Project ECHO®
Chronic Liver Disease Foundation
New Jersey

HBV Alliance:

Expert Recommendations on Managing Patients with Chronic Hepatitis B

Accredited by

Rehoboth McKinley Christian Health Care Services

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Provided by

CLDF
Chronic Liver Disease Foundation

HBV and Liver Cancer

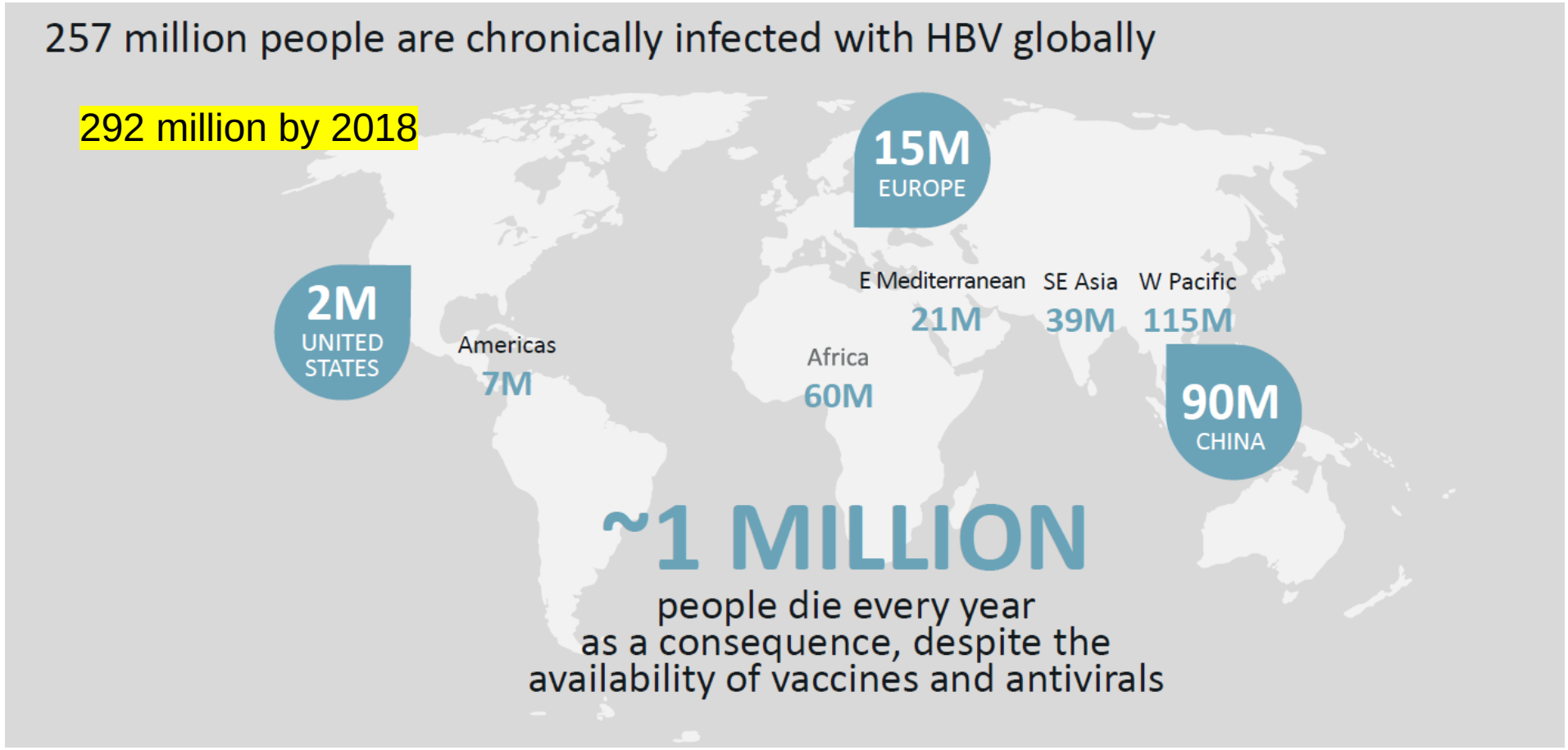
Learning Objectives
HBV ECHO Series

Upon completion of this activity, participants should be able to:

- Review data on the prevalence and transmission of HBV
- Define the risk of HBV among different patient populations, highlighting high-risk settings
- Describe the detrimental effects of untreated, chronic HBV to emphasize the need for diagnosis and treatment
- Demonstrate strategies to incorporate various diagnostic and treatment guidelines into clinical practice
- Analyze approved and emerging treatment options for HBV
- Identify patients that are likely to benefit from emerging treatment options versus currently available therapies

Understanding the Problem

Global Prevalence of HBV Infection (2017)



Hepatitis B. WHO (2017). http://www.who.int/mediacentre/factsheets/fs204/en/.

Global Impact of HCC

- In majority of countries HCC accounts for 75-90% of all primary liver cancer cases
  - 2nd-3rd leading cause of cancer-related deaths
  - Accounts for close to 700,000 deaths/year
- Most common etiology of HCC globally is chronic HBV (50-55%)
  - Annual incidence rate of HCC in CHB patients ranges from 2-5%
  - Confers a lifetime risk of 15-25%
- While decreases in incidence of HBV infection have been observed after the introduction of universal infant HBV vaccination programs, HBV-related HCC is projected to increase for at least the next two decades
- Striking global disparities in frequency exist with the largest burden of disease concentrated in countries with developing economies (85% of cases occur)
  - Highest rates of HCC seen in sub-Saharan Africa and Southeast Asia
  - Deaths from HBV-associated HCC occurs at a younger age in sub-Saharan Africa (median: 38.9 yrs) vs Western Pacific Region (median: 54.5 yrs)
- To reduce HBV-related HCC, continued expansion of universal infant HBV vaccination is required coupled with vigilant screening/surveillance and antiviral therapy targeted in those at risk

1. Ahmed F et al. *Prev Chronic Dis.* 2008; 5:A74; 2. Ferlay et al. *Int J Cancer.* 2015; 136: E359-E86; 3. WHO. *Global Hepatitis Report*. 2017; Geneva: WHO, 2016;
4. Balogh J et al. *J Hepatocell Carcinoma*. 2016; 3: 41-53; 5. Tong M et al. *Gastroenterology & Hepatology*. 2012; 8(12) 808-819;
6. El-Serag H. *Gastroenterology*. 2012; 142(6) 1264-1273; 7. Venook A et al. *The Oncologist.* 2010; 15: 5-13.

Risk Factors for HCC

- HBV in it of itself is considered to be a primary risk factor for HCC exerting pro-oncogenic effects via direct and indirect mechanisms
  - Direct mechanisms revolve around the ability of HBV to integrate into host's genome and to produce potentially carcinogenic proteins/genetic instability
  - Indirect mechanisms center on HBV to induce continuous/recurrent bouts of liver necroinflamation which culminates in the development of cirrhosis
- In addition, HCC risk is largely driven by underlying histological stage (fibrosis) as well as a number of other demographic, viral, and environmental factors
  - Male gender, older age, Asian/African ancestry, family history of HCC
  - Higher DNA levels, genotype, duration of infection, co-infection, elevated ALT
  - Aflatoxin B exposure, heavy ETOH or tobacco use
- Roughly 70-90% of HCC cases occur in those with co-existing cirrhosis

1. Di Bisceglie A. *Hepatology*. 2009; 49: S56-S60; 2. Bruix J et al. *Journal of Hepatology*. 2001; 35: 421-430;
3. El-Serag H. *Gastroenterology*. 2012; 142(6) 1264-1273; 4. Tong M et al. *Digestive Disease Science*. 2011; 56(11) 3143-3162;
5. Yang H et al. *Lancet Oncology*. 2011; 12: 568-574; 6. Yang J et al. *Clin Gastroenterol Hepatol*. 2011; 9: 64-70.

Who to Screen for HCC

Recommendations for HCC Surveillance in HBV Patients

AASLD Guidance

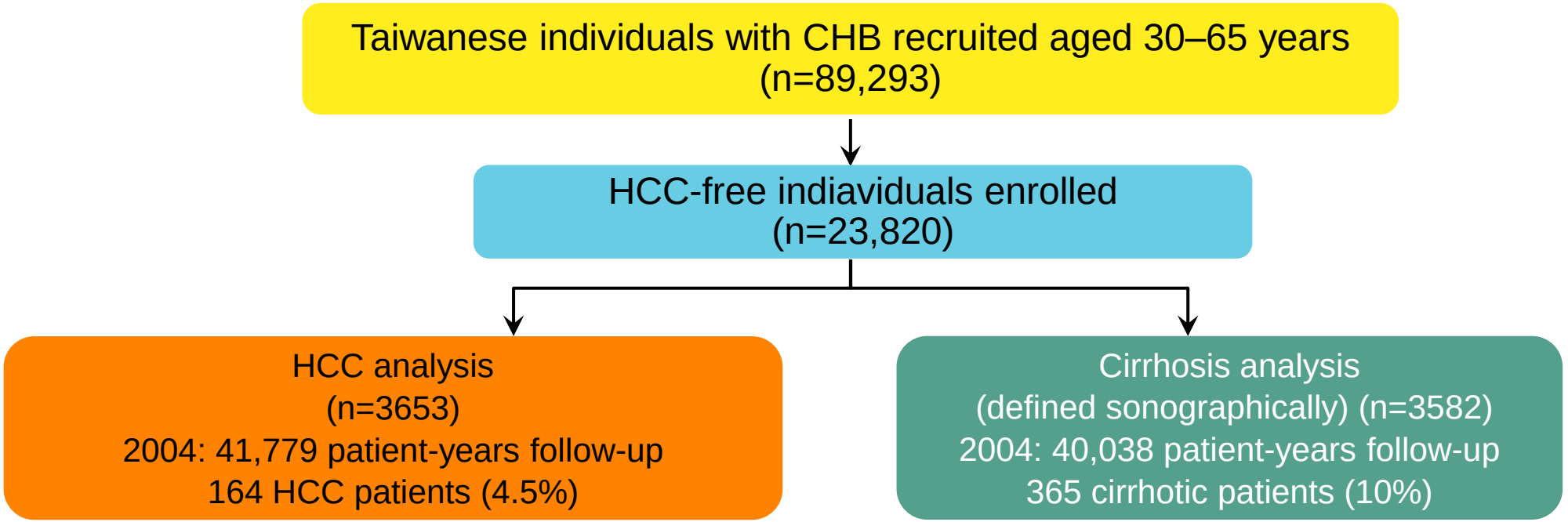
- All patients with cirrhosis should be screened with ultrasound ± AFP every 6 months
- High risk patients without cirrhosis should have ultrasound ± AFP every 6 months
  - Asian or black men >40 yrs
  - Asian women >50 yrs
  - First-degree relative with history of HCC
  - Patients with HDV co-infection
- CT or MRI as adjunct imaging for follow up of identified lesions or for inconclusive results
  - Obesity, may preclude adequate visualization of liver on ultrasound
  - Follow-up of “indeterminate” lesions
  - Elevated AFP and negative ultrasound – can also add on AFP-L3 and Des-Gamma-Craboxy Prothrombin (DCP)

Terrault NA et al. *Hepatology.* 2018;57:1560-99.

HBV Antiviral Therapy Reduces HCC Risk

Taiwan Natural History Study: REVEAL

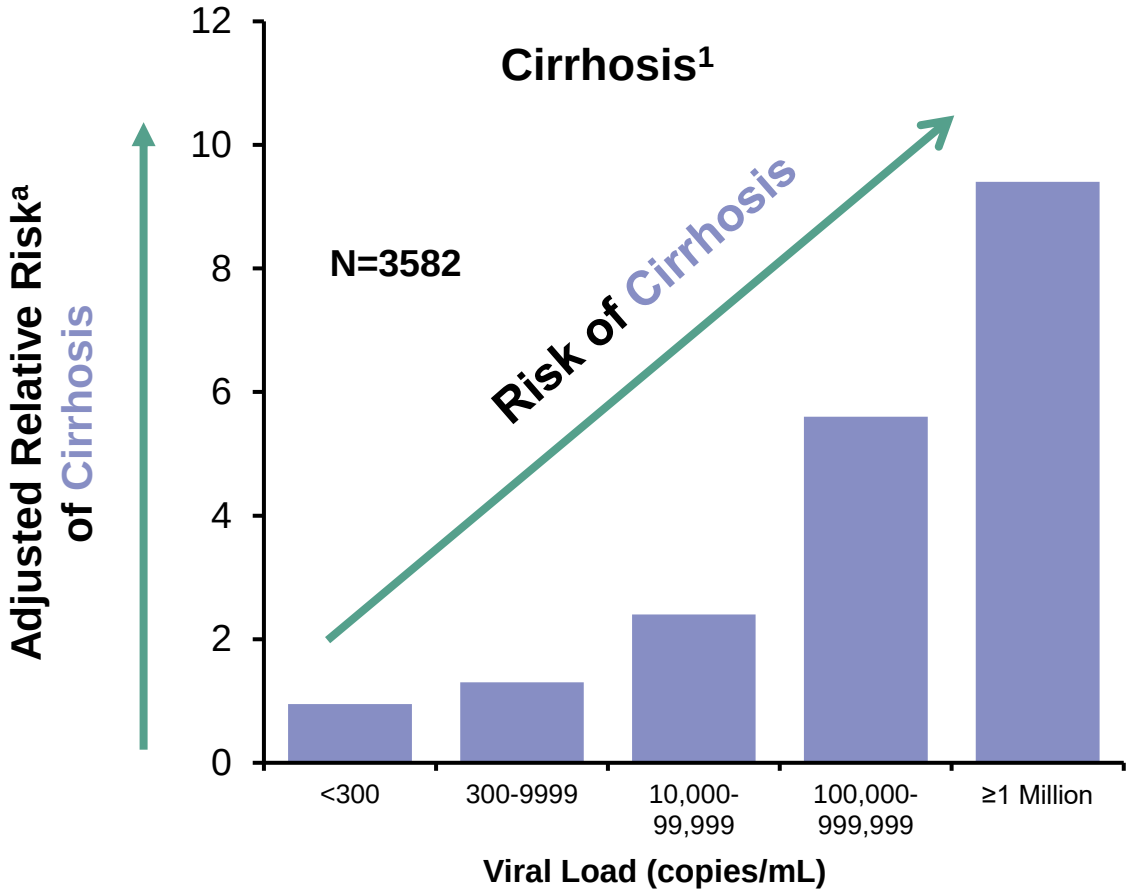
- Prospective, multicenter, observational cohort study
- Follow up >10 yrs (41,000 patient years)

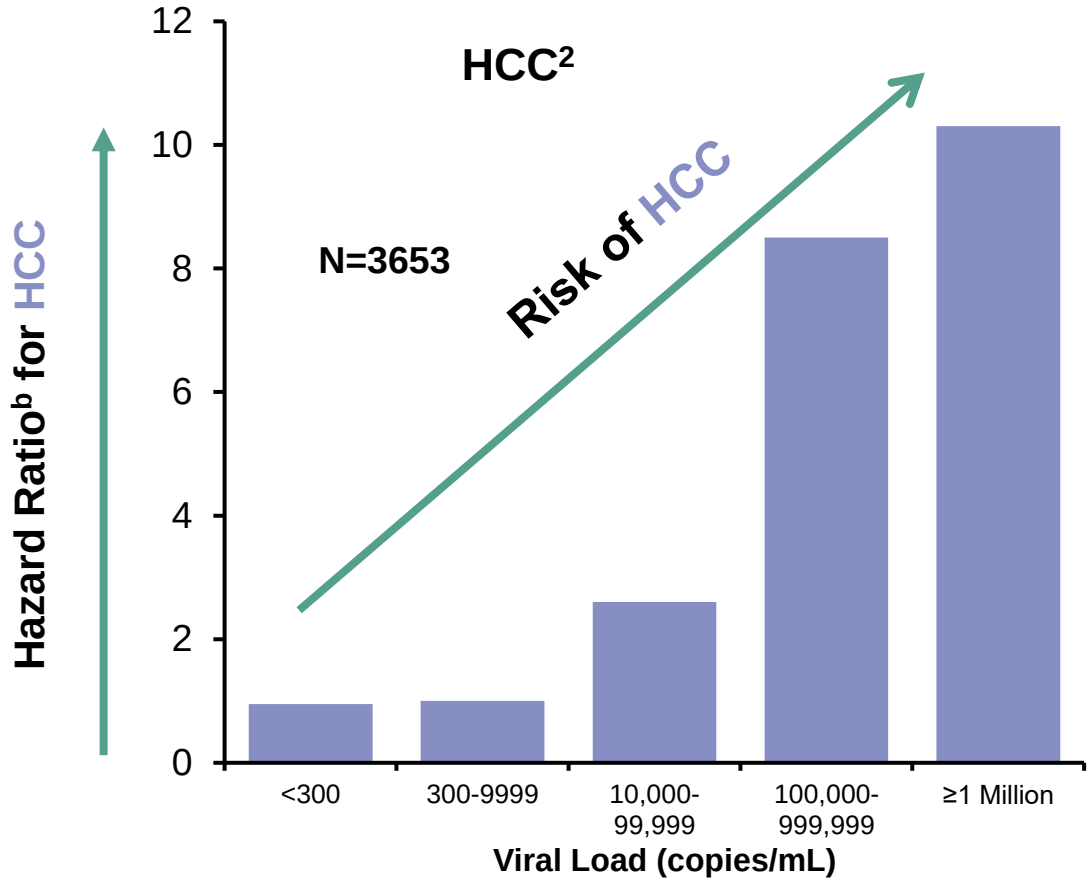


Chen et al. *JAMA.* 2006; 295: 65; Iloeje et al. *Gastroenterology.* 2006; 130: 678.

Higher HBV DNA Levels Are Associated With Increased Risk of Cirrhosis and HCC (REVEAL Study)

Previously <u>untreated</u> patients with CHB

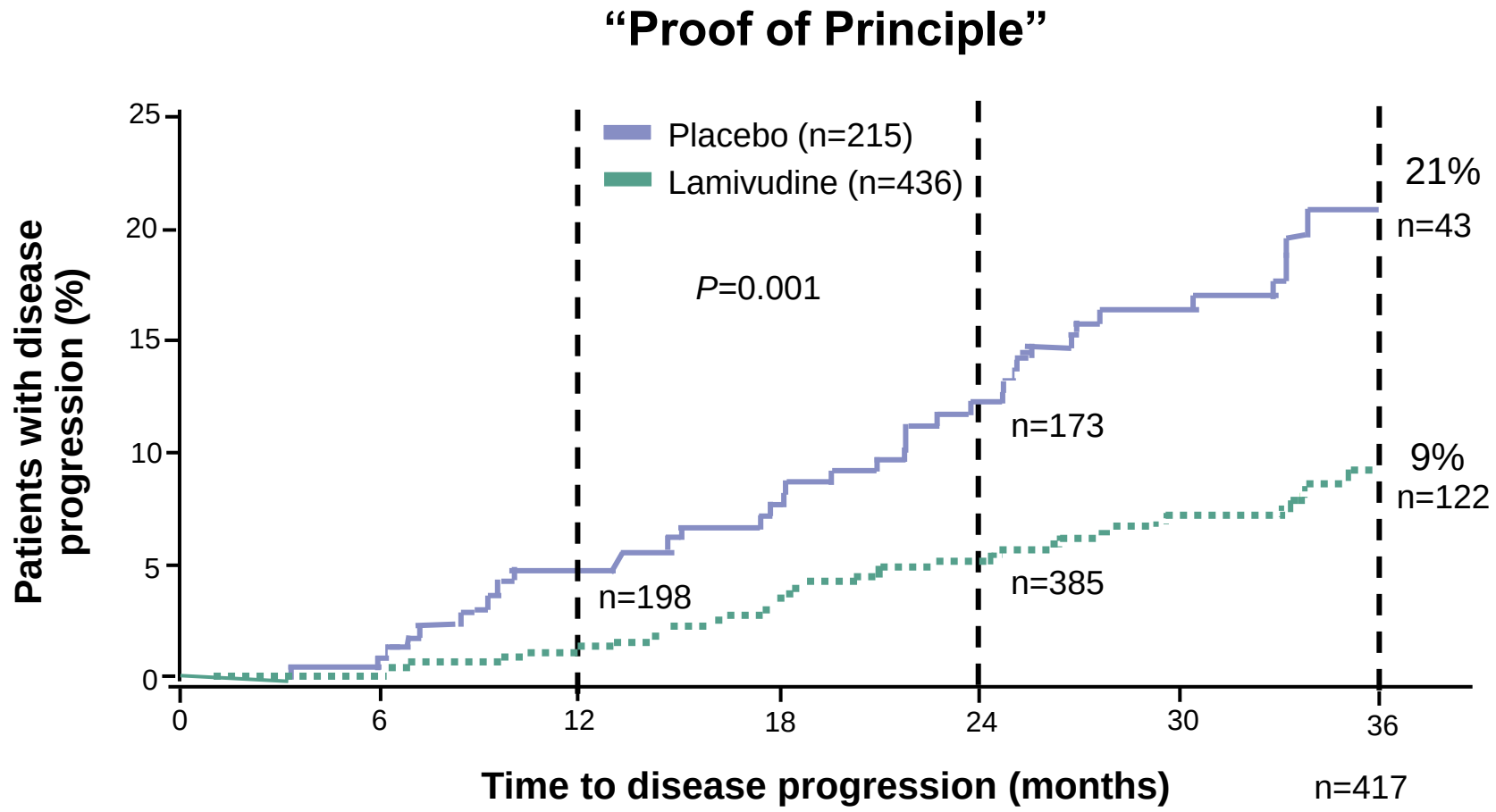




[a]Adjusted for age, sex, cigarette smoking, and alcohol consumption; risk of cirrhosis is independent of HBeAg status and ALT levels.
[b]Relative risk of an endpoint at any given time.

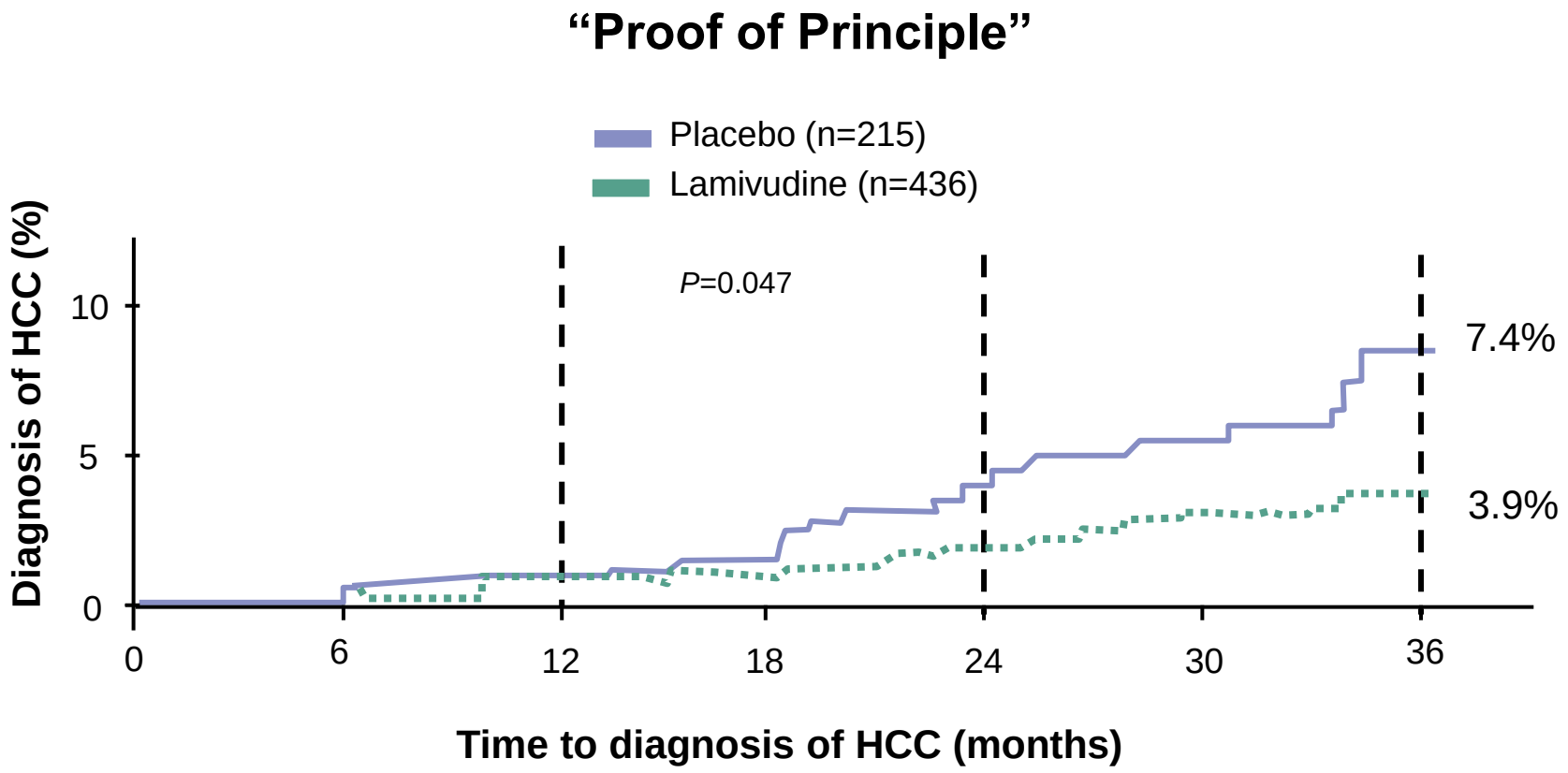
1. Iloeje UH et al. *Gastroenterology*. 2006;130:678-686; 2. Chen CJ et al. *JAMA*. 2006;295:65-73.

Antiviral Therapy Delays Overall Disease Progression in Chronic Hepatitis B



Liaw YF et al. *N Engl J Med.* 2004; 351:1521-1531.

Antiviral Therapy Suppresses Development of Hepatocellular Carcinoma in Chronic Hepatitis B



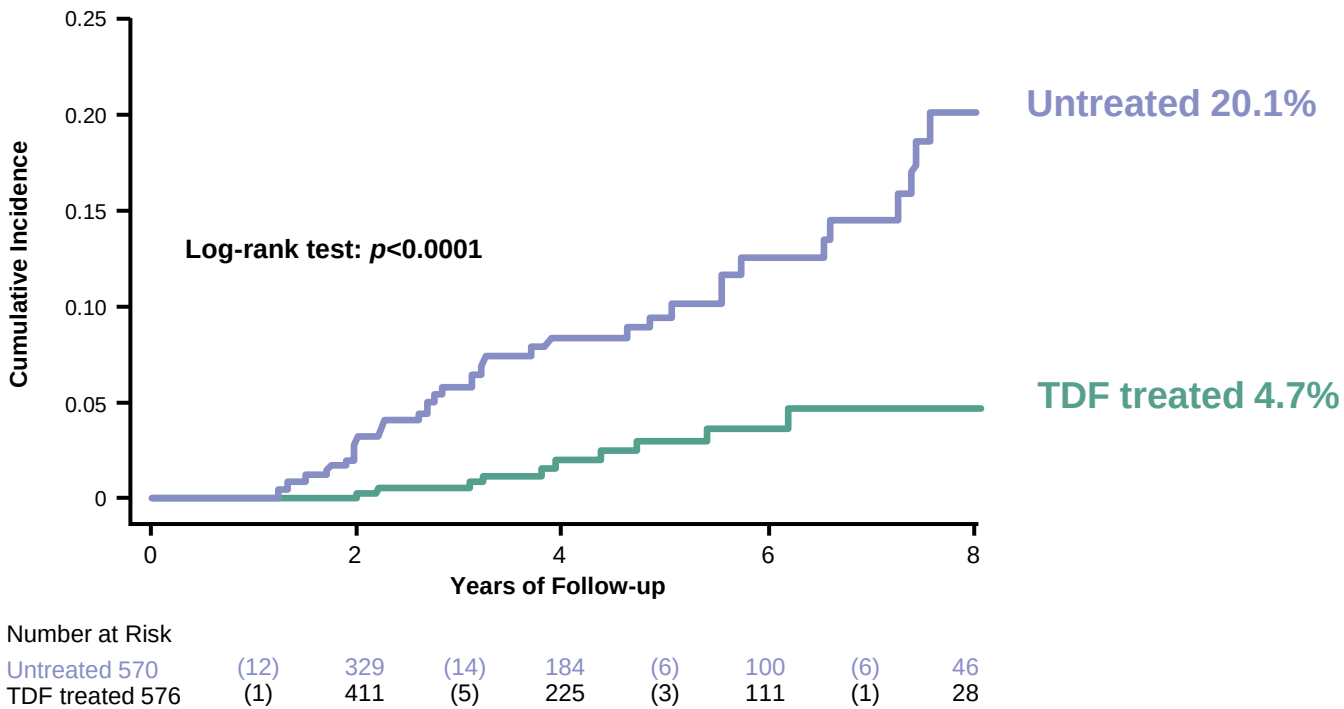
Liaw YF et al. *N Engl J Med.* 2004; 351:1521-1531.

Incidence of HCC in Cirrhotic and Noncirrhotic Patients With CHB Treated With TDF

Overall Cumulative Incidence of HCC

Propensity Score-Matched* Untreated and TDF-Treated Patients

	Untreated n=591	TDF Treated n=591	*p*-value
Age, years	44.6 ± 12.7	45.1 ± 13.4	0.50
Male sex (%)	59.1	59.6	0.86
Asian ethnicity (%)	96.6	94.3	0.051
Baseline cirrhosis (%)	8.5	8.3	0.92
HBeAg positivity (%)	29.6	28.1	0.56
Log_{10} HBV DNA level, IU/mL	4.5 ± 2.2	4.4 ± 2.3	0.23
ALT level, U/L	31 (19–51)	44 (30–71)	0.30
Follow-up duration, months	40.3 ± 36.7	43.7 ± 32.1	0.091



The 8-year cumulative incidence of HCC was significantly higher in the untreated group than in the TDF-treated group (*p*<0.0001)

* Propensity score matched by age, sex, HBeAg, HBV DNA, ALT, follow-up time, and baseline cirrhosis status

Nguyen MH, et al. *J Infect Dis*. 2019 Jan 1;219(1):10-18. doi: 10.1093/infdis/jiy391.

Incidence of HCC in Cirrhotic and Noncirrhotic Patients With CHB Treated With TDF

Multivariate Analysis of Risk Factors for HCC Among Cirrhotic and Noncirrhotic Patients with CHB

	Adjusted HR (95% CI)	*p*-value
Cirrhosis	5.36 (2.73-10.51)	<0.001
Male sex	2.28 (1.04-4.96)	0.038
Age (per 5-y interval)	1.37 (1.20-1.58)	<0.001
Log_{10} HBV DNA level (per IU/mL)	1.17 (0.99-1.36)	0.055
ALT level (per U/L)	0.997 (0.99-1.003)	0.33
TDF treatment	0.34 (0.16-0.71)	0.005

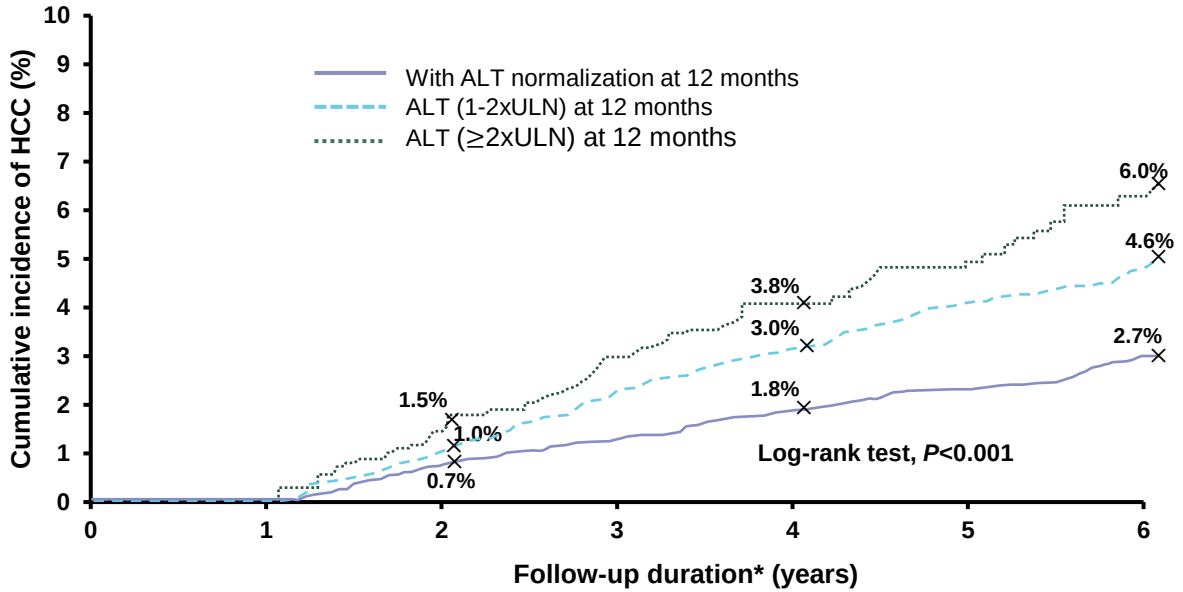
Overall, TDF therapy was significantly associated with a 66% reduction in the risk of HCC (*p*=0.005)

Nguyen MH, et al. *J Infect Dis*. 2019 Jan 1;219(1):10-18. doi: 10.1093/infdis/jiy391.

The Risk of HCC in Patients With Early On-Treatment ALT Normalization

- Risk of HCC in 21,182 patients from Hong Kong treated with ETV and/or TDF from 2005–2016

Baseline Characteristics	With ALT normalization at 12 months N=10,437	Without ALT normalization at 12 months N=10,745
Male sex, n (%)	8,027 (77)	6,272 (58)
Mean age, years	51	51
Platelets, x10^9/L	186	180
Albumin, g/L	41	41
Bilirubin, µmol/L	20	18
ALT, U/L	58	61
HBV DNA, log_{10}IU/mL	5.1	4.9
Comorbidities, n (%) Cirrhosis Diabetes mellitus	 921 (9) 1313 (13)	 1,133 (11) 1703 (16)



Variable	Multivariable analysis	
	Adjusted HR (95% CI)	P value
With ALT norm. at 12 mo.	1	<0.001
ALT (1-2xULN) at 12 mo.	2.07 (1.67-2.56)	<0.001
ALT (≥2xULN) at 12 mo.	3.21 (2.32-4.44)	<0.001

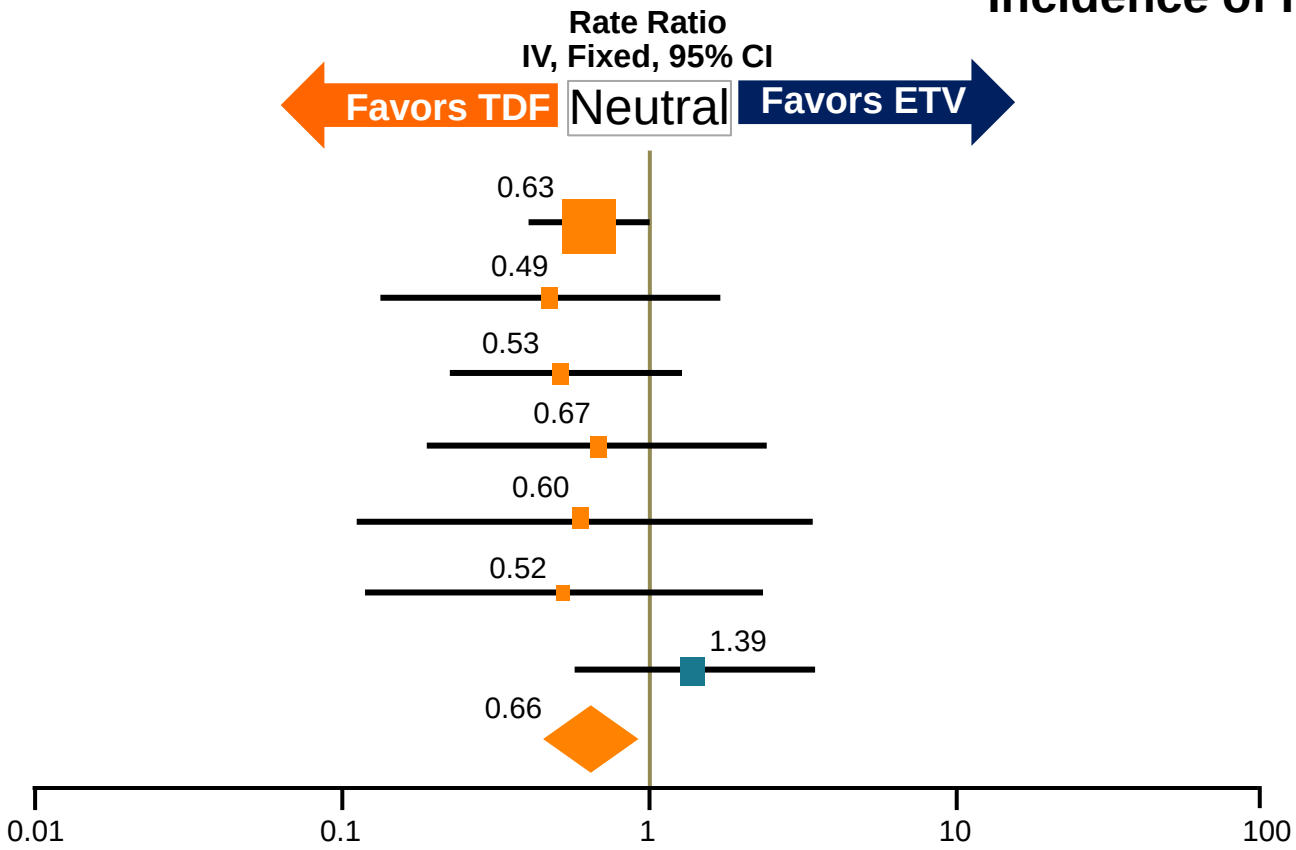
Early on-treatment ALT normalization is associated with reduced HCC risk

*Median duration of follow-up (years) was 4.0 years; Based on AASLD 2016 ALT criteria, ULN: 30 U/L in males, 19 U/L in females

Wong. *J Hepatol*. 2018: 69(4):793-802; Yip. *APASL*. 2018, Oral YIA-C-05.

Meta-analysis on Reduction of HCC in CHB Patients Taking TDF vs. ETV

Incidence of HCC



Study or Subgroup	Log [Rate Ratio]	SE	Weight	Rate Ratio IV, Fixed, 95% CI
Choi 2017	-0.462	0.2069	56.7%	0.63[0.42, 0.95]
Goyal 2015	-0.7215	0.6454	5.8%	0.49[0.14, 1.72]
Kim, BG 2018	-0.6349	0.4378	12.7%	0.53[0.22, 1.25]
Kim, YM 2018	-0.402	0.6406	5.9%	0.67[0.19, 2.35]
Koklu 2013	-0.5108	0.8661	3.2%	0.60[0.11, 3.28]
Tsai 2017	-0.6539	0.7405	4.4%	0.52[0.12, 2.22]
Yu 2018	0.3293	0.4638	11.3%	1.39[0.56, 3.45]
Subtotal (95% CI)			**100.0%**	**0.66[0.49, 0.89]**

Heterogeneity: $Chi^2=3.22$, $df=6(P=0.78)$; $I^2=0\%$
Test for overall effect $Z=2.67(P=0.008)$

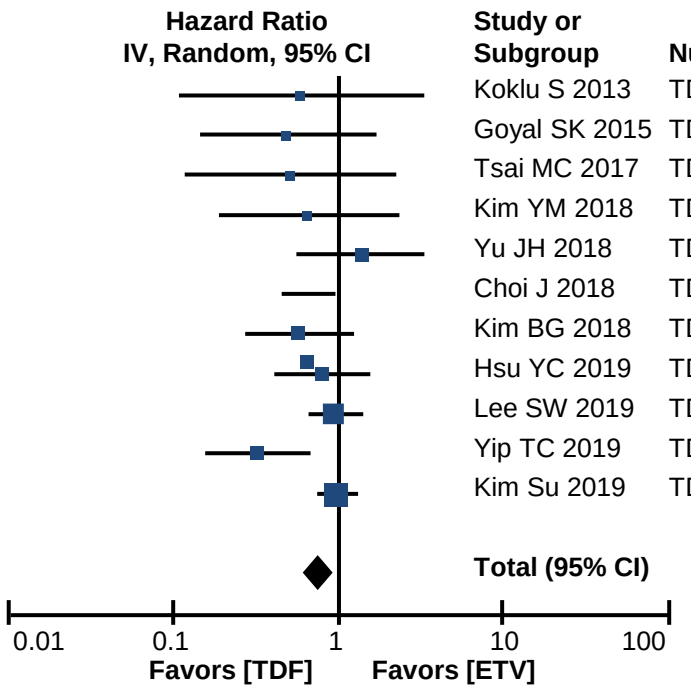
Significantly lower incidence of HCC among the TDF vs ETV groups [rate ratio (95% CI) of 0.66 (0.49, 0.89), *p*=0.008]

Subgroup analysis excluded 2 studies with significant differences in age.

Zhang Z. et al. *BMC Cancer.* 2019;19(1):511. doi: 10.1186/s12885-019-5735-9.

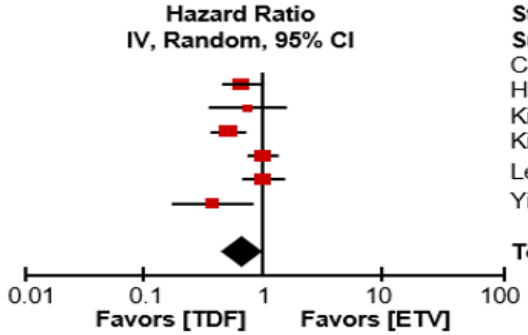
Meta-analysis on Reduction of HCC in CHB Patients Taking TDF vs. ETV

Forest plot of pooled HR for HCC between TDF and ETV



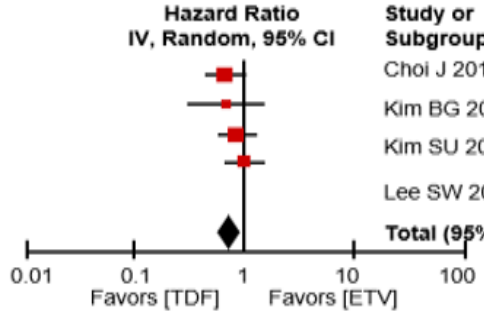
Study or Subgroup	Number of Patients	Hazard Ratio IV, Random 95% CI
Koklu S 2013	TDF 72, ETV 77	0.60 [0.11, 3.27]
Goyal SK 2015	TDF 180, ETV 220	0.49 [0.14, 1.72]
Tsai MC 2017	TDF 83, ETV 359	0.52 [0.12, 2.25]
Kim YM 2018	TDF 112, ETV 191	0.67 [0.19, 2.36]
Yu JH 2018	TDF 176, ETV 406	1.39 [0.56, 3.45]
Choi J 2018	TDF 1141, ETV 1560	0.66 [0.46, 0.95]
Kim BG 2018	TDF 604, ETV 721	0.58 [0.27, 1.25]
Hsu YC 2019	TDF 700, ETV 4837	0.81 [0.42, 1.56]
Lee SW 2019	TDF 1439, ETV 1583	0.97 [0.68, 1.38]
Yip TC 2019	TDF 1309, ETV 28041	0.33 [0.16, 0.68]
Kim Su 2019	TDF 1413, ETV 1484	0.98 [0.75, 1.28]
Total (95% CI)		**0.77 [0.62, 0.96]**

Forest plot of pooled HR for HCC between TDF and ETV in PSM cohorts



Study or Subgroup	Number of Patients	Hazard Ratio IV, Random 95% CI
Choi J 2018	TDF 869, ETV 869	0.68 [0.47, 0.99]
Hsu YC 2019	TDF 520, ETV 520	0.77 [0.37, 1.60]
Kim BG 2018	TDF 354, ETV 354	0.53 [0.39, 0.72]
Kim SU 2019	TDF 1278, ETV 1278	1.02 [0.77, 1.35]
Lee SW 2019	TDF 1370, ETV 1370	1.03 [0.70, 1.51]
Yip TC 2019	TDF 1200, ETV 4636	0.39 [0.18, 0.84]
Total (95% CI)		**0.73 [0.54, 0.98]**

Forest Plot of Pooled HR of HCC between TDF and ETV in Patients with Liver Cirrhosis



Study or Subgroup	Number of Patients	Hazard Ratio IV, Random 95% CI
Choi J 2018	TDF 653, ETV 935	0.64 [0.43, 0.95]
Kim BG 2018	TDF 267, ETV 346	0.68 [0.30, 1.54]
Kim SU 2018	TDF 411, ETV 499	0.83 [0.60, 1.14]
Lee SW 2019	TDF 483, ETV 567	0.99 [0.66, 1.48]
Total (95% CI)		**0.80 [0.65, 0.98]**

TDF therapy was associated with a significantly lower risk of HCC in patients with CHB compared with ETV therapy. This effect was observed even in PSM cohorts and in patients with cirrhosis

PSM: Propensity Score Matching, *Propensity score matching in the Yip study yielded 1:4 ratio for the number of patients in TDF:ETV arms. Size of square proportional to weight used in analysis for each study; diamond represents total result with horizontal points as the limits of the 95% CI

Choi W-M, et al. *AASLD*. 2019. 484.

Conclusions

- HBV accounts for the majority of HCC cases globally and contributes to significant morbidity and mortality
- HCC screening and surveillance with US +/- AFP every 6 months is recommended in all HBV patients with cirrhosis as well as high-risk non-cirrhotic HBV patients
  - Asian or black men >40 yrs, Asian women >50 yrs, first-degree relative with history of HCC, patients with HDV co-infection
- Early identification of HBV patients eligible for treatment and timely initiation of antiviral therapy significantly reduces the risk of HCC via suppression of HBV DNA and normalization of ALT

Case 1

- 38 yo man with HIV/HBV co-infection followed in our hepatology clinic
- Currently on HAART with Biktarvy (which includes TAF) with CD4 855, HIV VL <15
- HBV DNA 800 IU/mL
- No family history of HCC or HBV
- PMH: HTN
- SH: ½ ppd, “occasional” ETOH, prior IV drug use, quit 2 years ago
- Meds: Biktarvy, methadone, HCTZ

Case 1, Cont.

- On recent clinic follow up
- Labs:
- Hgb 13, platelets 138
- AST 32, ALT 20, T bili 0.9, Albumin 3.8
- BMP normal, INR 1.05
- FIB-4: 2.02
- Fibroscan: LSM 8.5
- HBV DNA 560 IU/mL
- Does this person need to start HCC screening?

Which HBV Patients Should We Screen for HCC?

AASLD Guidance

- All patients with cirrhosis should be screened with ultrasound ± AFP every 6 months
- High risk patients without cirrhosis should have ultrasound ± AFP every 6 months
  - Asian or black men >40 yrs
  - Asian women >50 yrs
  - First-degree relative with history of HCC
  - Patients with HDV co-infection

HCC Risk Factors in This Patient

- Platelets 138
  - One of the earliest predictors of advanced fibrosis or cirrhosis in liver disease
- HIV/HBV co-infection
  - HIV co-infection associated with higher HCC risk
- FIB-4: 2.02
  - <1.45 NPV 90% for advanced fibrosis; >2.67 PPV 80% for advanced fibrosis
- Fibroscan: LSM 8.5
  - Cutoffs for ≥F3 range 7.0-13.5 (AUROC 0.91); F4 range 9.0-16.9 (AUROC 0.93)

Case 1, Cont.

- US and AFP ordered
- US mild nodularity of liver capsule, hepatomegaly, heterogenous enhancement suggest of steatosis, no mass legions
- AFP 49 ng/mL (normal <20 ng/mL)

Case 1, Cont.

- CT quad phase was ordered, which showed no evidence of any hepatic lesions
- Would you continue HCC surveillance in this patient?
- How often and with what modality?

Case 2

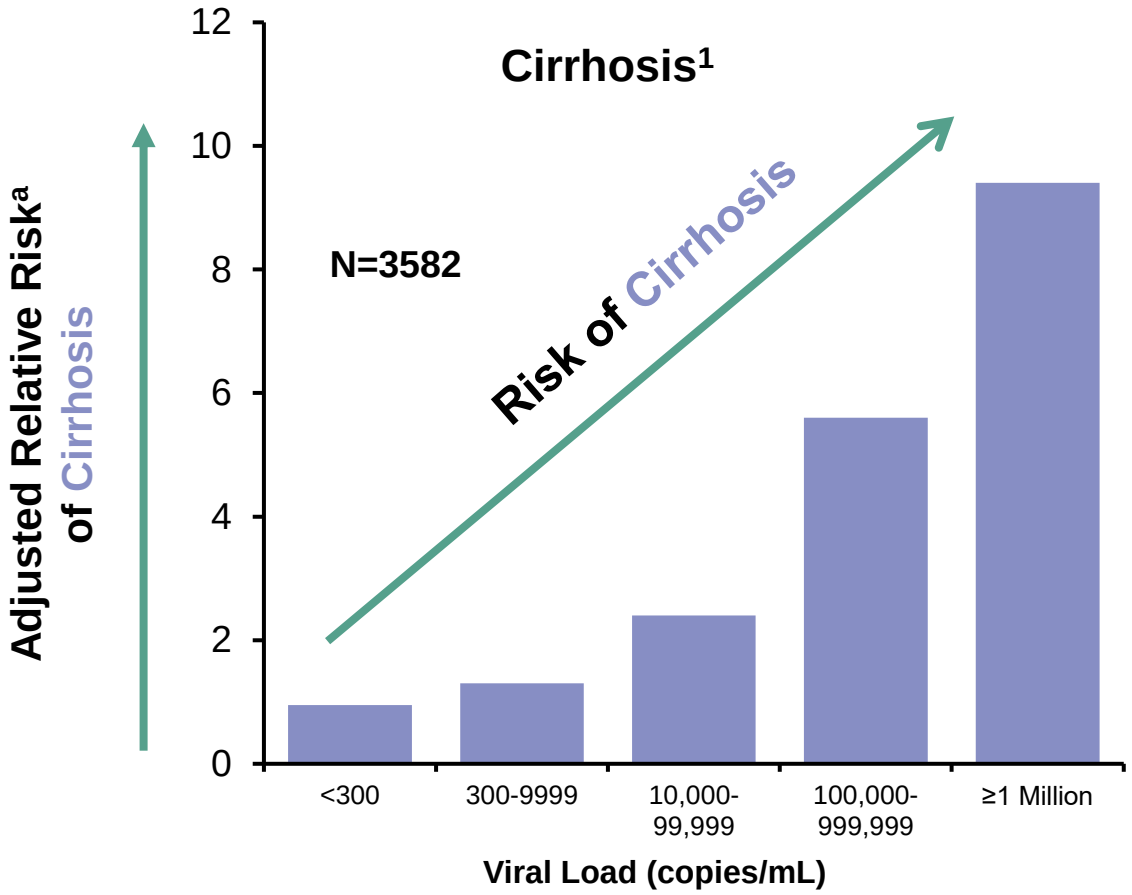
- 68yo Asian woman with chronic HBV
- Diagnosed more than 40 years ago in China
- Has been on HBV treatment for past 20+ years
- Currently on entecavir 1mg daily for at least 10 years
- FH: mother with HCC, brother in China with HBV without HCC
- SH: denies tob, etoh, drugs. Regularly uses traditional Chinese medicine to help with her arthritis symptoms
- Meds: Entecavir 1mg daily, occasionally Advil

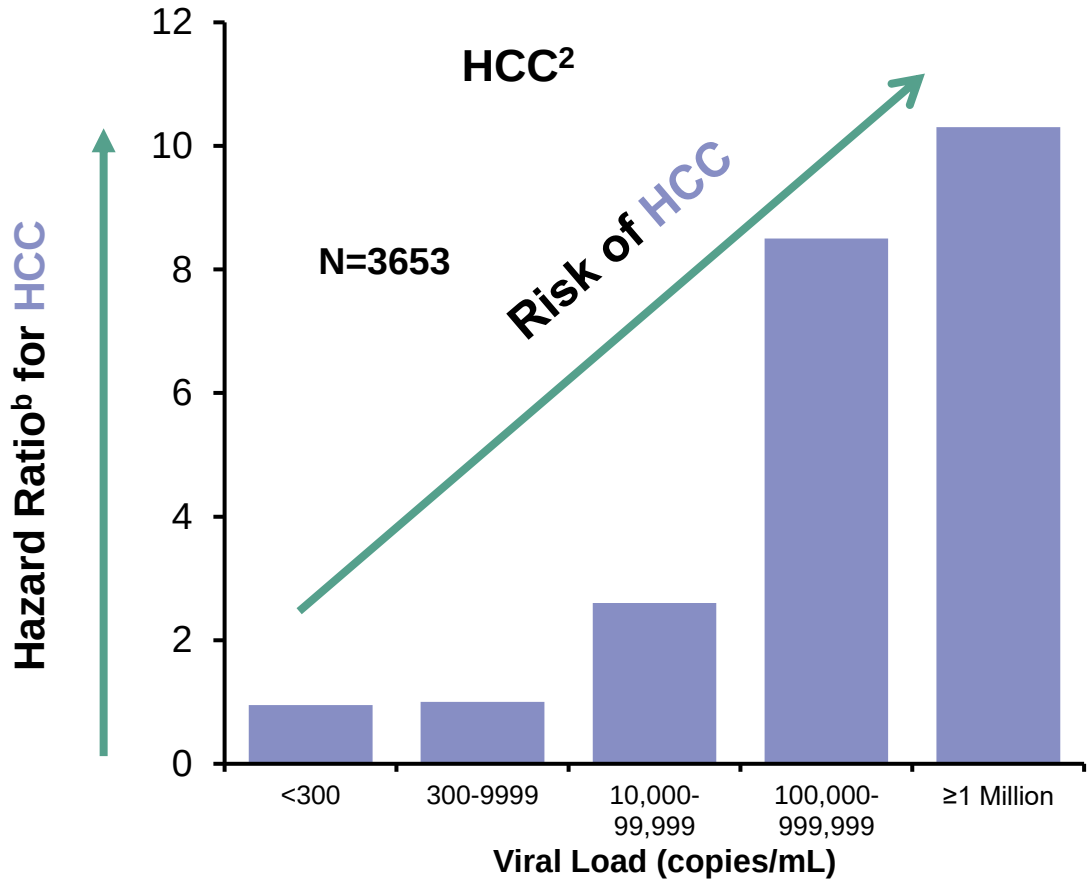
Case 2, Cont.

- Labs 6 months ago:
- CBC normal
- CMP notable for BUN 23, Cr 0.9 (GFR 68), AST 22, ALT 19, albumin 3.9
- HBV DNA 120 IU/mL, AFP 7 ng/mL
- US 8 months ago – no evidence of hepatic lesions

Higher HBV DNA Levels Are Associated With Increased Risk of Cirrhosis and HCC (REVEAL Study)

Previously <u>untreated</u> patients with CHB





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Overall Cumulative Incidence of HCC

Propensity Score-Matched* Untreated and TDF-Treated Patients

	Untreated n=591	TDF Treated n=591	*p*-value
Age, years	44.6 ± 12.7	45.1 ± 13.4	0.50
Male sex (%)	59.1	59.6	0.86
Asian ethnicity (%)	96.6	94.3	0.051
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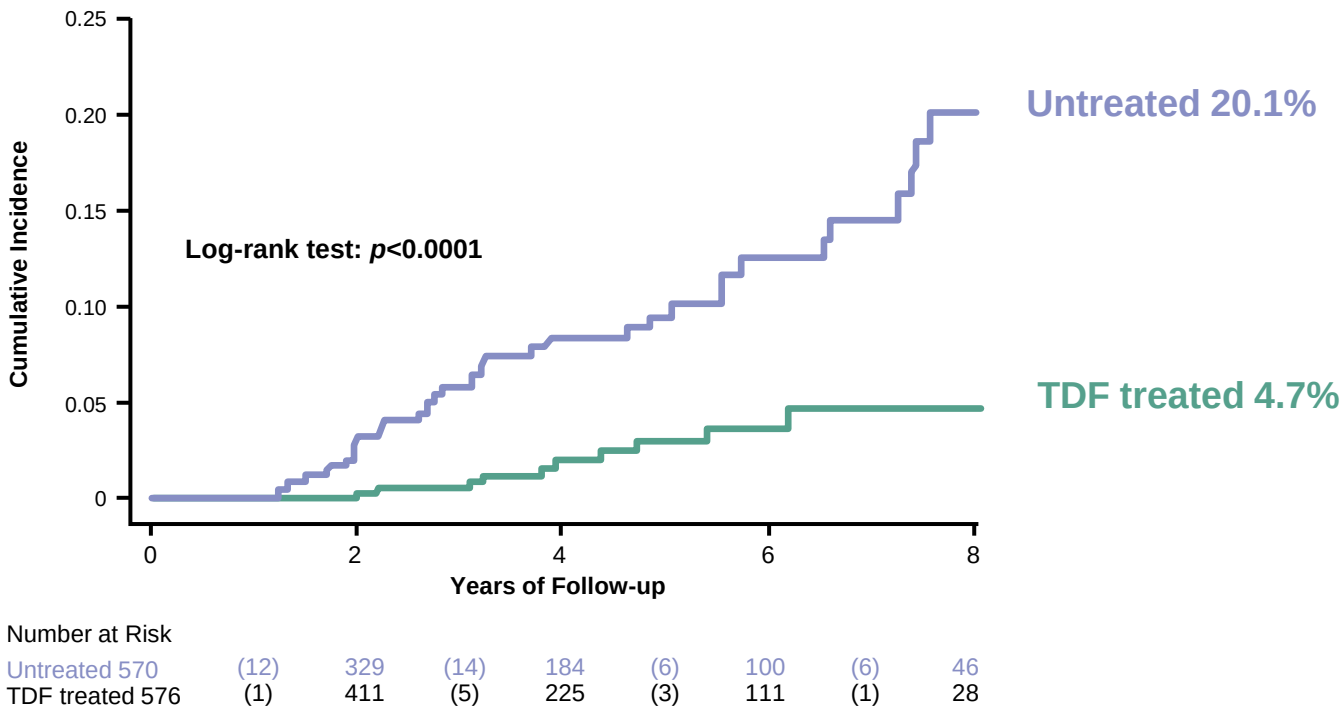

The 8-year cumulative incidence of HCC was significantly higher in the untreated group than in the TDF-treated group (*p*<0.0001)

* Propensity score matched by age, sex, HBeAg, HBV DNA, ALT, follow-up time, and baseline cirrhosis status

Nguyen MH, et al. *J Infect Dis*. 2019 Jan 1;219(1):10-18. doi: 10.1093/infdis/jiy391.

Case 2, Cont.

- Labs today
- CBC normal
- CMP notable for BUN 23, Cr 1.0, AST 20, ALT 21, albumin 3.9
- HBV VL 200 IU/mL undetectable, AFP 9 ng/mL
- US ordered and pending
- Are you worried about the HBV VL?

- AASLD HBV guidelines
- Persistent low level viremia (<2,000 IU/mL) can maintain on monotherapy regardless of ALT
- If there is evidence of virologic breakthrough (>1 log increased compared to nadir or HBV VL >100 IU/mL in previously undetectable)
  - Confirmatory testing to ensure true virologic breakthrough
  - Entecavir → switch to TDF or TAF
  - TDF or TAF → add entecavir
  - May consider resistance testing

Case 2, Cont.

- Despite the lack of true virologic breakthrough per AASLD definitions, the patients was switched to TAF 25mg daily
- Provider cited also potential benefits of improved bone and renal safety given age and ethnicity of the patients

Thank you!