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HEPATITIS

# Hepatitis Now: Expanding HBV Treatment Candidacy

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# General Considerations

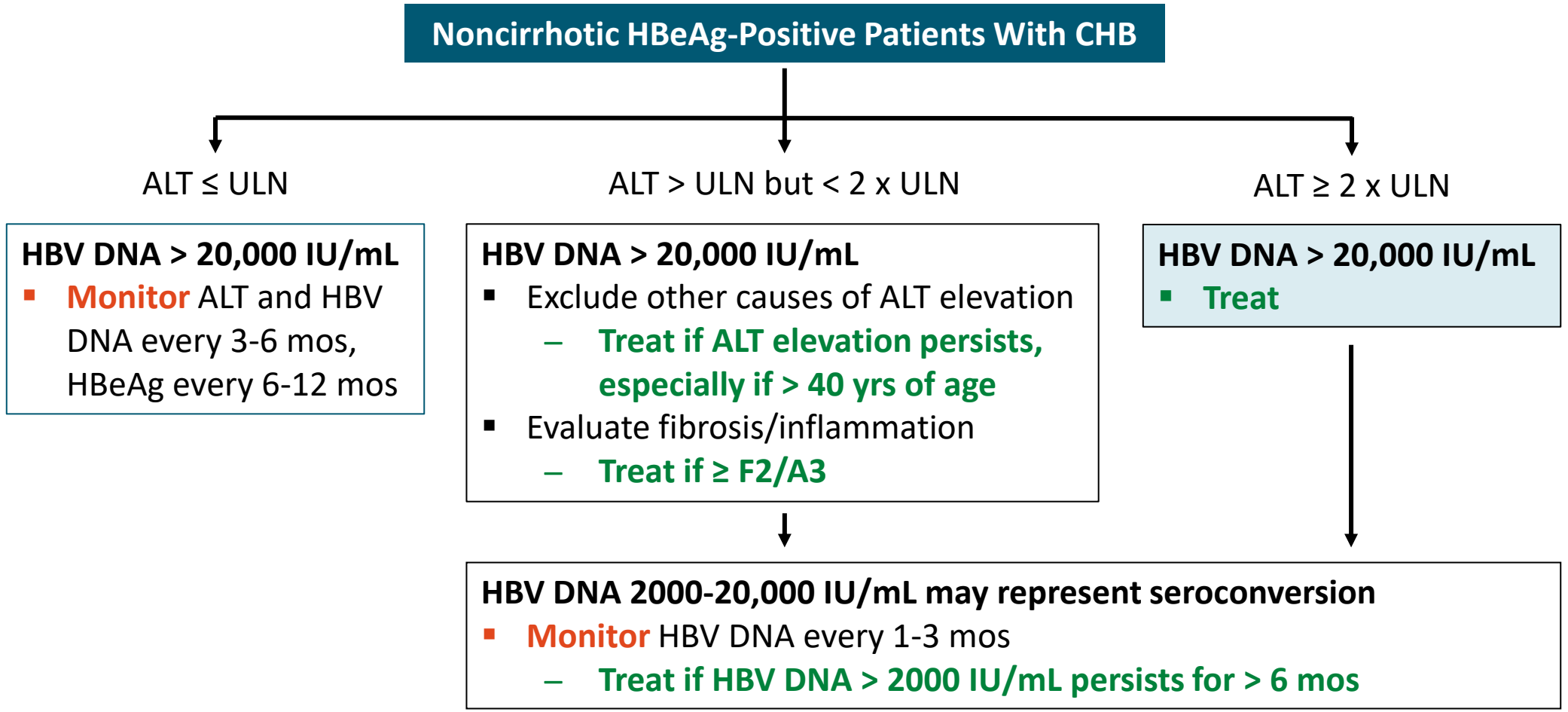
# Defining the Upper Limit of Normal for ALT

| ALT ULN | AASLD 2018[1] | EASL 2017[2] |
|---|---|---|
| Males | 35 U/L | 40 IU/L |
| Females | 25 U/L | 40 IU/L |

1. Terrault. Hepatology. 2018;67:1560. 2. EASL. J Hepatol. 2017;67:370.

Slide credit: clinicaloptions.com

# 2018 AASLD Guidance for HBeAg-Positive CHB




Terrault. Hepatology. 2018;67:1560.

Slide credit: clinicaloptions.com

# 2018 AASLD Guidance for HBeAg-Negative CHB

**Noncirrhotic HBeAg-Negative Patients With CHB**

## ALT ≤ ULN

**HBV DNA ≥ 2000 IU/mL**

- **Monitor** ALT and HBV DNA every 3 mos for 1 yr, then every 6 mos

**HBV DNA < 2000 IU/mL**

- **Monitor** ALT and HBV DNA every 3-6 mos
- **Monitor** HBsAg annually

## ALT > ULN but < 2 x ULN

**Any Detectable HBV DNA**

- Exclude other causes of ALT elevation
  - **Treat if ALT elevation persists with HBV DNA ≥ 2000 IU/mL, especially if > 40 yrs of age**
- Evaluate fibrosis/inflammation
  - **Treat if ≥ F2/A3**

## ALT ≥ 2 x ULN

**HBV DNA ≥ 2000 IU/mL**

- **Treat**

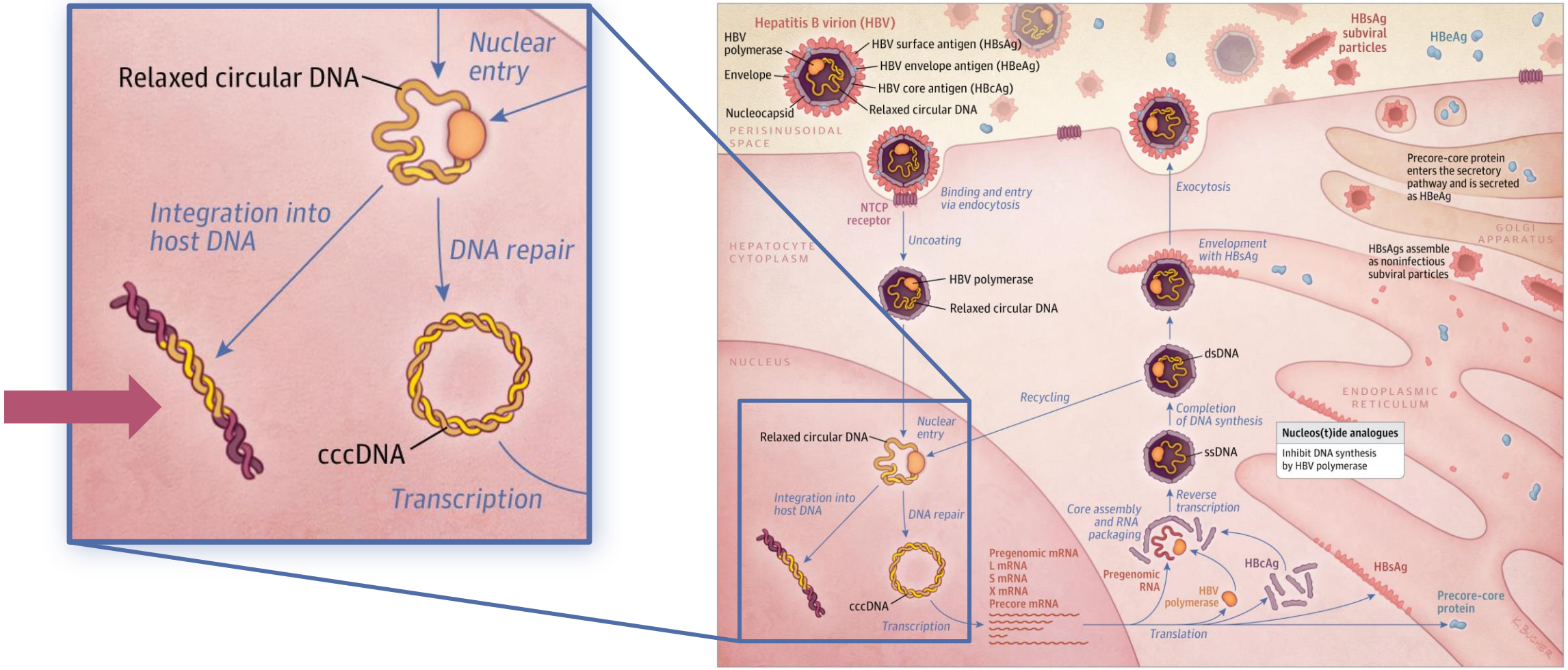
**HBV DNA < 2000 IU/mL**

- Exclude other causes of ALT elevation and evaluate fibrosis/inflammation
  - **Treat if ≥ F2/A3**

Terrault. Hepatology. 2018;67:1560.

Slide credit: clinicaloptions.com

# HBV Life Cycle




Tang. JAMA. 2018;319:1802. Reproduced with permission.

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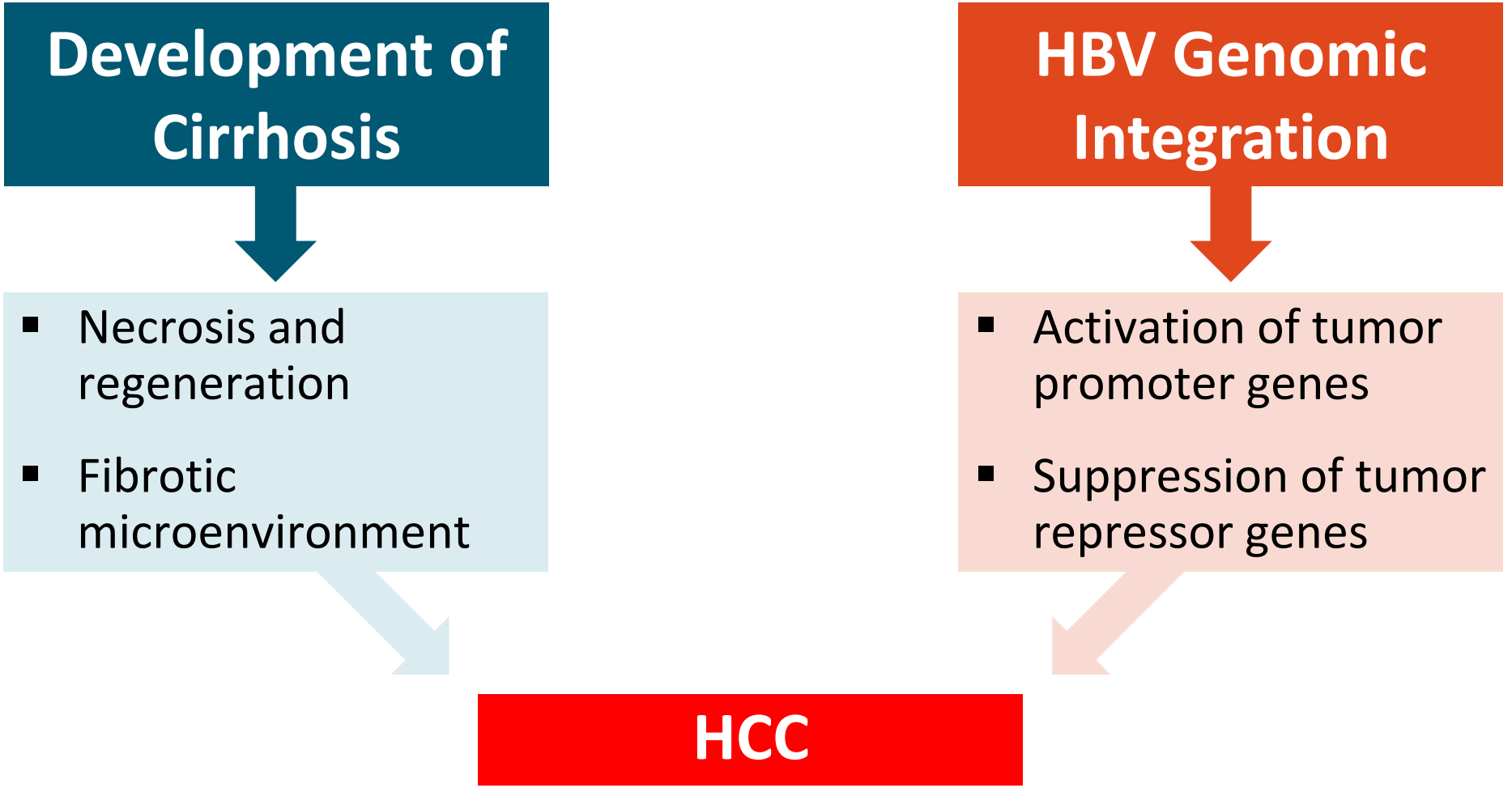
# 2 Key Pathways to HCC in Patients With Hepatitis B




Zamor. J Gastrointest Oncol. 2017;8:229. Zhao. Nat Commun. 2016;7:12992.

Slide credit: clinicaloptions.com

# Natural History of HBV: New Nomenclature From EASL

| Parameter | HBeAg Positive | | HBeAg Negative | | Resolved HBV Infection |
|---|---|---|---|---|---|
| | Chronic *Infection* | Chronic *Hepatitis* | Chronic *Infection* | Chronic *Hepatitis* | |
| HBsAg | High | High/ intermediate | Low | Intermediate | Negative |
| HBeAg | Positive | Positive | Negative | Negative | Negative |
| HBV DNA | > $10^7$ IU/mL | $10^4$ to $10^7$ IU/mL | < 2000 IU/mL* | > 2000 IU/mL | Undetectable‡ |
| ALT | Normal | Elevated | Normal | Elevated† | Normal |
| Liver disease | None/minimal | Moderate/severe | None | Moderate/severe | None§ |
| *Older term* | *Immune tolerant* | *Immune reactive HBeAg positive* | *Inactive carrier* | *HBeAg negative chronic hepatitis* | *HBsAg negative, anti-HBc positive* |

*HBV DNA levels up to 20,000 IU/mL can occur without signs of chronic hepatitis. †Persistently or intermittently.
‡cccDNA frequently detected in the liver. § Residual HCC risk only if cirrhosis developed before HBsAg loss.

EASL. J Hepatol. 2017;67:370.

Slide credit: clinicaloptions.com

# REVEAL-HBV: Landmark Study of CHB Natural History

- Prospective cohort study of patients recruited to a community-based cancer screening program in Taiwan, 1991-1992

**Enrolled in Study**
(N = 23,820)

**HBsAg Positive**
(n = 4155)

**Adequate Serum for HBV DNA Test**
(n = 3851)

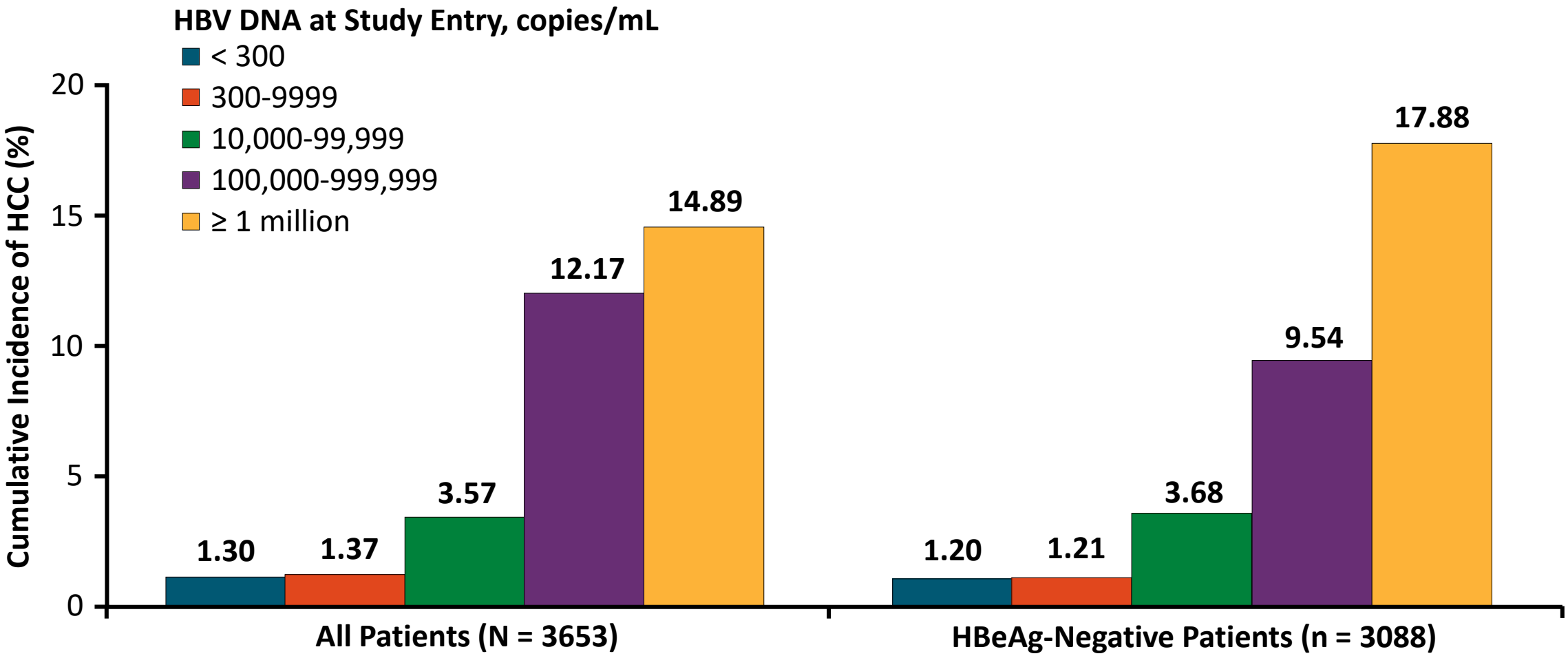
**Anti-HCV Negative**
(n = 3653)

| Characteristic, n (%) | Study Cohort (n = 3653) |
|---|---|
| Male | 2260 (62) |
| Age | |
| ▪ 30-39 yrs | 1216 (33) |
| ▪ 40-49 yrs | 1014 (28) |
| ▪ 50-59 yrs | 1058 (29) |
| ▪ ≥ 60 yrs | 365 (10) |
| No cigarette smoking | 2416 (66) |
| No alcohol consumption | 3195 (87) |
| HBeAg negative | 3088 (85) |
| ALT < 45 U/L | 3435 (94) |
| No cirrhosis by ultrasound | 3584 (98) |

Chen. JAMA. 2006;295:65.

Slide credit: clinicaloptions.com

# REVEAL-HBV: Cumulative Incidence of HCC After 13 Yrs




Chen. JAMA. 2006;295:65.

Slide credit: clinicaloptions.com

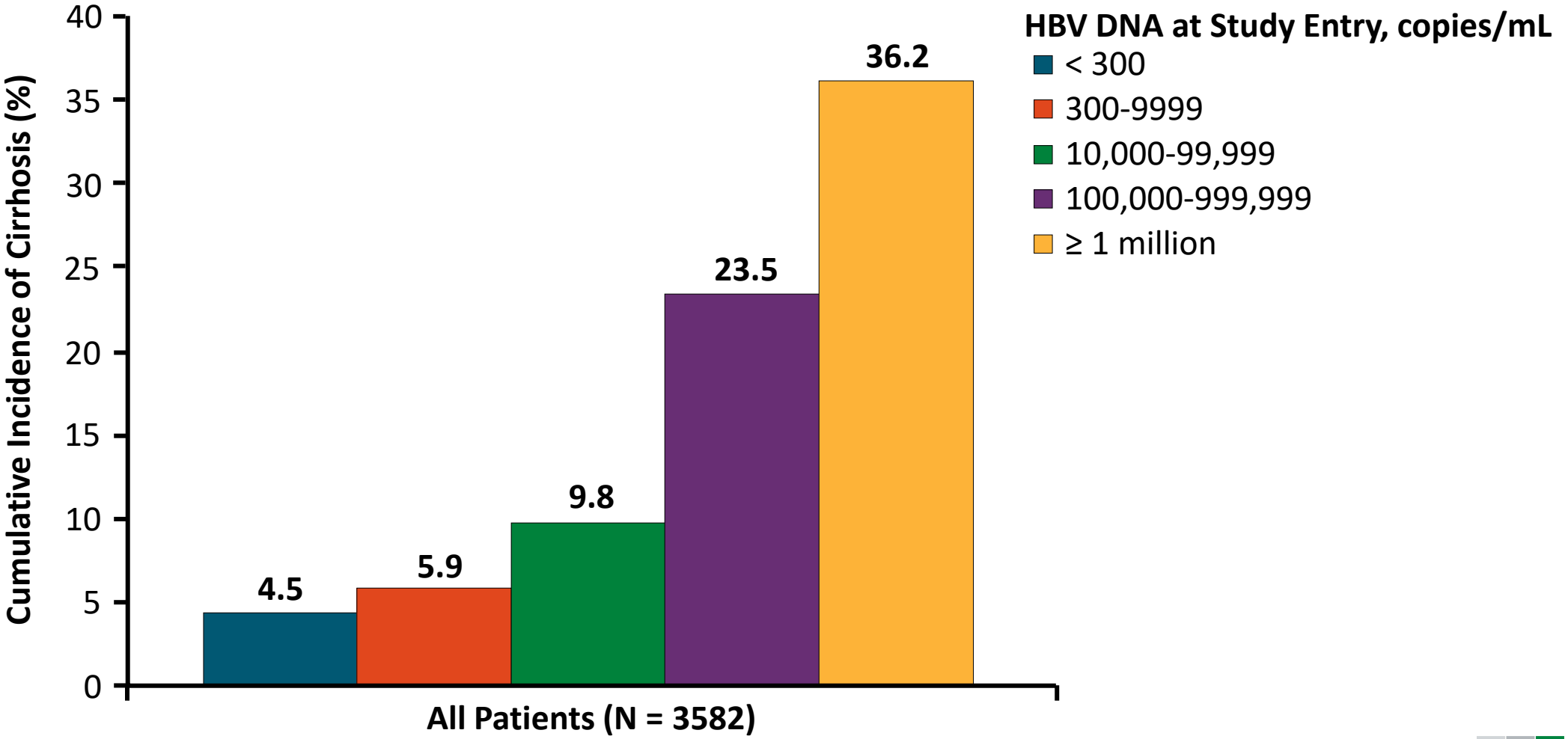
# REVEAL-HBV: Risk of HCC by HBV DNA Level

| HBV DNA, copies/mL | | Patients, n | HCC Cases, n | Median Time From BL to Last F/u Exam, Yrs | Adjusted HR (95% CI) | |
|---|---|---|---|---|---|---|
| Study Entry | Follow-up | | | | Sex, Age, Cigarette Smoking, Alcohol Consumption | Plus HBeAg Positivity, Cirrhosis, ALT Level |
| < 10,000 | Not tested | 2034 | 26 | | 1.0 | 1.0 |
| 10,000-99,999 | < 10,000 | 256 | 6 | 10.7 | 1.6 (0.7-3.9) | 1.3 (0.5-3.1) |
| 10,000-99,999 | 10,000-99,999 | 161 | 1 | 9.2 | 0.5 (0.1-3.6) | 0.4 (0.1-3.2) |
| 10,000-99,999 | ≥ 100,000 | 110 | 5 | 9.9 | 3.5 (1.4-9.2) | 2.9 (1.0-9.8) |
| ≥ 100,000 | < 10,000 | 146 | 8 | 11.1 | 3.8 (1.7-8.4) | 1.9 (0.8-4.4) |
| ≥ 100,000 | 10,000-99,999 | 120 | 10 | 10.5 | 7.3 (3.5-15.3) | 4.3 (2.0-9.3) |
| ≥ 100,000 | ≥ 100,000 | 537 | 55 | 9.9 | 10.1 (6.3-16.2) | 5.3 (2.9-9.7) |

Chen. JAMA. 2006;295:65.

Slide credit: clinicaloptions.com

# REVEAL-HBV: Cumulative Incidence of Cirrhosis




Iloeje. Gastroenterology. 2006;130:678.

Slide credit: clinicaloptions.com

# REVEAL-HBV: Risk Factors Associated With HCC

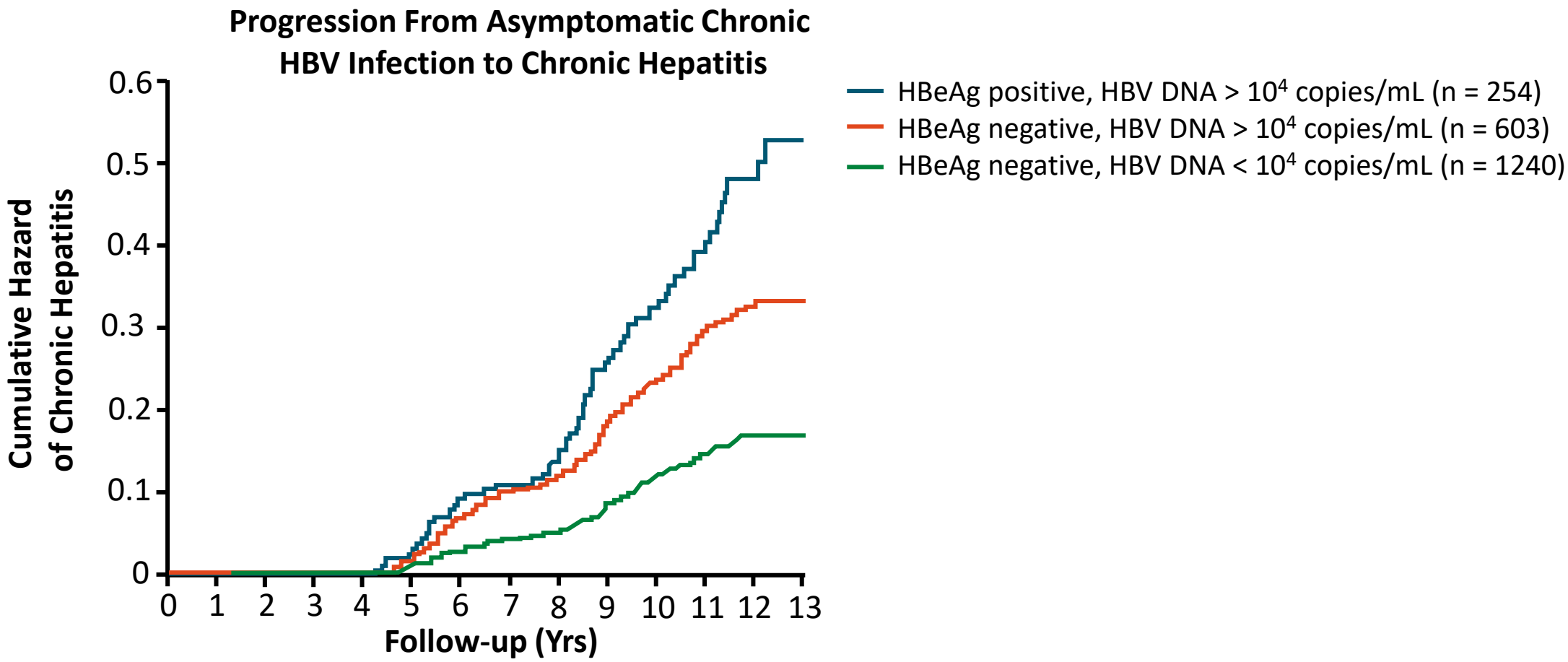
| Risk Factor | All Patients (N = 3653) | | HBeAg Negative (n = 3088) | | HBeAg Negative, Normal ALT (n = 2966) | | HBeAg Negative, Normal ALT, No Cirrhosis (n = 2925) | |
|---|---|---|---|---|---|---|---|---|
| | HR | *P* Value | HR | *P* Value | HR | *P* Value | HR | *P* Value |
| Male sex | 2.1 | .001 | 2.0 | .03 | 1.6 | .16 | 1.5 | .24 |
| Age in 1-yr increment | 1.09 | < .001 | 1.08 | < .001 | 1.09 | < .001 | 1.11 | < .001 |
| Cigarette smoking | 1.0 | .84 | 0.9 | .69 | 1.1 | .76 | 1.3 | .35 |
| Alcohol consumption | 1.6 | .009 | 1.7 | .05 | 1.8 | .03 | 1.7 | .08 |
| HBeAg positive | 2.6 | < .001 | | | | | | |
| ALT ≥ 45 U/L | 1.1 | .64 | 0.8 | .62 | | | | |
| Liver cirrhosis* | 9.1 | < .001 | 7.9 | < .001 | 11.7 | < .001 | | |
| HBV DNA at study entry, copies/mL | | | | | | | | |
| ▪ < 300 | 1.0 | < .001† | 1.0 | < .001† | 1.0 | < .001† | 1.0 | < .001† |
| ▪ 300-9999 | 1.1 | .86 | 1.0 | .94 | 1.3 | .55 | 1.4 | .56 |
| ▪ 10,000-99,999 | 2.3 | .02 | 2.6 | .01 | 2.7 | .02 | 4.5 | .001 |
| ▪ 100,000-999,999 | 6.6 | < .001 | 6.1 | < .001 | 7.2 | < .001 | 11.3 | < .001 |
| ▪ ≥ 1 million | 6.1 | < .001 | 10.6 | < .001 | 14.3 | < .001 | 17.7 | < .001 |

*Diagnosed by ultrasound within 6 mos of study entry. †For trend.

Chen. JAMA. 2006;295:65.

Slide credit: clinicaloptions.com

# REVEAL-HBV: Disease Progression in Persons With Persistently Normal ALT at Study Entry




Chen. EASL 2008. Abstr 644.

Slide credit: clinicaloptions.com

# REVEAL-HBV: Implications for Treatment of HBV Infection

- Viral level is the most important predictor of outcome
- Reductions in HBV DNA level occurring spontaneously have favorable prognostic import
  - **Reasonable to infer that pharmacologic reductions in HBV DNA would have similar favorable import**
- Minimally elevated or even normal ALT not protective from adverse outcomes

Chen. JAMA. 2006;295:65. Iloeje. Clin Gastroenterol Hepatol. 2007;5:921.

# Should Patients With Immune-Tolerant CHB Be Treated?

# Defining Immune-Tolerant CHB

- Typically infected at birth; most are younger than 40 yrs of age
- HBeAg positive
- HBV DNA levels very high (typically > 1 million IU/mL)
- Normal or minimally elevated ALT and/or AST
  - Immune-tolerant status defined by ALT levels, utilizing 35 U/L for men and 25 U/L for women as ULN rather than local laboratory ULN
- Liver biopsy or noninvasive test results showing no fibrosis and minimal inflammation

McMahon. Hepatology. 2009;49:S45. Terrault. Hepatology. 2018;67:1560.

# AASLD Guidance on Immune-Tolerant CHB

- *"The AASLD recommends against antiviral therapy for adults with immune-tolerant CHB"*
- *"The AASLD suggests antiviral therapy in the select group of adults > 40 yrs of age with normal ALT and elevated HBV DNA (1 million IU/mL) and liver biopsy specimen showing significant necroinflammation or fibrosis"*

Terrault. Hepatology. 2018;67:1560.

Slide credit: clinicaloptions.com

# Treatment Indications for Patients With HBeAg-Positive Immune-Tolerant CHB

| AASLD[1] | APASL[2] | EASL[3] |
|---|---|---|
| ▪ ALT < 70 U/L if male, < 50 U/L if female: **no therapy** | ▪ ALT ≤ 80 IU/mL: **no therapy** | ▪ ALT ≤ 40 IU/L, if ≤ 30 yrs of age: **no therapy** |
| ▪ Consider liver biopsy, especially if > 40 yrs of age<br>– Treat if ≥ A3/F2 | ▪ Consider liver biopsy if significant fibrosis by noninvasive tests, ALT persistently elevated, > 35 yrs of age, or family history of HCC/cirrhosis<br>– Treat if ≥ A3/F2 | ▪ ALT 41-80 IU/L: evaluate by elastography and/or liver biopsy<br>– Treat if stiffness ≥ 12 kPa or ≥ A3/F2<br>▪ Treat if > 30 yrs of age or family history of HCC/ cirrhosis |

1. Terrault. Hepatology. 2018;67:1560. 2. Sarin. Hepatol Int. 2016;10:1. 3. EASL. J Hepatol. 2017;67:370.

Slide credit: clinicaloptions.com

# Traditional Arguments Against Treating Immune-Tolerant CHB

- ~~Rates of HBeAg seroconversion very low; indefinite treatment required~~
- ~~Lower rates of complete viral suppression at defined time points~~
- ~~Possibility of resistance~~
- ~~Uncertain long-term safety of antiviral therapy~~
- Patients do well in the short and intermediate term
- No evidence that treatment alters clinical outcomes in these patients
- Expense

Slide credit: clinicaloptions.com

# Arguments Favoring Treatment of Immune-Tolerant CHB

- Good prognosis in the short or intermediate term does not ensure good long-term outlook
- Reasons to fear that ongoing high-level viremia can be oncogenic
- Marked viral suppression, even if not complete, can be achieved in nearly all patients
- Transition to immune-active phase may go unrecognized
- Some patients with normal ALT do have fibrosis
- Risk of transmission in viremic patients, especially younger patients

Slide credit: clinicaloptions.com

# Fibrosis Progression Uncommon in Patients With Immune-Tolerant CHB

- N = 48 immune-tolerant patients with paired liver biopsy at 5 yrs
  - 3 patients had fibrosis progression; 4 patients with F1 at baseline had regression to F0

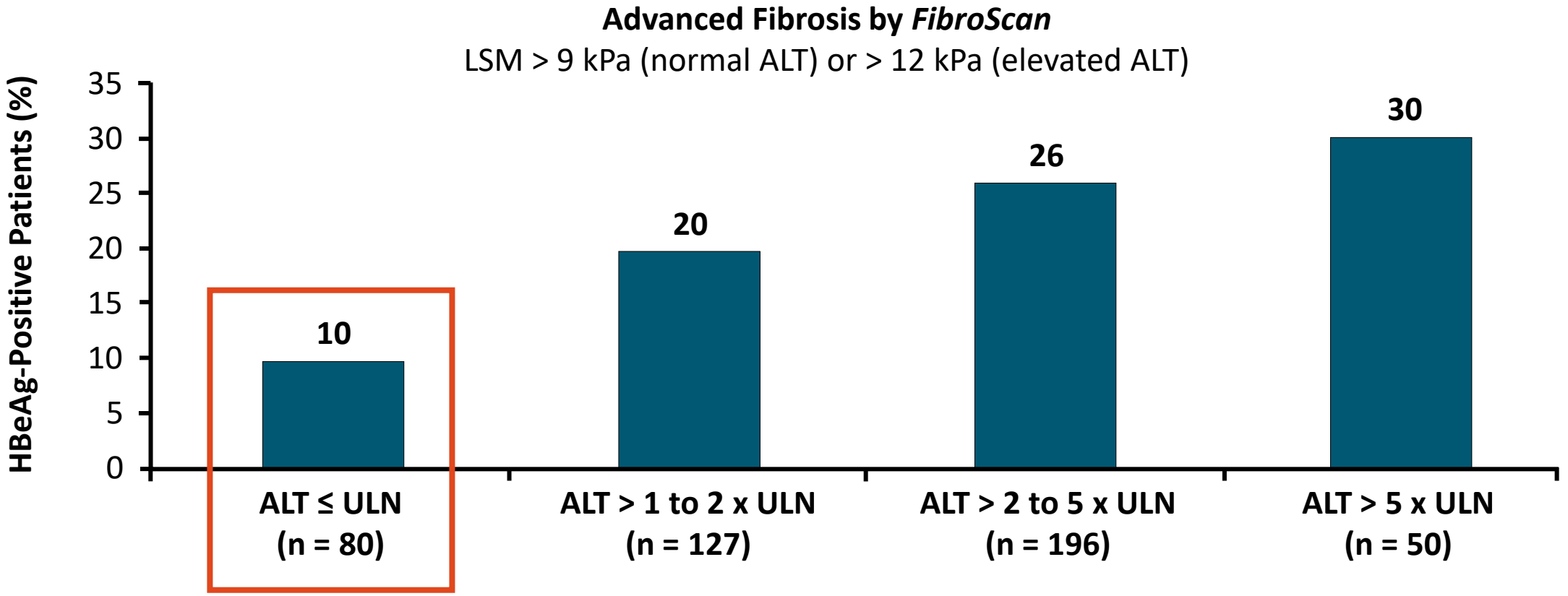
| Fibrosis Stage | CHB Patients Remaining in Immune-Tolerant Phase After 5 Yrs (N = 48) | | |
|---|---|---|---|
| | Initial Liver Biopsy, n | Follow-up Liver Biopsy, n | *P* Value |
| F0 | 15 | 16 | |
| F1 | 33 | 31 | .58 |
| F2 | 0 | 1 | |

Hui. Hepatology. 2007;46:395.

Slide credit: clinicaloptions.com

# Elevated ALT Associated With Fibrosis in Patients With HBeAg-Positive CHB

- 10% of HBeAg-positive patients with normal ALT have advanced fibrosis




Wong. Clin Gastroenterol Hepatol. 2009;7:227.

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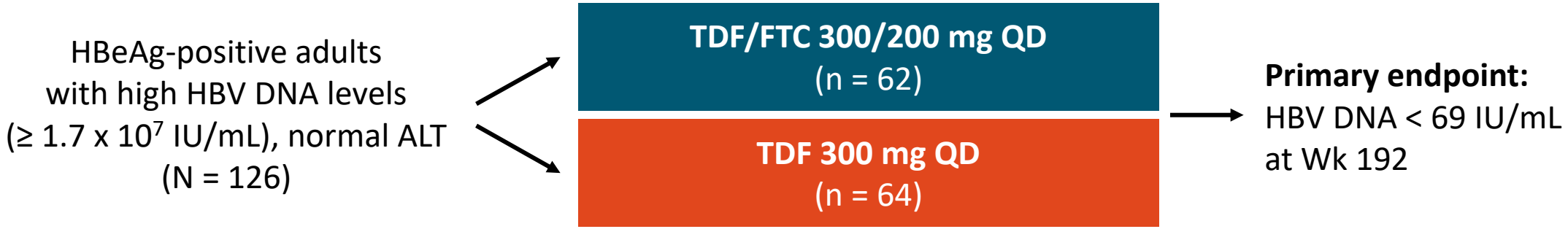
# "Low" Virologic Response Rate Among Patients With Immune-Tolerant CHB Receiving TDF

- Multicenter, randomized, double-blind phase II trial




| Outcome at Wk 192 in ITT Population, % | TDF/FTC (n = 62) | TDF (n = 64) | *P* Value |
|---|---|---|---|
| HBV DNA < 69 IU/mL | 75.8 | 54.7 | .016 |
| HBeAg seroconversion | 0 | 4.8 | .244 |
| Mean HBV DNA Δ from BL, $\log_{10}$ IU/mL | -6.70 | -6.32 | .070 |

- No HBsAg loss or resistance observed

Chan. Gastroenterology. 2014;146:1240.

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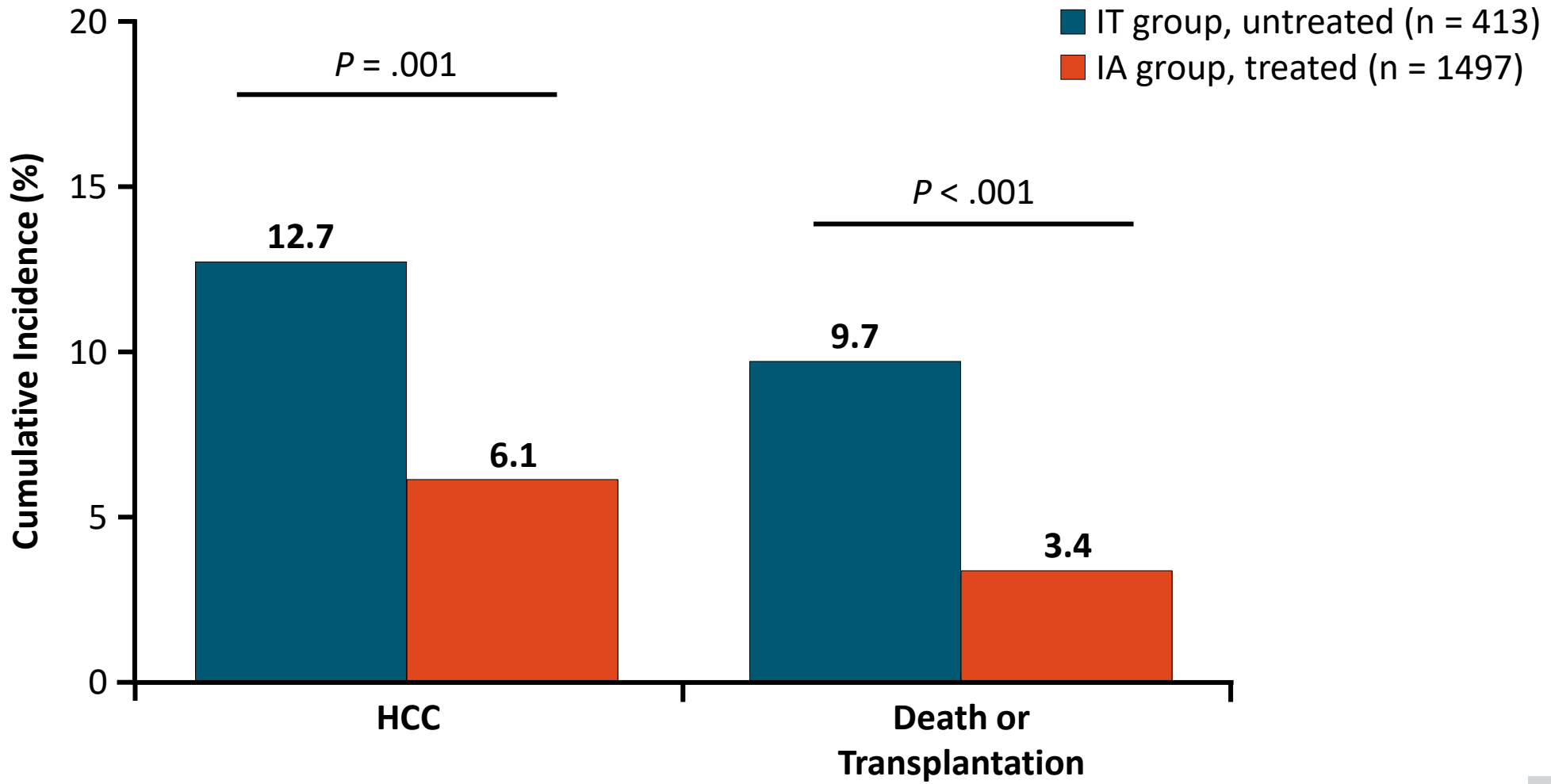
# Historical Korean Cohort Study: Study Design

- Historical cohort study of patients with immune-tolerant CHB seen at a tertiary referral hospital in Korea, Jan 2000 to Dec 2013 (n = 413)
  - HBeAg positive
  - HBV DNA ≥ 20,000 IU/mL; ALT < 19 U/L (women), < 30 U/L (men) for ≥ 1 yr
  - No cirrhosis (ie, coarse liver echotexture or nodularity on ultrasound, clinical features of portal hypertension, or thrombocytopenia)
- Clinical outcome comparators: immune-active phase patients with ALT ≥ 80 IU/mL and receipt of NA therapy (n = 1497), mildly active phase patients with ALT 1-2 x ULN (n = 1141)

Kim. Gut. 2018;67:945.

# Historical Korean Cohort Study: Cumulative Incidence of HCC, Death, or Transplantation After 10 Yrs




Kim. Gut. 2018;67:945.

Slide credit: clinicaloptions.com

# Historical Korean Cohort Study: Risk of HCC, Death, or Transplantation

| HR (95% CI)* | HCC | Death or Transplantation |
|---|---|---|
| Immune-tolerant | 2.54 (1.54-4.18) | 3.38 (1.85-6.16) |
| Mildly active phase | 3.23 (2.28-4.57) | 3.21 (3.07-4.95) |
| Immune-active phase | Reference | |

*All $P < .001$

- NA therapy initiated due to transition to immune-active phase in:
  - 26.2% of immune-tolerant patients (median follow-up: 4.7 yrs)
  - 32.5% of mildly active phase patients (median follow-up: 3.6 yrs)

Kim. Gut. 2018;67:945.

# HBV Integration and Clonal Hepatocyte Expansion in "Immune-Tolerant" Patients

- Examined liver tissue from 26 patients for HBV integration, clonal hepatocyte expansion, and expression of HBsAg and HBcAg
  - HBeAg-positive IT disease, n = 9; HBeAg-positive IA disease, n = 10; HBeAg-negative IA disease, n = 7
- High levels of HBV DNA integration randomly distributed in chromosomes of all 3 groups
- Clonal hepatocyte expansion in IT patients was greater than expected
- HBV-specific T-cells detected in blood of patients in all 3 phases
  - Hepatocyte turnover driven by immune response may be driving clonal hepatocyte expansion
- Authors proposed name change from IT to "high-replication, low-inflammation phase"
- **Conclusion: Withholding antiviral therapy in IT patients requires reconsideration**

Mason. Gastroenterology. 2016;151:986.

# Recent Literature Suggesting a Paradigm Shift for Immune-Tolerant Patients

*"This review challenges the notion that the immune-tolerant phase is truly benign and considers the possibility that events during this phase may contribute significantly to cirrhosis, HCC, and the premature death of 25% of HBV carriers worldwide. Thus, earlier treatment than recommended by current guidelines should be considered."*

Kennedy. Viruses. 2017;9:96.

Slide credit: clinicaloptions.com

# Recent Literature Suggesting a Paradigm Shift for Immune-Tolerant Patients

*"While current guidelines advise against starting antiviral treatment for immune-tolerant CHB patients, some new data suggest treating such patients may reduce the risk of liver fibrosis progression and hepatocellular carcinoma."*

Wong. Clin Mol Hepatol. 2018;24:108.

Slide credit: clinicaloptions.com

# Immune-Tolerant Patients: A Proposal

- Allow for **consideration of treatment** after discussion of rationale and limitations with individual patients
  - Strong evidence for long-term efficacy, minimal to no resistance, and safety of currently available antiviral agents
- Immune-tolerant patients with family history of HCC should be treated
- Treatment must be regarded as indefinite in absence of new therapies unless seroconversion occurs
- Combination therapy (ie, 2 NAs)?

Slide credit: clinicaloptions.com

# Should ALT ≥ 2 x ULN
# Define HBV Treatment Candidacy?

# AASLD Guidance: Monitoring

| HBeAg Positive | HBeAg Negative |
| --- | --- |
| HBV DNA > 20,000 IU/mL | HBV DNA > 2000 IU/mL |
| ALT > ULN but < 2 x ULN* | ALT > ULN but < 2 x ULN* |

*36-69 U/L if male, 26-49 U/L if female.

- Testing recommended to evaluate histologic disease severity, especially if > 40 yrs of age or long infection duration
- Liver biopsy is the only method to assess both fibrosis and inflammation; fibrosis assessment also possible via elastography (preferred) or biomarker testing (eg, FIB-4, *FibroTest*)
  - Treatment recommended if testing reveals significant fibrosis (≥ F2) or moderate/severe inflammation (A2/3)

Terrault. Hepatology. 2018;67:1560.

Slide credit: clinicaloptions.com

# EASL Guidelines: Indications for Treatment

- Primarily based on HBV DNA, serum ALT, and severity of liver disease

| Recommendation | | Level of Evidence | Grade of Recommendation |
|---|---|---|---|
| **Should Be Treated** | ▪ HBeAg-positive or HBeAg-negative chronic hepatitis B* | I | 1 |
| | ▪ Cirrhosis (compensated or decompensated), any detectable HBV DNA, regardless of ALT level | I | 1 |
| | ▪ HBV DNA > 20,000 IU/mL and ALT > 2 x ULN, regardless of degree of fibrosis | II-2 | 1 |
| **May Be Treated** | ▪ HBeAg-positive chronic HBV infection,† if > 30 yrs of age, regardless of severity of liver histological lesions | III | 2 |
| **Can Be Treated** | ▪ HBeAg-positive or HBeAg-negative chronic HBV infection, extrahepatic manifestations, and family history of HCC/cirrhosis‡ | III | 2 |

*Defined by HBV DNA > 2000 IU/mL, ALT > ULN and/or at least moderate liver necroinflammation or fibrosis.
†Defined by high HBV DNA and persistently normal ALT. ‡Even if typical treatment indications not present.

EASL. J Hepatol. 2017;67:370.

Slide credit: clinicaloptions.com

# Rationale for Treating Patients With ALT > 2 x ULN

- Presumably have more active disease with more serious prognosis[1]
- 1990s: IFN treatment resulted in HBeAg seroconversion more commonly in patients with higher ALT levels[2]
- Late 1980s: evaluated prednisone priming[3]

**Emphasis on ALT level to define treatment candidacy is "old thinking"**

1. EASL. J Hepatol. 2017;67:370. 2. Rijckborst. Curr Hepat Rep. 2010;9:231. 3. Perillo. Ann Intern Med. 1988;109:95.

Slide credit: clinicaloptions.com

# Why ALT Level May Not Be a Good Parameter for Treatment

- "It's the virus!"
- Long-term risk of complications related to viremia more than to ALT
  - REVEAL-HBV study and others
- HBeAg seroconversion is useful for assessment of therapy duration, but not related to viral suppression induced by nucleotides
- If long-term treatment is needed, so be it
  - No resistance
  - Long-term safety abundantly demonstrated

Slide credit: clinicaloptions.com

# ETV-022/027: Inflammation and Fibrosis Common Among Patients With Minimally Elevated ALT

| Characteristic | HBeAg-Positive Patients | | HBeAg-Negative Patients | |
|---|---|---|---|---|
| | ALT 1.3-2 x ULN (n = 190) | All (n = 709) | ALT 1.3-2 x ULN (n = 146) | All (n = 638) |
| Mean age, yrs | 35 | 35 | 46 | 44 |
| Male, % | 70 | 75 | 72 | 76 |
| HBV DNA, $\log_{10}$ copies/mL | 9.6 | 9.7 | 6.9 | 7.6 |
| ALT, IU/L | 65 | 143 | 62 | 142 |
| Mean Knodell necroinflammatory score* | 6 | 8 | 7 | 8 |
| Mean Ishak fibrosis score* | 2 | 2 | 2 | 2 |
| HBV genotype A/B/C/D/F/other, % | 25/16/29/18/4/6 | 27/20/28/12/5/6 | 14/18/16/40/1/5 | 10/17/17/46/0/6 |
| BL Knodell necroinflammatory score ≥ 7,* % | 60 | 78 | 72 | 80 |
| BL Ishak fibrosis score ≥ 4,* % | 8 | 14 | 15 | 18 |

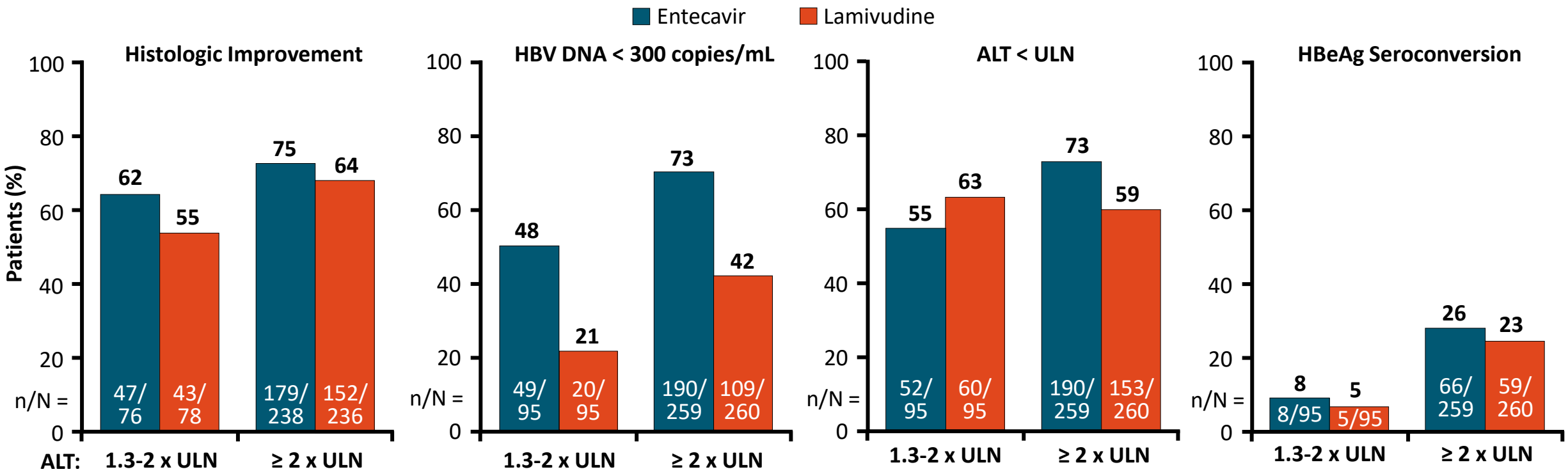
*Patients with adequate BL biopsy.

Wu. Hepatology. 2010;51:1185.

Slide credit: clinicaloptions.com

# ETV-022: Treatment Efficacy in HBeAg-Positive CHB

- Lower responses to entecavir in patients with mildly elevated baseline ALT vs those with ALT ≥ 2 x ULN

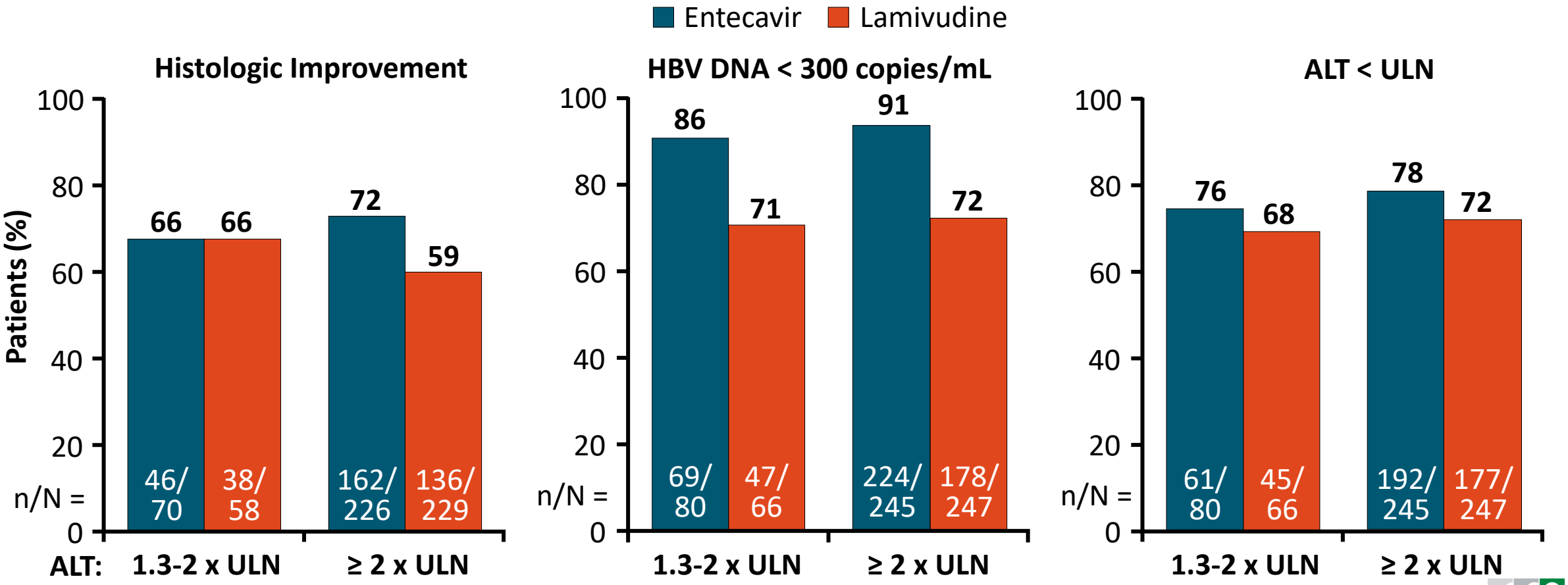



Wu. Hepatology. 2010;51:1185.

Slide credit: clinicaloptions.com

# ETV-027: Treatment Efficacy in HBeAg-Negative CHB

- Response to entecavir similar irrespective of baseline ALT level

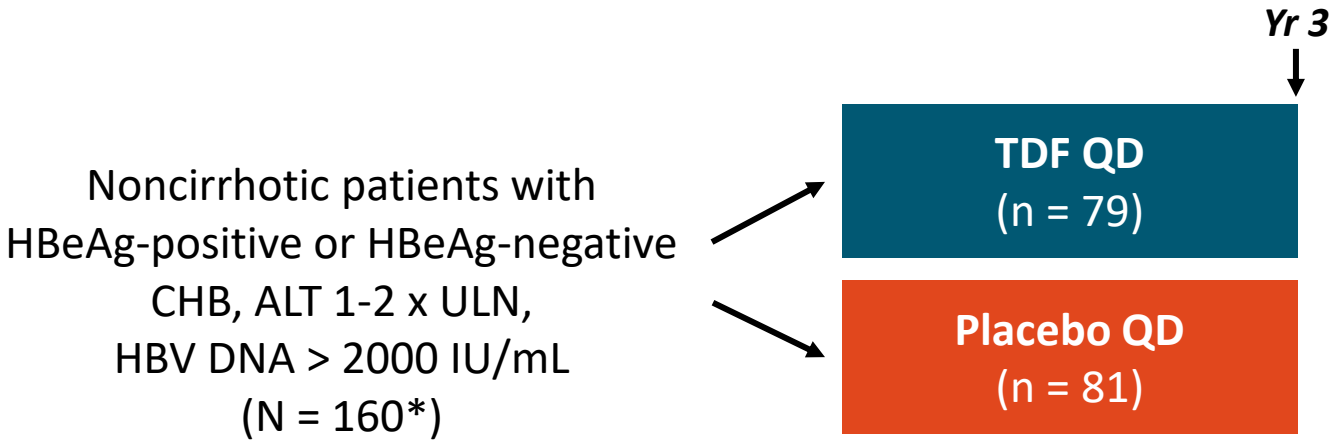



Wu. Hepatology. 2010;51:1185.

Slide credit: clinicaloptions.com

# TDF vs Placebo for Patients With CHB and Minimally Elevated ALT

- Multicenter, randomized, triple-blind phase IV trial in Taiwan




*Results for 132 patients completing treatment with paired biopsy; last patient to finish in December 2018.

- Primary endpoint: histological progression of liver fibrosis, resolution of necroinflammation

Hsu. AASLD 2018. Abstr 264. NCT01522625.

Slide credit: clinicaloptions.com

# CHB Patients With Minimally Elevated ALT: Baseline Characteristics

| Baseline Characteristic | TDF (n = 65) | Placebo (n = 67) | *P* Value |
|---|---|---|---|
| HBeAg positive, % | 20.0 | 26.9 | .41 |
| Median HBV DNA, log IU/mL (IQR) | 5.32 (4.30-6.47) | 5.32 (4.39-6.29) | .74 |
| Median ALT, U/L (IQR) | 53 (46-63) | 52 (46-66) | .66 |
| Ishak fibrosis stage, % | | | .20 |
| ▪ 0 | 9.2 | 10.5 | |
| ▪ 1 | 43.1 | 34.3 | |
| ▪ 2 | 35.4 | 28.4 | |
| ▪ 3 | 9.2 | 13.4 | |
| ▪ 4 | 3.1 | 13.4 | |

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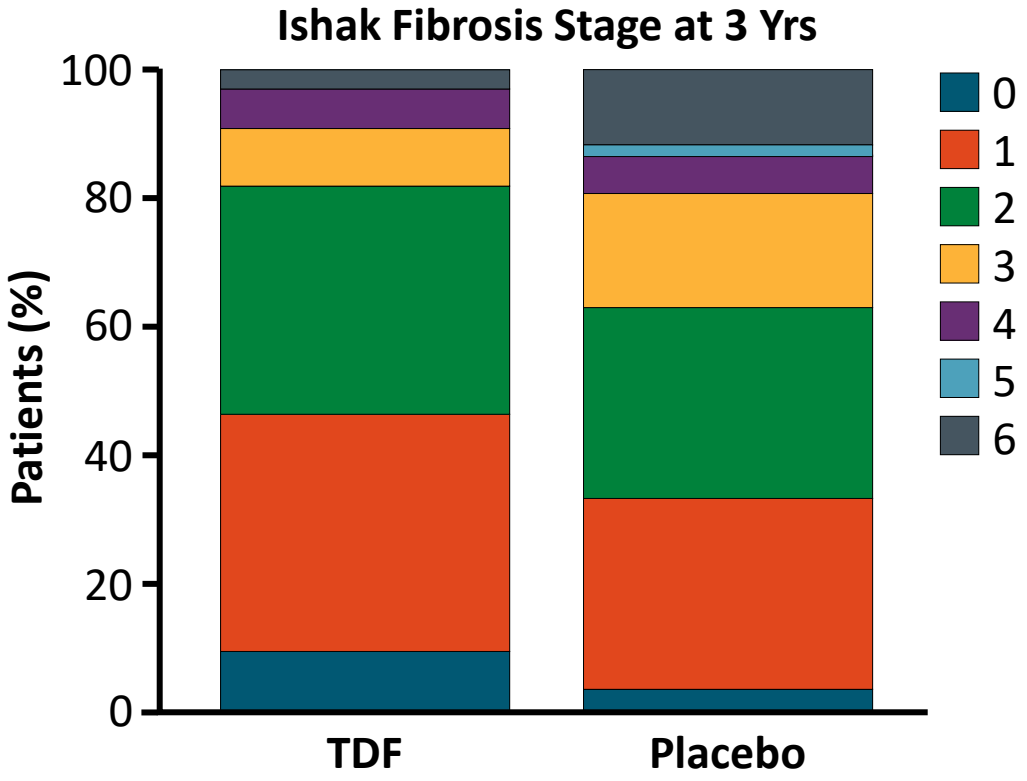
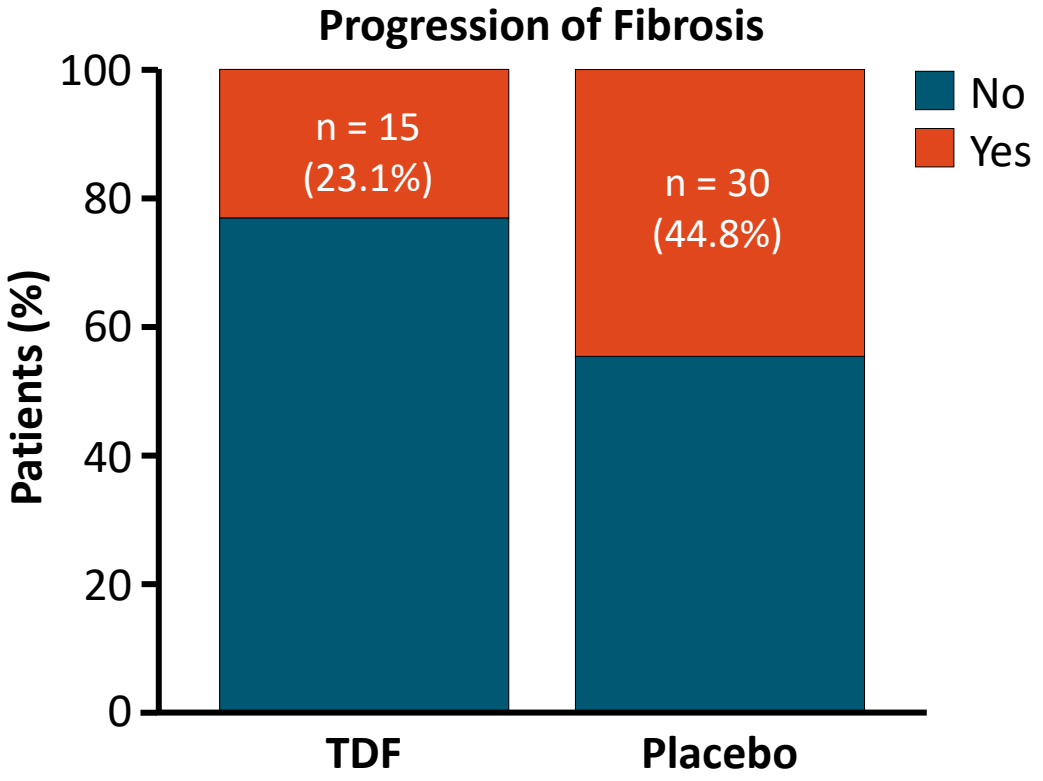
# CHB Patients With Minimally Elevated ALT: Fibrosis

- Use of TDF reduces risk of liver fibrosis progression in this population




For cirrhosis (ie, Ishak 5/6)
RR: 0.23; *P* = .05




For any increase in Ishak fibrosis
RR: 0.52; *P* = .01

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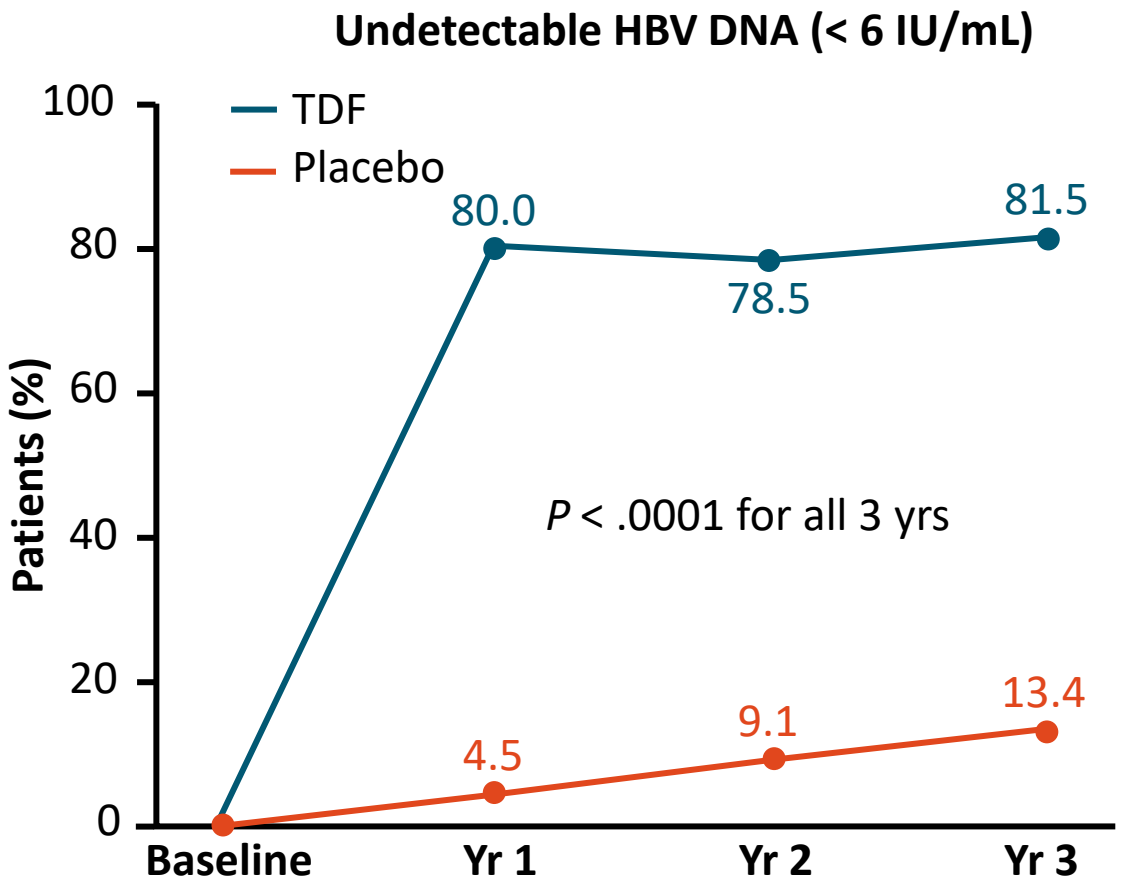
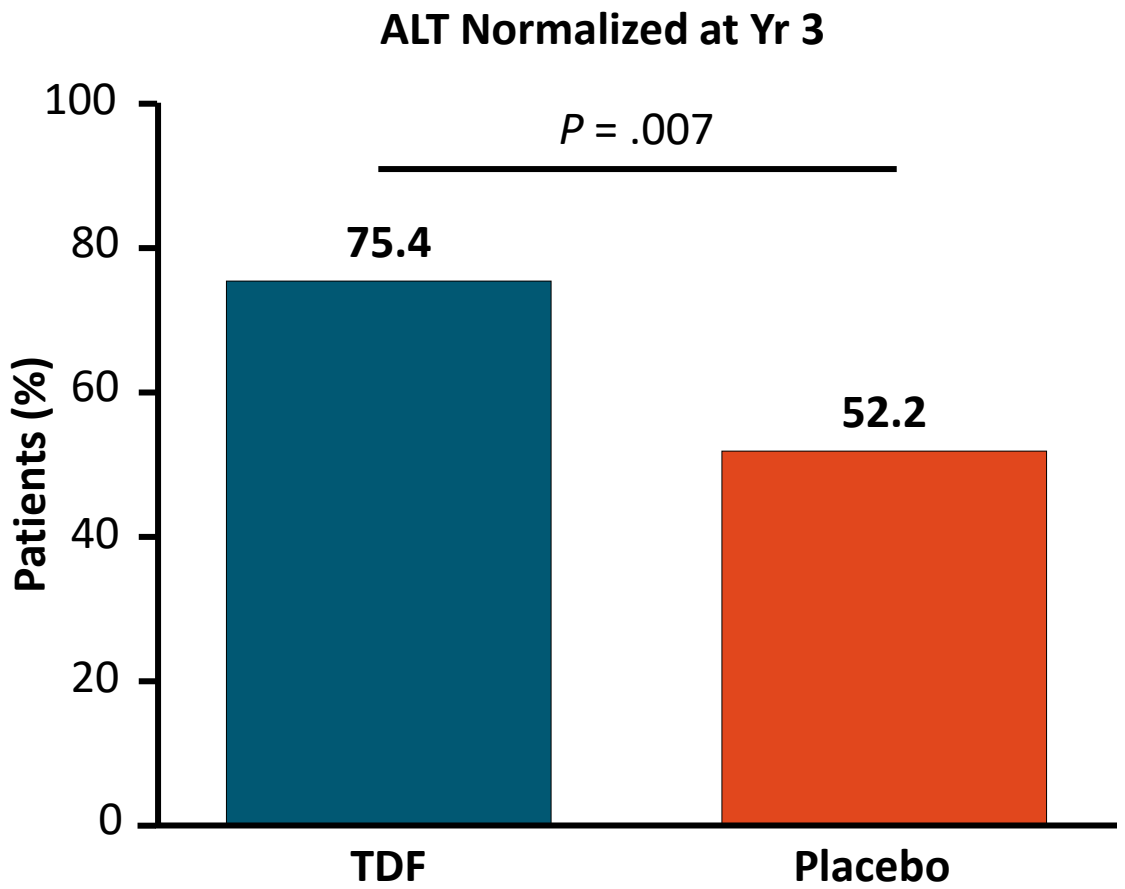
# CHB Patients With Minimally Elevated ALT: Viral Suppression and ALT Normalization

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# ALT Cutoffs For CHB Therapy: Key Take-home Points

- Rigid adherence to arbitrary ALT cutoffs should not be key to treatment decision-making in patients with CHB
- Patients with normal ALT can/should be offered treatment after discussion of advantages and risks
- Patients with mildly elevated ALT should be treated

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