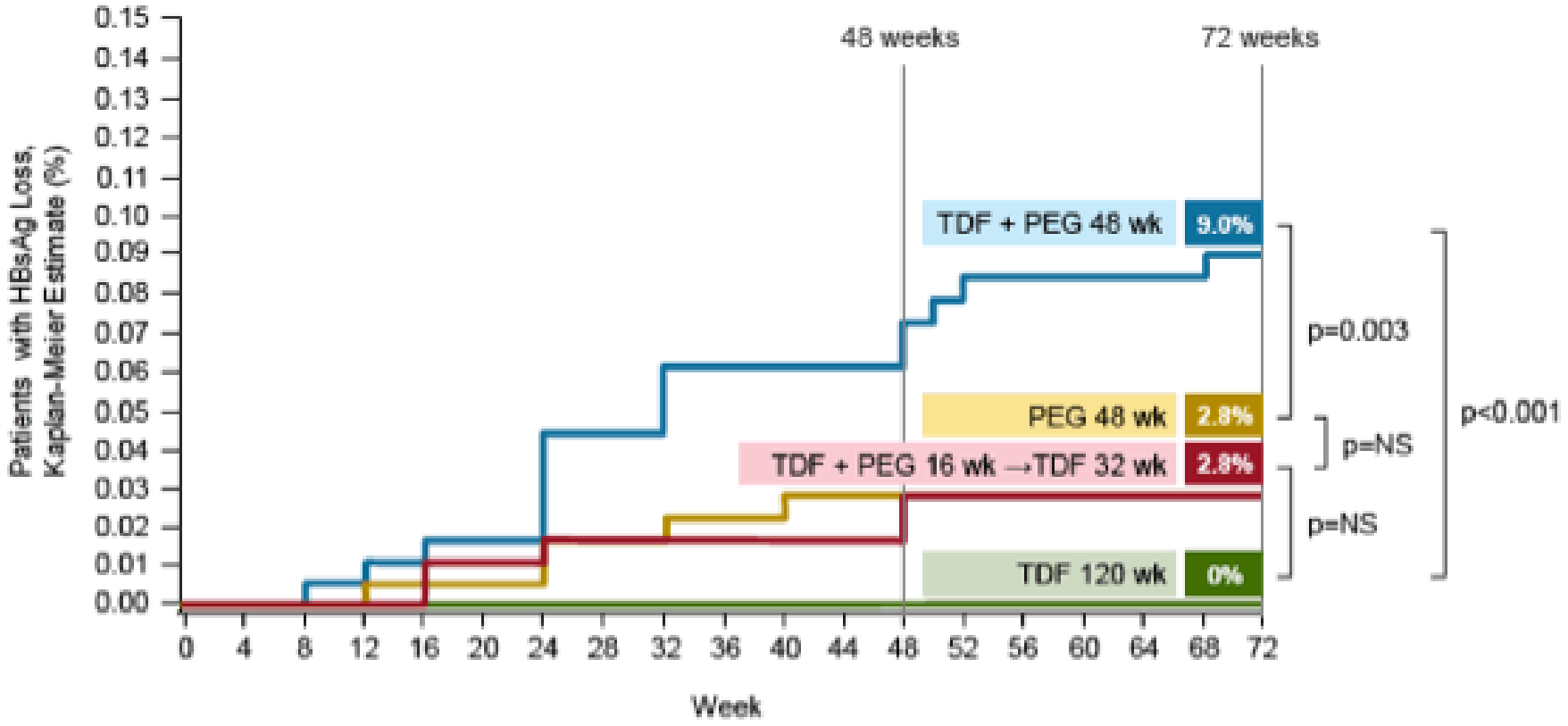
Chu & Liaw J Viral Hepat 2007; 14: 147

Which Treatment?
Interferon or Nucleos(t)ide Analogue?

Treatment	Interferon	Nucleos(t)ide Analogues
Route	Parenteral	Oral
Duration of treatment	Finite duration ~12 mos	Long duration, yrs to life-long
Antiviral activity	Modest, also immunomodulatory effects	Potent ETV/TDF/TAF/TBV >LAM >ADV
HBsAg loss	1%-3% after 1 yr	Rare, 0%-1% after 1 yr
Resistance mutations	None	0%-25% after 1 yr LAM>TBV>ADV>ETV/TDF/TAF
Side effects	Frequent	Rare

ADV: adefovir, ETV: entecavir; LAM: lamivudine, TBV: telbivudine; TDF: tenofovir

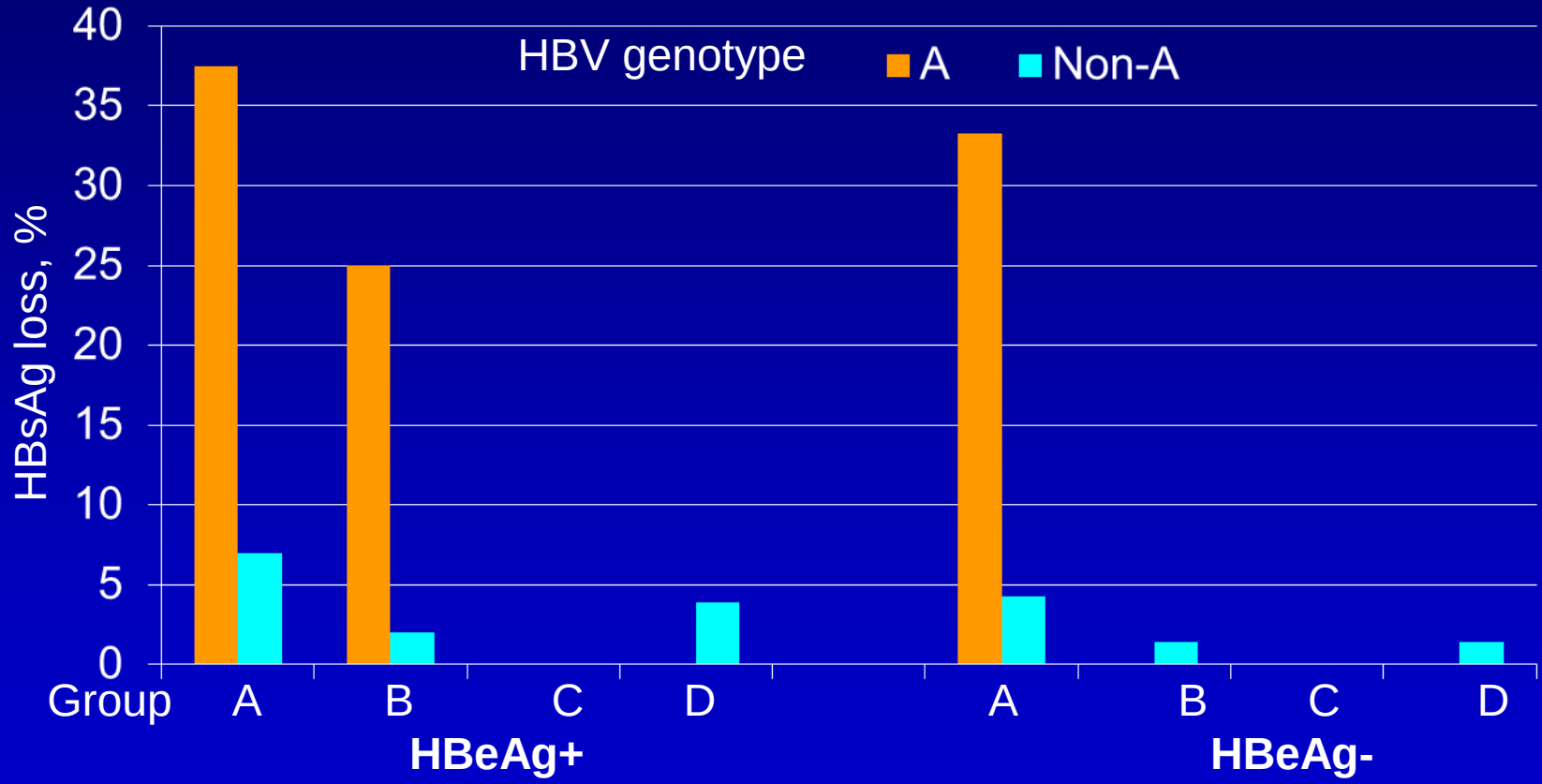
Combination of Tenofovir and Peg-IFN Increases Rate of HBsAg Loss Compared with Monotherapy



- 7 patients had HBsAg seroreversion on or after Week 48 (4 [TDF + PEG 48 wk], 3 [TDF + PEG 16 wk →TDF 32 wk])
  - 5/7 had ≤1 week of therapy after HBsAg loss

Marcellin P, Gastroenterol 2016; 150: 134

Combination of Tenofovir and Peg-IFN Increases HBsAg Loss Only in Genotype A



A= TDF+PEG x 48 wk
C= TDFx120 wk

B= TDF+PEG x 16 wk + TDF x 32 wk
D= PEGx48 wk

Marcellin P, Gastroenterol 2016; 150: 134

Tailoring Treatment to Patient

IFN

- No contraindications
- Willing to try
- Genotype A
- High ALT

Nucleos(t)ide analogues

- Cirrhosis
- Severe flares of chronic hepatitis
- Contraindications to IFN
- Unwilling to try IFN
- Willing to accept long-term treatment

Entecavir, tenofovir: potent antiviral activity, high barrier to resistance. Tenofovir alafenamide: less renal and bone toxicity vs tenofovir disoproxil fumarate

When to Stop Interferon Treatment?

Finite duration

- **Immunomodulatory effects may persist after cessation of treatment**
- **Need for parenteral administration, side effects, and high costs**
- **48-52 weeks for both HBeAg+ and HBeAg- patients**
  - **Week-12 stop rule for futility, genotype-specific, not validated?**

Guideline Recommendations Regarding When to Stop Nucleos(t)ide Analogues

	AASLD 2015	APASL 2016	EASL 2017
HBeAg+	HBeAg seroconversion and undetectable HBV DNA plus ≥12 mo consolidation	HBeAg seroconversion and undetectable HBV DNA plus preferably 3-yr consolidation	HBeAg seroconversion plus ≥12-mo consolidation
HBeAg-	HBsAg loss?	HBsAg loss + anti-HBs seroconversion or ≥12-mo consolidation	HBsAg loss or after ≥ 3 years of udetectable HBV DNA if close FU possible
Cirrhosis	DO NOT STOP	May be considered with careful off-therapy monitoring plan	DO NOT STOP

Terrault N, Hepatology 2016; 63: 261; Sarin S, Hepatol Int 2016; 10: !; EASL, J Hepatol 2017 (in press)

Risks of Stopping Nucleos(t)ide Analogues

- Risk of relapse
  - HBeAg+ patients who completed ≥12 mos consolidation therapy after HBeAg seroconversion: 10%-50% viral relapse
  - HBeAg- patients who completed >2 yr treatment: 100% viral relapse, ~40% sustained clinical relapse
- Risk of hepatic decompensation
  - Limited data, ~3% among cirrhotics
  - Depends on vigilance of post-treatment monitoring

HIV Management
Hepatitis Management

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