SHC-HKASLD HBV webinar series
14th September 2020

Does antiviral therapy reduce HCC in chronic hepatitis B?

Dr. Grace Lai-Hung Wong
MBChB (Hons, CUHK), MD (CUHK), FRCP(Lond, Edin), FHKCP, FHKAM (Medicine)

Director, CUHK Medical Data Analytics Centre (MDAC)
Professor, Institute of Digestive Disease
The Chinese University of Hong Kong

Reducing the risk of HCC is the primary goal in managing patients with chronic hepatitis B (CHB)

To improve survival and quality of life by preventing disease progression, and reducing complications including HCC[1-4]

1. Terrault NA, et al. Update on Prevention, Diagnosis, and Treatment and of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance.
2. EASL. J Hepatol. 2017 Aug;67(2):370-398.
3. Sarin SK, et al. Hepatol Int. 2016 Jan;10(1):1-98.
4. Chien RN, et al. Taiwan Consensus Statement on the Management of Chronic Hepatitis B. J Formos Med Assoc. 2019 Jan;118:7-38.

Reducing HCC risk requires long-term effective antiviral therapy

Continued inhibition of viral replication by antiviral therapy, can eliminate chronic HBV-induced necrotic inflammatory activity and progression of liver fibrosis, and may correspondingly reduce HCC risk

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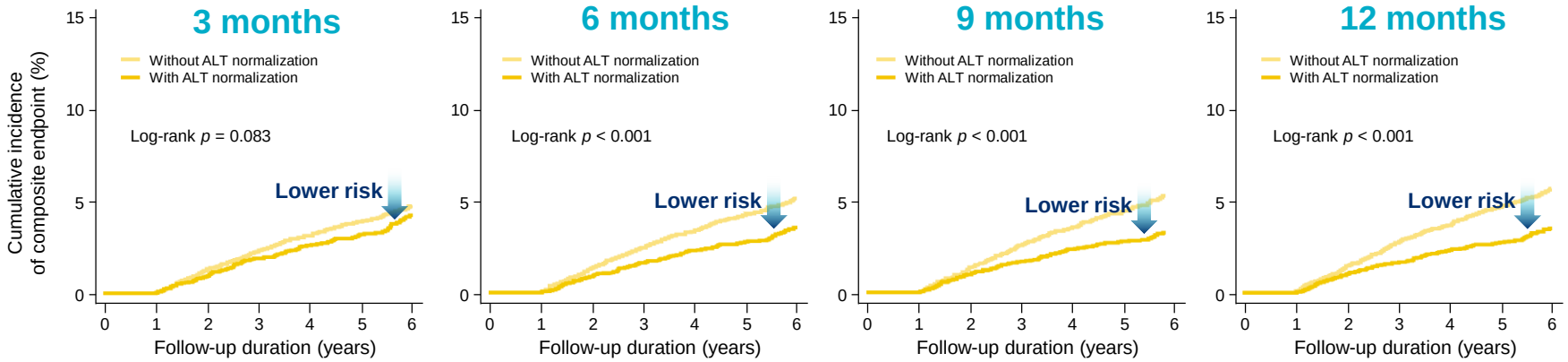
- Long-term treatment with NAs can bring benefits from reduced HCC risk
- Regardless of the severity of liver disease, long-term treatment should be initiated with a NUC that provides high genetic barrier to resistance

EASL. J Hepatol. 2017 Aug;67(2):370-398.

ALT normalization is associated with reduced risk of HCC

Kaplan-Meier analysis of the cumulative incidence of HCC or hepatic events according to normalization of ALT after antiviral treatment



		3 months	6 months	9 months	12 months
Cumulative incidence of composite endpoint at 6 years (%) (95% CI)	Without ALT normalization	4.76 (4.34-5.21)	5.24 (4.76-5.77)	5.57 (5.04-6.16)	5.70 (5.15-6.32)
	With ALT normalization	4.27 (3.54-5.15)	3.60 (3.07-4.21)	3.44 (2.98-3.97)	3.51 (3.06-4.02)
Adjusted HR (95% CI) (all p < 0.001)		0.61 (0.48-0.76)	0.54 (0.44-0.66)	0.53 (0.44-0.64)	0.50 (0.42-0.61)

Normal on-treatment ALT during the 1st year of treatment in patients with CHB is associated with a lower risk of hepatic events.

ALT, alanine aminotransferase; CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; CI, confidence interval; HR, hazard ratios.

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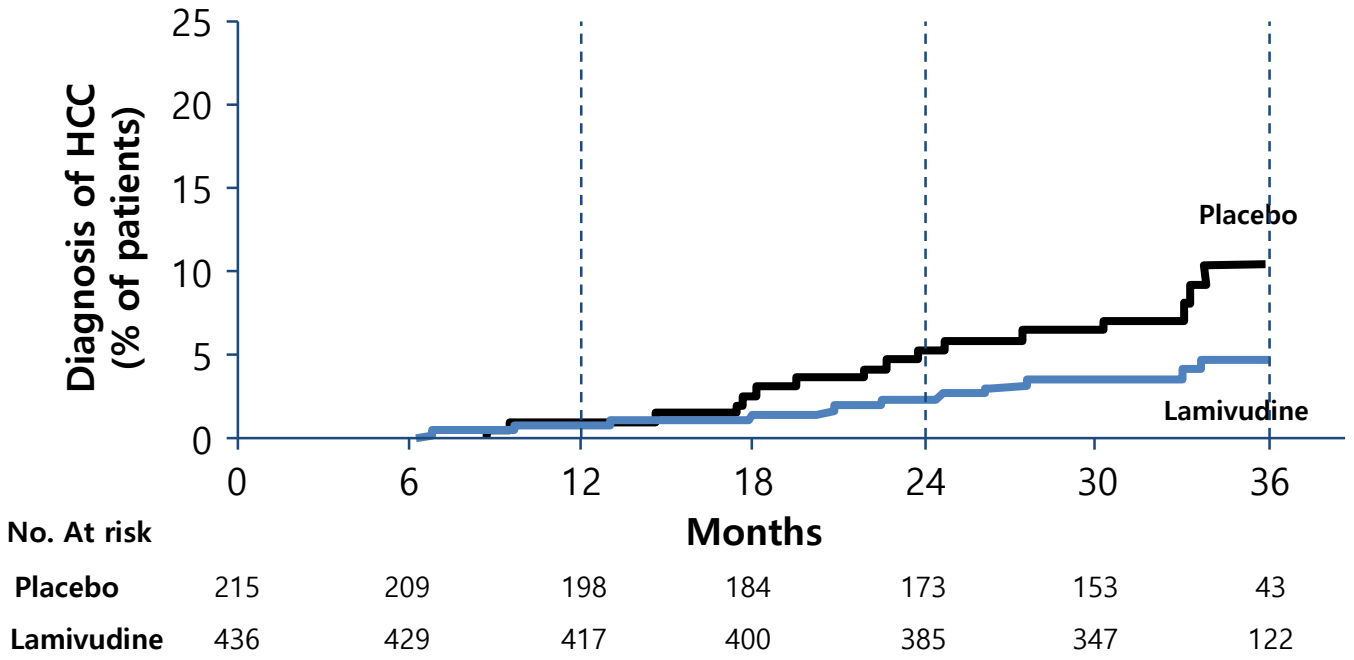
CU Medicine 香港中文大學醫學院 Faculty of Medicine The Chinese University of Hong Kong

Wong GL, et al. J Hepatol. 2018 Oct;69(4):793-802.

The first study of antiviral therapy lowering HCC risks



No. At risk							
Placebo	215	209	198	184	173	153	43
Lamivudine	436	429	417	400	385	347	122

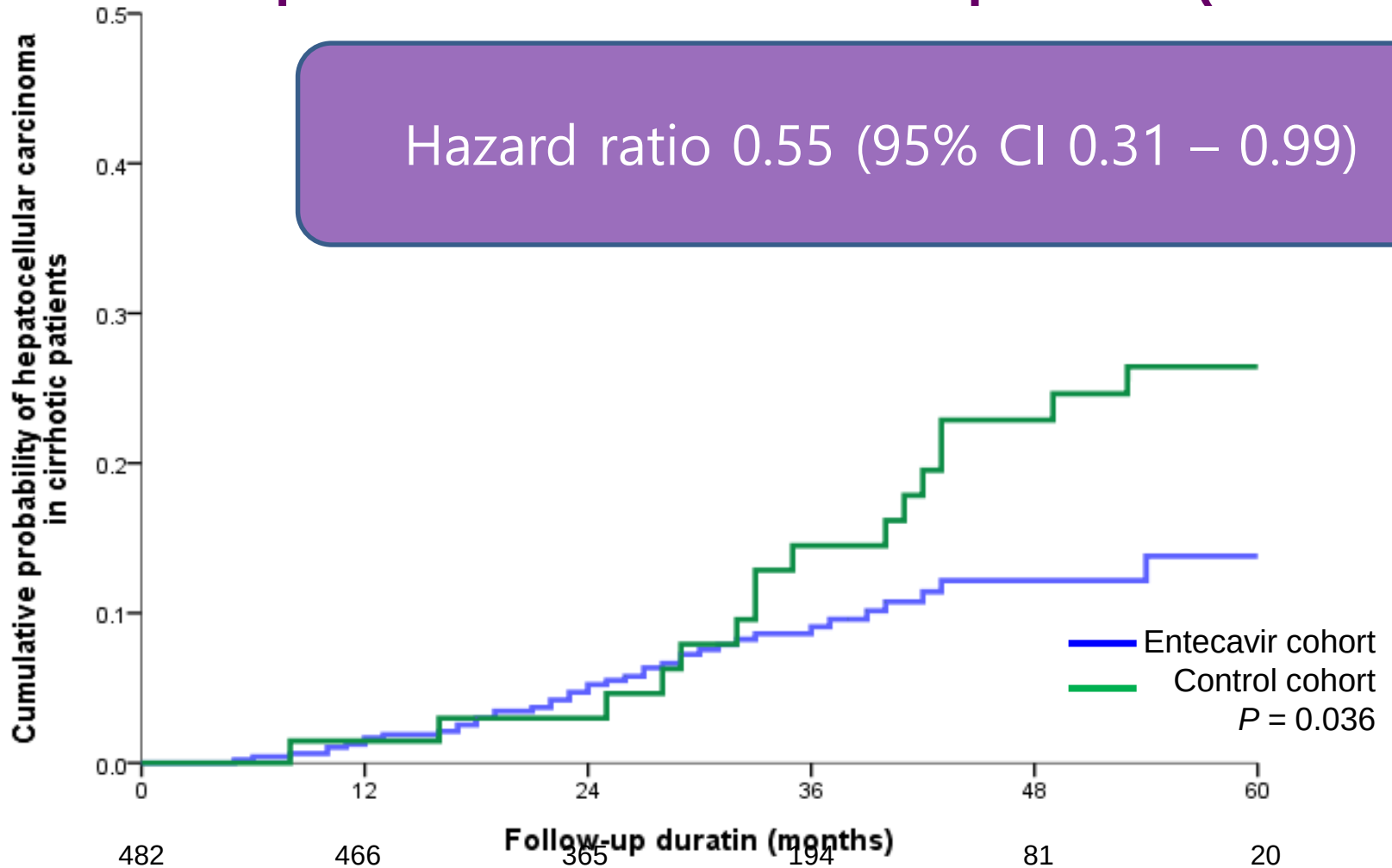
HCC occurred in 3.9% of lamuvidine-treated group, versus 7.4% of the placebo group (HR=0.47; p=0.047)

Liaw YF, Sung JJ et al. N Engl J Med 2004 ;351:1521-31.

Entecavir therapy reduces HCC in cirrhotic patients

1,466 entecavir-treated patients vs. 424 untreated patients (historical control)

Hazard ratio 0.55 (95% CI 0.31 – 0.99)



Patients at risk						
Entecavir cohort	482	466	365	194	81	20
Control cohort	69	65	60	52	45	41

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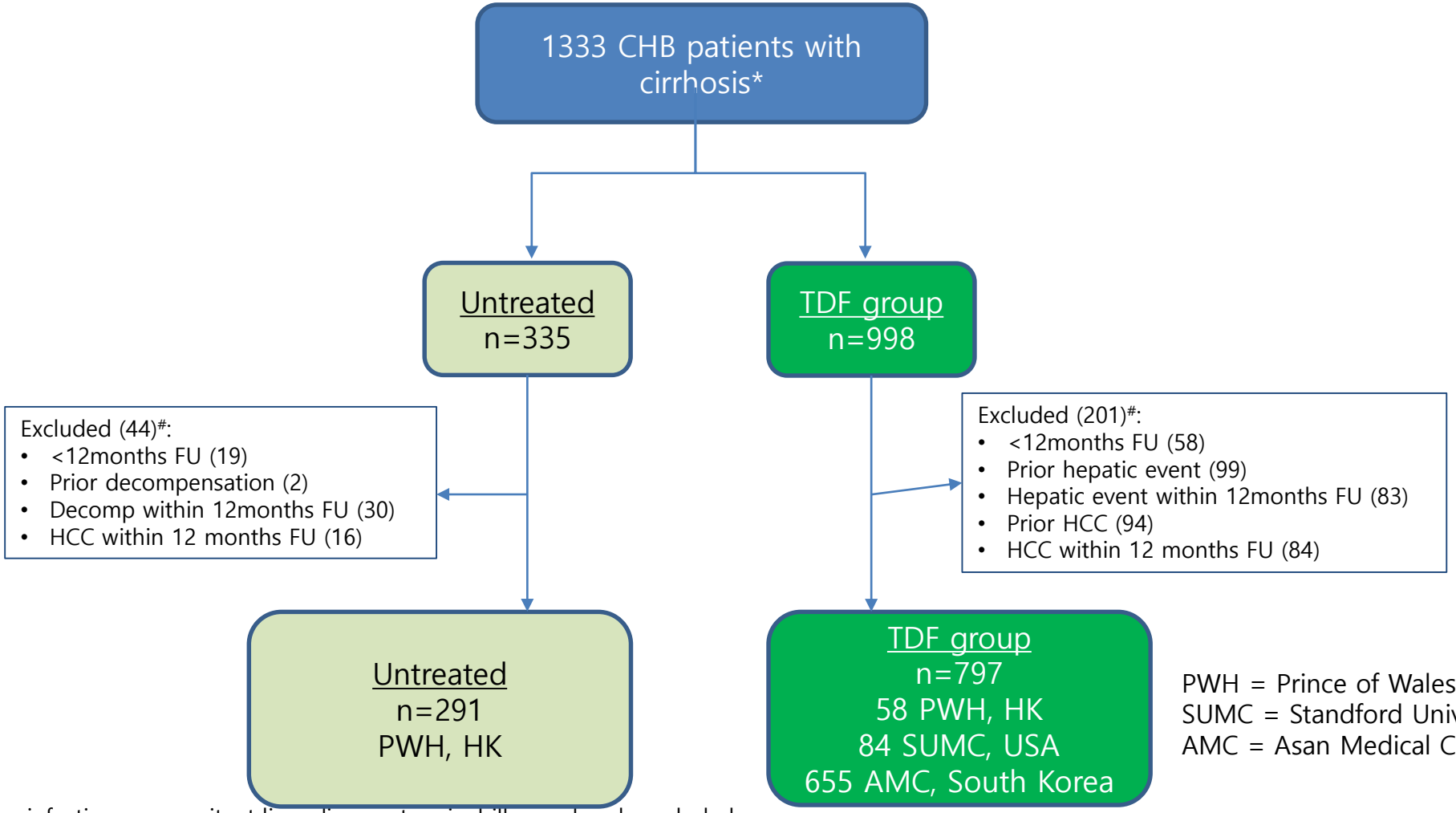
Wong GL, et al. Hepatology 2013;58:1537–1547.

Lower HCC Risk / Hepatic events with TDF vs untreated patients in a multicenter study (Hong Kong, Korea, the US)



PWH = Prince of Wales Hospital, Hong Kong
SUMC = Standford University Medical Center, USA
AMC = Asan Medical Centre, South Korea

* Those with co-infection, concomitant liver disease, terminal illness already excluded
\# Some patients had more than 1 exclusion criteria

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Liu K, et al. Hepatol Int 2019;13(Suppl 2):S37. (Abstract selected for oral presentation in the oral plenary session and APASL-AASLD Research Workshop in APASL 2019, Manila)

Cumulative events after 5 years

	All n (%)	Untreated n (%)	TDF n (%)
HCC (n=1,088)	**112 (10.3)**	**41 (14.1)**	**71 (8.9)**
Decompensating events (PWH and SUMC patients only, n=433)	**70 (16.2)**	**63 (21.6)**	**7 (4.9)**
New ascites	61 (14.1)	56 19.2)	5 (3.5)
Spontaneous bacterial peritonitis	17 (3.9)	15 (5.2)	2 (1.4)
Hepatic encephalopathy	21 (4.8)	18 (6.2)	3 (2.1)
Variceal bleeding	14 (3.2)	12(4.1)	2 (1.4)
Hepatorenal syndrome	3 (0.7)	3 (1.0)	0 (0)
Liver Transplant or Death (n=1,088)	**43 (4.0)**	**36 (12.4)**	**7 (0.9)**
Liver transplant	7 (0.6)	4 (1.4)	3 (0.4)
All-cause death	36 (3.3)	32 (11.0)	4 (0.5)
Liver-related death	25 (2.3)	21 (7.2)	4 (0.5)

HCC	HR	95% CI	P
TDF (y vs n)	0.462	0.286-0.746	0.002
Albumin (per g/L inc)	0.933	0.900-0.967	<0.001
Decompensation	HR	95% CI	P
TDF (y vs n)	0.282	0.105-0.761	0.012
Platelet count (per 109/L inc)	0.992	0.984-0.999	0.039
INR (per unit inc)	9.238	2.147-39.739	0.003
Albumin (per g/L inc)	0.908	0.849-0.971	0.005
Liver death	**HR**	**95% CI**	***P***
TDF (y vs n)	**0.103**	**0.040-0.269**	**<0.001**
Platelet count (per 10^9/L inc)	0.982	0.971-0.993	0.001
Albumin (per g/L inc)	0.873	0.810-0.941	<0.001
All cause death	**HR**	**95% CI**	***P***
TDF (y vs n)	**0.026**	**0.008-0.090**	**<0.001**
INR (per unit inc)	26.362	5.568-124.81	<0.001

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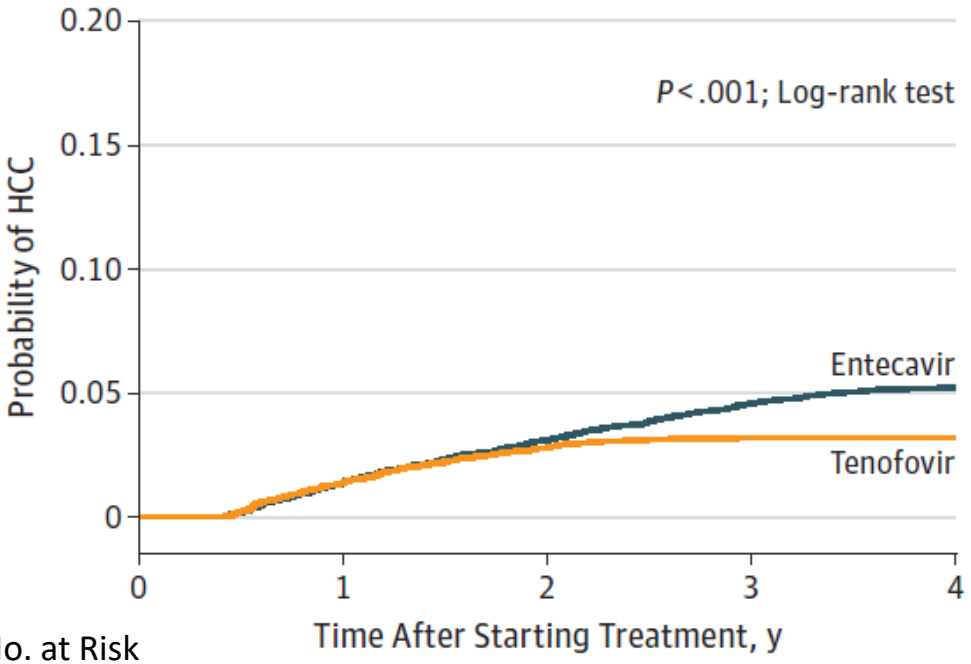
Liu K, et al. Hepatol Int 2019;13(Suppl 2):S37. (Abstract selected for oral presentation in the oral plenary session and APASL-AASLD Research Workshop in APASL 2019, Manila)

Lower HCC Risk with TDF vs ETV In Korean CHB Patients: Propensity Score-Matched

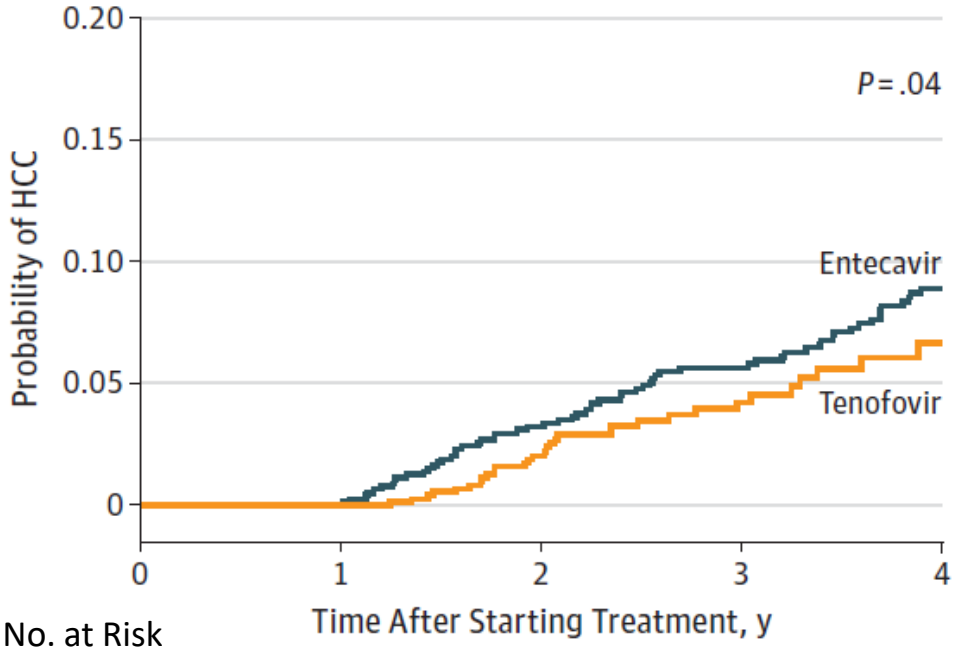
HCC in propensity score-matched nationwide cohort



32%

No. at Risk					
ETV	10,923	10,762	10,542	8,602	6,383
TDF	10,923	10,763	10,574	5,188	419

HCC in propensity score-matched hospital validation cohort



32%

No. at Risk					
ETV	869	815	710	606	490
TDF	869	821	596	336	124

The annual incidence of HCC was significantly lower in the TDF group* compared to the ETV group (HR 0.68; p<0.001)#

*The annual incidence of HCC was significantly lower in both cirrhotic and non-cirrhotic patients who used TDF compared to those on ETV; #Treatment with TDF and ALT levels were significantly associated with the lower risk of HCC while old age, male sex, presence of diabetes and cirrhosis were significantly associated with higher risk of HCC

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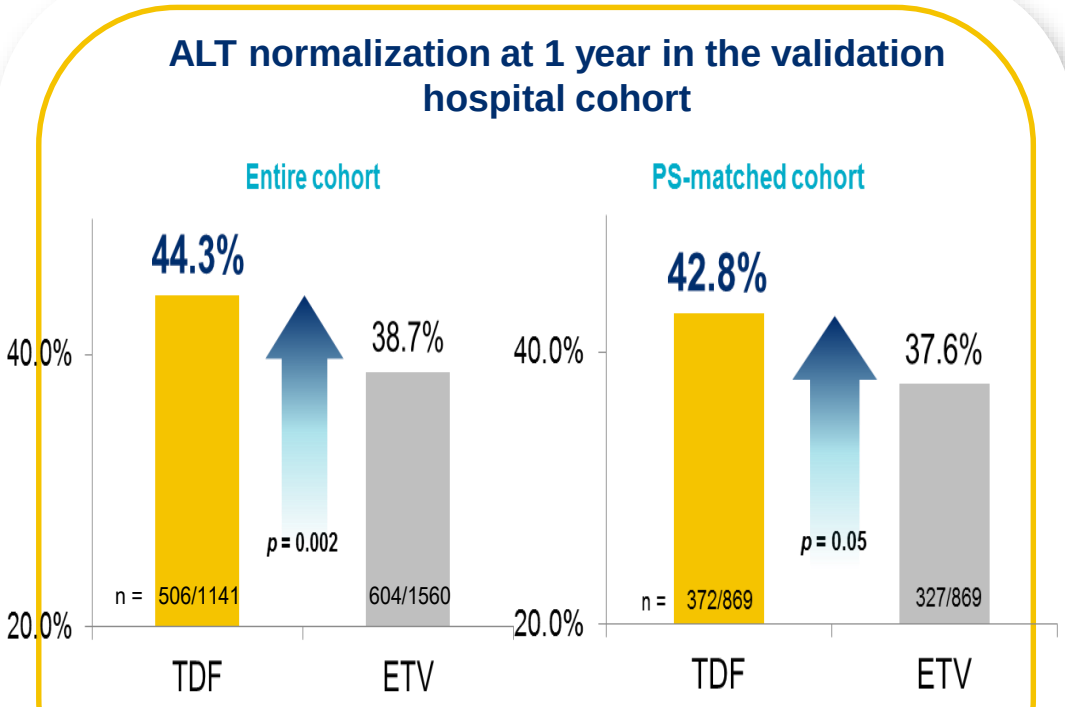
Choi J, et al. JAMA Oncol 2019 Jun 1;5(6):916-917

Higher rate of surrogate endpoints with TDF vs ETV in hospital validation cohort

The proportion of patients with ALT level* normalization was significantly higher in the TDF group compared with EVT group



* ALT ≤ 30 IU/mL for male and ALT ≤ 19 IU/mL for female.

By multivariable analysis showed that ALT was a risk of HCC

Variables	Hepatocellular carcinoma (Competing risk analysis)		
	HR	95% CI	*P* value
Treatment with TDF	0.66	0.46-0.96	0.03
Age	1.04	1.02-1.06	<0.001
Male sex	2.54	1.73-3.73	<0.001
ALT, log_{10} IU/mL	**0.79**	**0.63-0.99**	**0.04**
Diabetes mellitus	1.79	1.12-2.87	0.02

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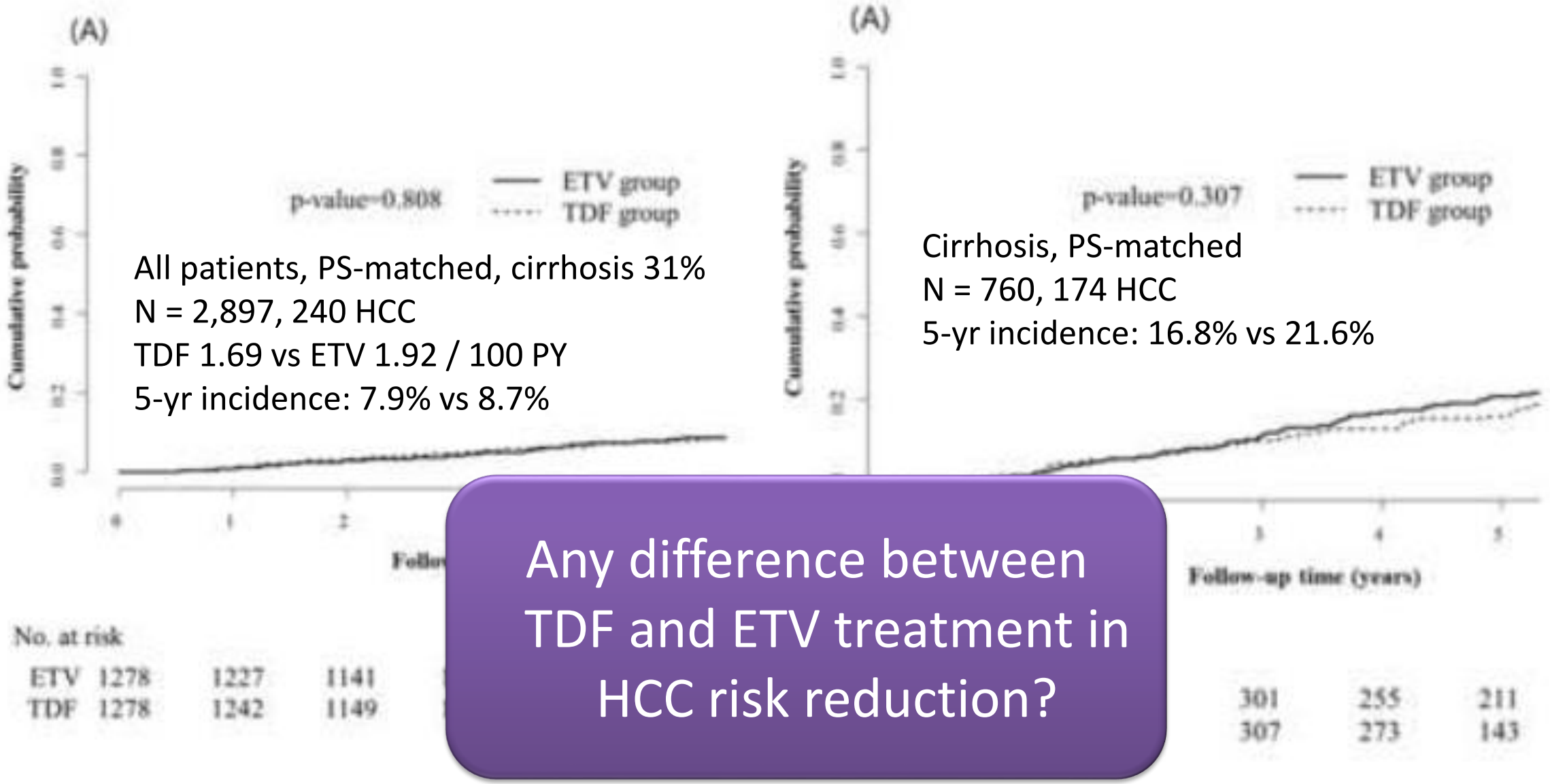
Choi J, et al. JAMA Oncol 2019 Jun 1;5(6):916-917

Korean multicenter study (four territory centers)



All patients, PS-matched, cirrhosis 31%
N = 2,897, 240 HCC
TDF 1.69 vs ETV 1.92 / 100 PY
5-yr incidence: 7.9% vs 8.7%

Cirrhosis, PS-matched
N = 760, 174 HCC
5-yr incidence: 16.8% vs 21.6%

Any difference between TDF and ETV treatment in HCC risk reduction?

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Kim SU, et al. J Hepatol 2019 2019 Sep;71(3):456-464.

EASL Press Release: TDF Associated With A Lower Risk Of HCC Than ETV In Large Hepatitis B Study

"Tenofovir was associated with a significantly lower risk of HCC than entecavir in this large population of adults with chronic HBV infection," said Dr Terry Yip from The Chinese University of Hong Kong, China… "Although we recognize the inherent limitations of observational data, our findings are consistent with those of the Korean group."


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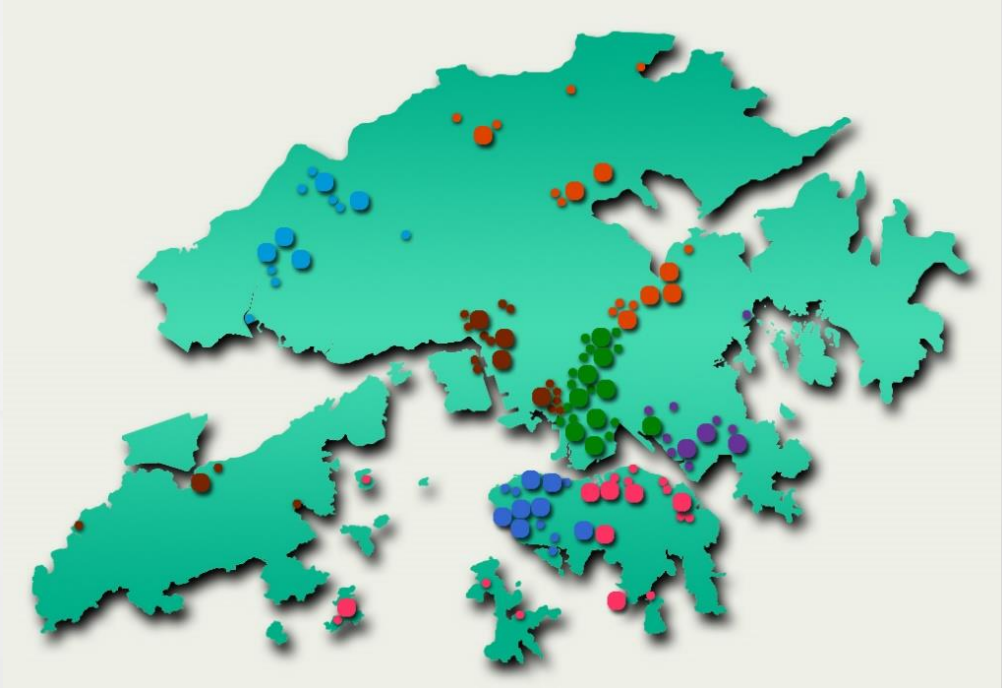
TENOFOVIR ASSOCIATED WITH A LOWER RISK OF HEPATOCELLULAR CARCINOMA THAN ENTECAVIR IN LARGE HEPATITIS B STUDY
ILC 2019: Study involving >29,000 individuals with chronic hepatitis B virus infection reports that the risk of hepatocellular carcinoma is at least one-third lower in those treated with tenofovir than in those treated with entecavir
PRESS RELEASE

In a study involving >29,000 individuals with CHB, the risk of HCC is at least one-third lower in subjects treated with TDF than those treated with ETV

https://ilc-congress.eu/press-release/tenofovir-associated-with-a-lower-risk-of-hepatocellular-carcinoma-than-entecavir-in-large-hepatitis-b-study/. April 13, 2019
https://easl.meta-dcr.com/ilc2019/crs/tenofovir-treatment-has-lower-risk-of-hepatocellular-carcinoma-than-entecavir-treatment-in-patients-with-chronic-hepatitis-b

A Hong Kong Territory-wide cohort study

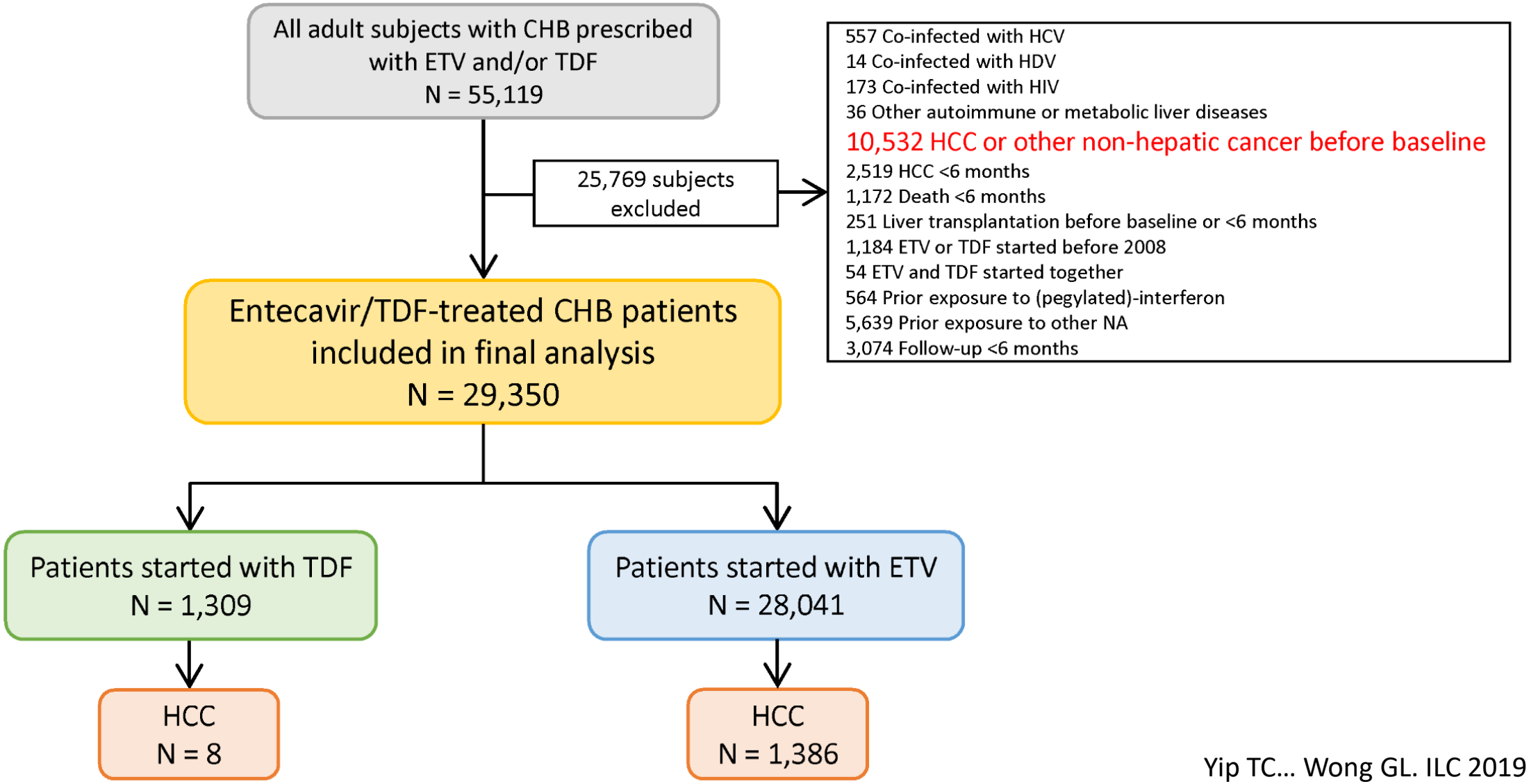
- To compare TDF and ETV treatment on the risk of HCC in a territory-wide cohort of CHB patients in Hong Kong.



Yip TC… Wong GL. ILC 2019 LB-03

Yip TC…Wong GL. ***Gastroenterology.*** 2020

29,350 patients were included in the analysis



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More TDF-treated patients were younger, female and without cirrhosis

Baseline clinical characteristics	ETV N=28,041	TDF N=1,309
Age (years)	53	43
Male sex (n, %)	65%	45%
Cirrhosis (n, %)	13.6%	2.9%
Diabetes mellitus (n, %)	23%	7%
Hypertension (n, %)	39%	14%
HBeAg+ (n, %)	30%	55%
HBV DNA (log IU/mL)	5.3	4.8
Platelet ($x10^9$/L)	183	205
Albumin (g/L)	40	42
ALT (U/L)	62	43
Total bilirubin (µmol/L)	20	16
Creatinine (µmol/L)	85	71
Follow-up duration (years)	3.7	2.8

Result from a single imputation data set.

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Patients who received TDF had milder fibrosis / cirrhosis, and a lower risk of HCC at baseline

Baseline clinical characteristics	ETV N=28,041	TDF N=1,309
APRI score *	0.7	0.4
FIB-4 score *	1.8	1.1
Child-Pugh class (n, %) A B C	 25,335 (90) 2,533 (9) 173 (0.6)	 1,255 (96) 49 (4) 5 (0.4)
CU-HCC score	7	4
GAG-HCC score	82	64
PAGE-B score	14	8
REACH-B score	11	8

Result from a single imputation data set. Data represented as median except Child-Pugh class.

* Among patients (51%) with available AST measurement. Baseline AST was not imputed.

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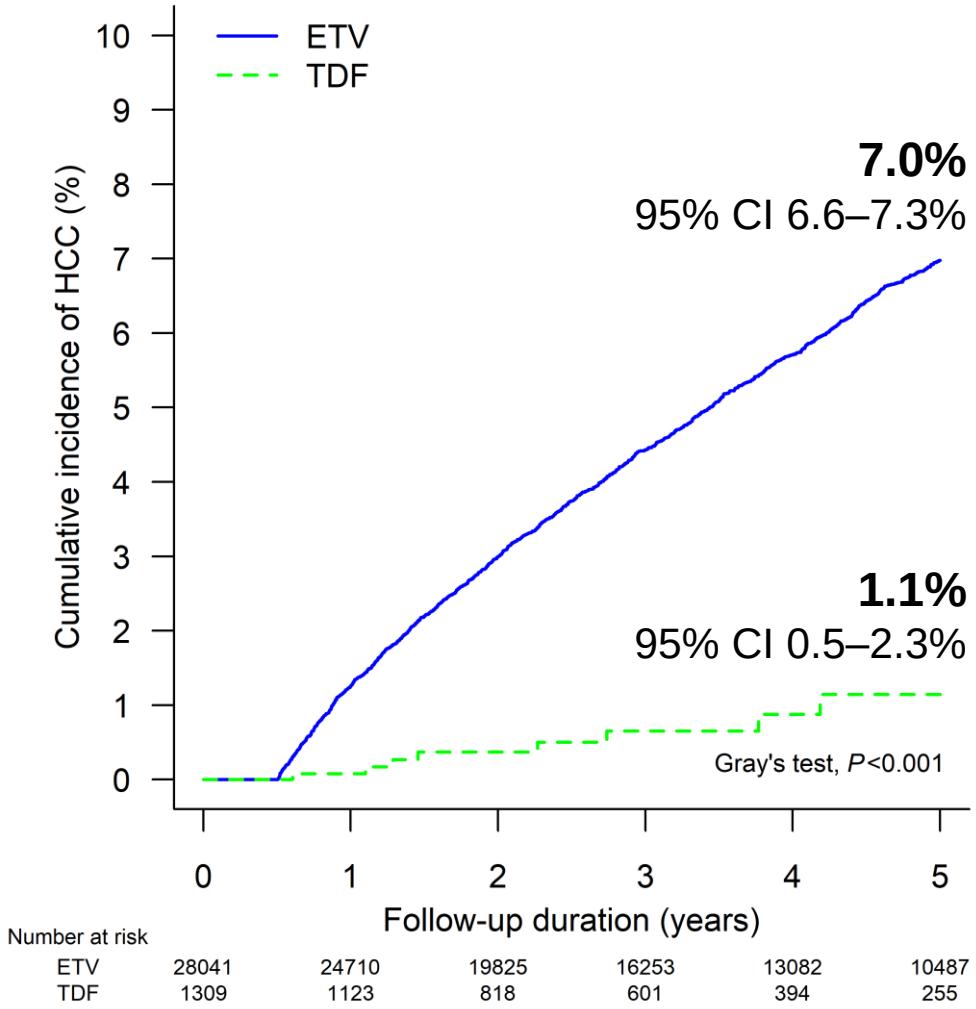
TDF-treated patients have a lower risk of HCC than ETV-treated patients



Parameters	Univariate analysis$		Multivariable analysis†	
	SHR	95% CI	Adjusted SHR	95% CI
TDF *vs.* ETV	0.15	0.07–0.29	0.33	0.16–0.67
Age	1.06	1.06–1.06	1.05	1.04–1.05
Male sex	2.16	1.90–2.47	2.39	2.08–2.73
Cirrhosis	7.06	6.35–7.84	3.21	2.80–3.68
Hypertension	2.71	2.42–3.02	–	–
Platelet*	0.36	0.32–0.40	0.59	0.53–0.65
Albumin	0.91	0.91–0.92	0.98	0.97–0.99
ALT*	0.80	0.77–0.84	0.89	0.85–0.93
Total bilirubin*	1.48	1.41–1.56	–	–
HBeAg+	0.81	0.73–0.93	1.42	1.24–1.64

*Log-transformed in the model; †P-value =0.002 for TDF *vs.* ETV. All other P-values <0.001
$ P-value =0.003 for HBeAg+. All other P-values <0.001. SHR = subdistribution hazard ratio

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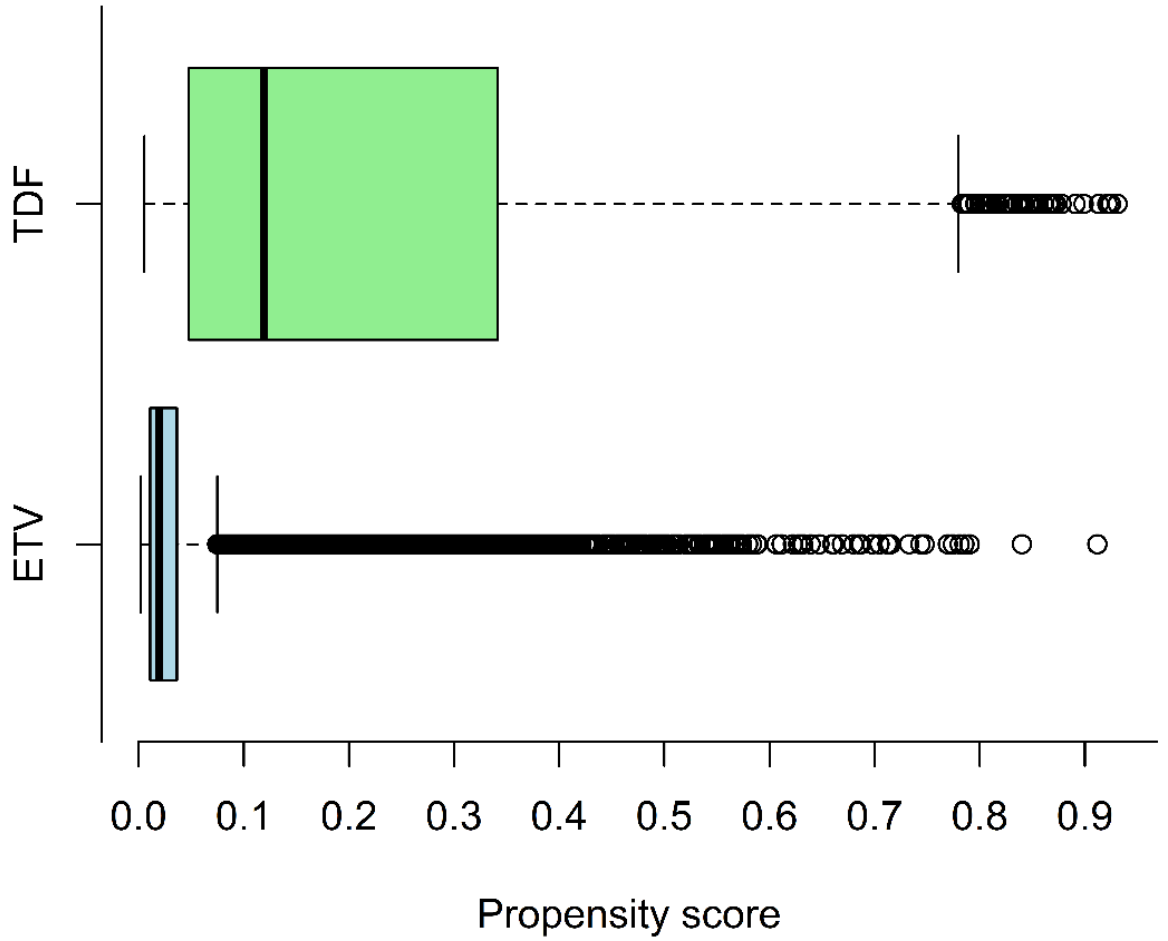
Propensity score estimation

Categories	Parameters
Demographics	Age
	Sex
Virological markers	HBeAg positivity
	Serum HBV DNA levels*
Liver function	ALT*
	Albumin
	Total bilirubin*
	INR
	Platelet*
Renal function	Creatinine*
	Renal replacement therapy
Cirrhosis and complications	Cirrhosis
	Ascites
	Hepatic encephalopathy
Comorbidities	Diabetes mellitus
	Hypertension
Treatment initialization	Calendar year of treatment initialization

*Log-transformed in the model



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Patients' clinical characteristics were balanced after PS weighting

Baseline clinical characteristics	Before PS weighting		After PS weighting	
	ETV	TDF	ETV	Absolute standardized difference*
Age (years)	53	43	44	0.05
Male sex (%)	65%	45%	47%	0.04
Cirrhosis (%)	13.6%	2.9%	4.6%	0.09
Diabetes mellitus (%)	23%	7%	9%	0.08
Hyperte				0.07
HBeAg+ (%)	30%	55%	52%	0.06
HBV DNA (log IU/mL)	5.3	4.8	4.8	0.02
Platelet (x10^9/L)	183	205	205	0.05
Albumin (g/L)	40	42	42	0.02
ALT (U/L)	62	43	44	0.002
Total bilirubin (µmol/L)	20	16	15	0.04
Creatinine (µmol/L)	85	71	74	0.07
Follow-up duration (years)	3.7	2.8	2.8	–

Absolute standardized difference below 0.1 indicated good balance

Result from a single imputation data set. * Absolute standardized difference below 0.1 indicated good balance.
Data were represented as mean unless specified. ALT and FU duration were represented as median.

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Patients' clinical characteristics were balanced after PS weighting

Parameters that were not included in the propensity score

Baseline parameters	Before PS weighting		After PS weighting
	ETV	TDF	ETV
APRI score *	0.7	0.4	0.5
FIB-4 score *	1.8	1.1	1.1
Child-Pugh class (%) A B C	 90% 9% 0.6%	 96% 4% 0.4%	 95% 5% 0.3%
CU-HCC score	7	4	4
GAG-HCC score	82	64	66
PAGE-B score	14	8	10
REACH-B score	11	8	8

Result from a single imputation data set. Data were represented as median unless specified.

* Among patients (51%) with available AST measurement. Baseline AST was not imputed.

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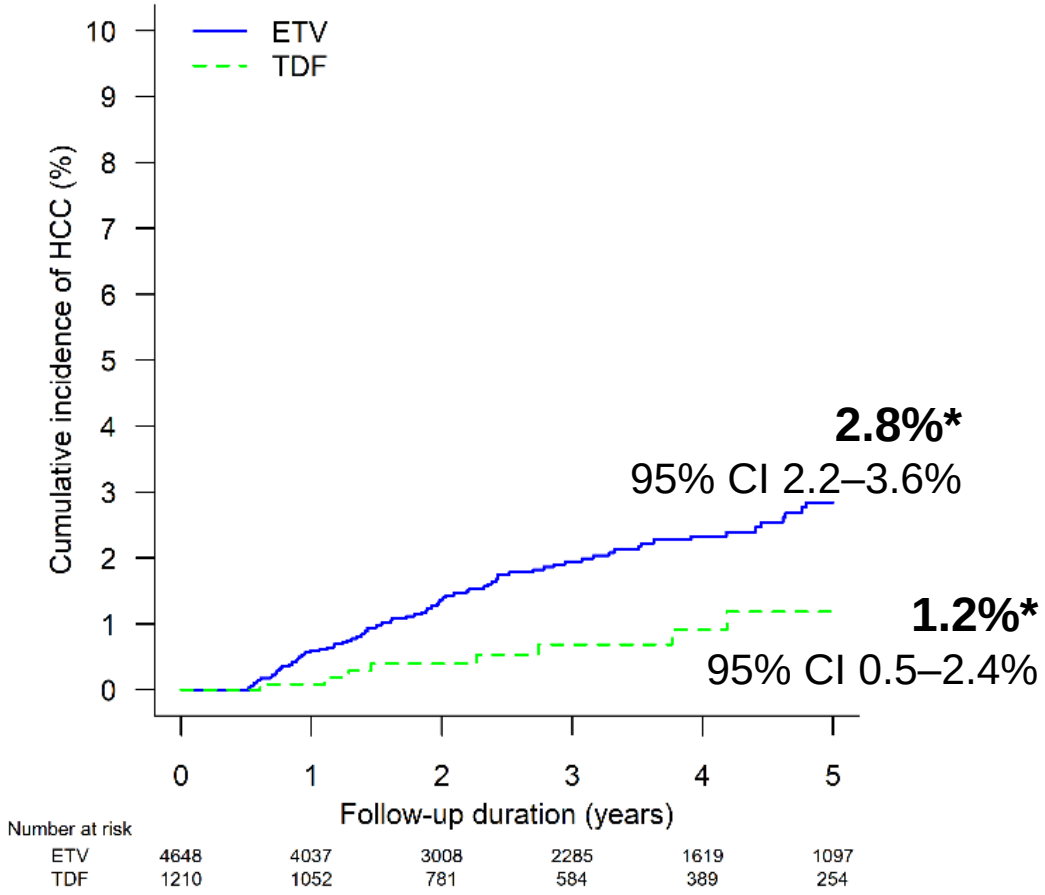
TDF-treated patients have a lower risk of HCC than ETV-treated patients in PS weighting analysis



In cohort after PS weighting

Parameters	Propensity score weighting analysis		
	SHR	95% CI	*P* value
TDF *vs.* ETV	0.36	0.16–0.80	0.013

In cohort before PS weighting

Parameters	Multivariable analysis		
	SHR	95% CI	*P* value
TDF *vs.* ETV	0.33	0.16–0.67	0.016

*Result from a single imputation data set.
Cumulative incidence estimated by Kaplan-Meier method in the PS-weighted cohort.
SHR = subdistribution hazard ratio

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1-year HBV DNA suppression and ALT normalization rate

In PS-weighted cohort†

At 1 year	ETV	TDF
HBV DNA suppression (%)	72%	75%
ALT normalization (%)*	69%	58%
HBeAg seroclearance (%)	22%	19%

After adjusting for HBV DNA suppression and ALT normalization at 1 year (N=17,712)

Parameters	Propensity score weighting analysis		
	Weighted SHR	95% CI	*P* value
TDF *vs.* ETV	0.35	0.12–0.98	0.045
HBV DNA suppression	2.23	0.64–7.77	0.207
ALT normalization*	0.47	0.19–1.18	0.108

† Result from a single imputation data set.

* ALT normalization was defined as ALT <35 U/L in males and <25 U/L in females.

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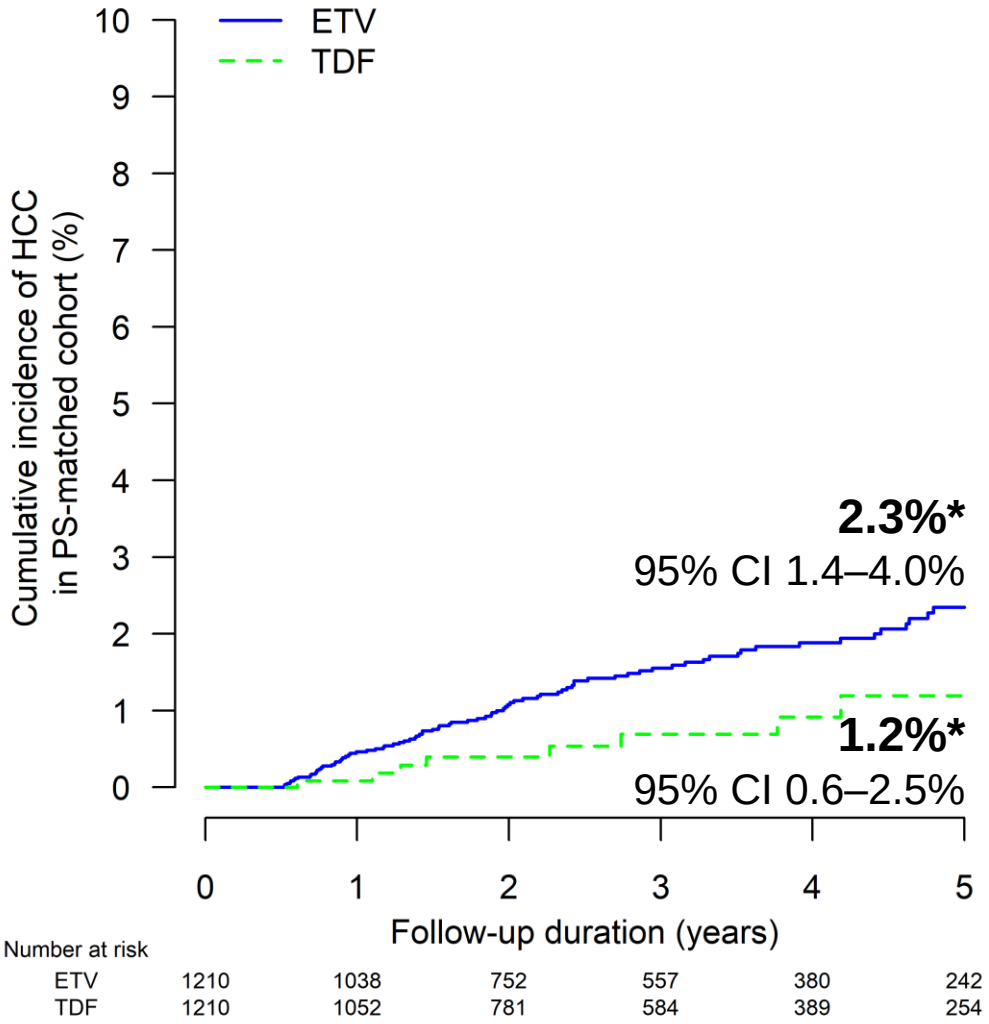
1:5 PS matching analysis



Parameters	Propensity score matching analysis		
	SHR	95% CI	*P* value
TDF *vs.* ETV	0.39	0.18–0.84	*0.016*

TDF-treated patients matched to ETV-treated patients (n, %)*
1:1 = 202 (17%) 1:2 = 119 (10%) 1:3 = 77 (6%) 1:4 = 83 (7%) 1:5 = 729 (60%)
Percentage of TDF-treated patients matched = 1,210/1,309 (92%)

*Result from a single imputation data set.

Cumulative incidence estimated by Kaplan-Meier method in the PS-matched cohort.

SHR = subdistribution hazard ratio

Yip TC… Wong GL. ILC 2019 LB-03

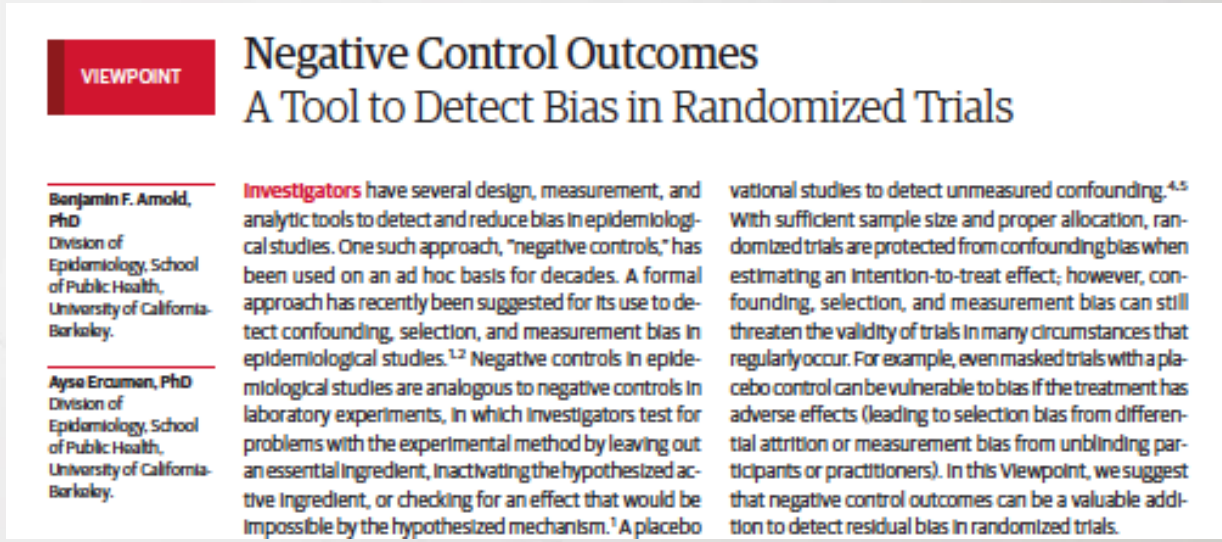
Yip TC…Wong GL. ***Gastroenterology.*** 2020

Negative control outcomes

- A negative control outcome shares the same potential sources of bias with the primary outcome but cannot plausibly be related to the treatment of interest (e.g. use of TDF vs. ETV on the risk of lung cancer).

- It is used in observational studies to detect unmeasured confounding.

- The finding of no association between treatment and the negative control outcome provides additional support for no obvious residual bias from unmeasured confounding.



VIEWPOINT

Negative Control Outcomes
A Tool to Detect Bias in Randomized Trials

Benjamin F. Arnold, PhD
Division of Epidemiology, School of Public Health, University of California-Berkeley.

Ayse Ercumen, PhD
Division of Epidemiology, School of Public Health, University of California-Berkeley.

Investigators have several design, measurement, and analytic tools to detect and reduce bias in epidemiological studies. One such approach, "negative controls," has been used on an ad hoc basis for decades. A formal approach has recently been suggested for its use to detect confounding, selection, and measurement bias in epidemiological studies.[1,2] Negative controls in epidemiological studies are analogous to negative controls in laboratory experiments, in which investigators test for problems with the experimental method by leaving out an essential ingredient, inactivating the hypothesized active ingredient, or checking for an effect that would be impossible by the hypothesized mechanism.[1] A placebo vational studies to detect unmeasured confounding.[4,5] With sufficient sample size and proper allocation, randomized trials are protected from confounding bias when estimating an intention-to-treat effect; however, confounding, selection, and measurement bias can still threaten the validity of trials in many circumstances that regularly occur. For example, even masked trials with a placebo control can be vulnerable to bias if the treatment has adverse effects (leading to selection bias from differential attrition or measurement bias from unblinding participants or practitioners). In this Viewpoint, we suggest that negative control outcomes can be a valuable addition to detect residual bias in randomized trials.

Lipsitch M et al. Epidemiology. 2010
Arnold BF et al. JAMA. 2016

Yip TC… Wong GL. ILC 2019 LB-03
Yip TC…Wong GL. ***Gastroenterology.*** 2020

Two negative control outcomes chosen

Lung cancer

Parameters	Propensity score weighting analysis		
	Weighted SHR	95% CI	*P* value
TDF *vs.* ETV	0.78	0.21–2.93	0.711

Acute myocardial infarction

Parameters	Propensity score weighting analysis		
	Weighted SHR	95% CI	*P* value
TDF *vs.* ETV	1.44	0.31–6.73	0.644

Negative control outcome analysis supports no obvious residual bias on unmeasured confounding.

SHR = subdistribution hazard ratio

Yip TC… Wong GL. ILC 2019 LB-03
Yip TC…Wong GL. ***Gastroenterology.*** 2020

Summary of Hong Kong Territory-wide cohort study

- TDF treatment is associated with a lower risk of HCC than ETV treatment in a territory-wide cohort of CHB patients in Hong Kong.

- The association remains robust in PS weighting, PS matching and negative control outcome analysis.

Yip TC… Wong GL. ILC 2019 LB-03
Yip TC…Wong GL. ***Gastroenterology.*** 2020

Three key studies comparing TDF vs ETV

	Choi et al	Kim et al	Yip et al
Patient sources	Nationwide + Hospital	4 Hospitals	Territory-wide
No. of patients (TDF:ETV)	10,923:10,923 869:869	1,278:1,278	1,309:28,401
Cirrhosis	58% / 24.1%; decomp	31%; no decomp	2.9% vs 13.6%/4.6%
No. of HCC	984 / 154	240	8 vs 1,386
HCC incidence	0.66 vs 1.07 / 100 PY 1.37 vs 2.17 / 100 PY	1.69 vs 1.92 per 100 PY 5-yr incidence: 7.9% vs 8.7%	5-yr incidence: 2.8% vs 1.2%

Choi J, et al. JAMA Oncol 2019; Kim SU, et al. J Hepatol 2019
Yip TC… Wong GL. ILC 2019 LB-03; Yip TC…Wong GL. Gastroenterology. 2020

Trend of HCC risk reduction with TDF in Asian patient vs ETV

Longitudinal data from the Chronic Hepatitis Cohort Study (CHeCS), a US-based cohort that includes both Asian and non-Asian patients

CHeCS CHB patients that initiated TDF or ETV during 2005-2017 were included, after excluding patients with a history of:

- Liver transplant
- HIV co-infection
- Treatment with both [illegible]

Among the 822 patients, 40[illegible]ce of HCC and all-cause mortality

Asian: aHR 0.70 (0.29-1.68)
Non-Asian: aHR 1.87 (0.60-5.87)
Racial difference?

Number of subjects		
Baseline characteristics		
Age in years, mean (SD)		
Male	[illegible]	[illegible]
Race		
Asian/Pacific Islander/Native American	63%	100%
Black/African American	11%	
White	26%	
Cirrhotic	18%	27%
Prior treatment naïve	80%	100%
Treated with ETV/TDF	50.5% / 49.5%	47.5% / 52.5%
Follow-up and clinical outcomes		
Median follow-up (yrs)	3.2	3.6
Hepatocellular cancer (HCC)	31 (3.8%)	984 (4.1%)
All-cause deaths	115 (14.0%)	
Death or liver transplant		509 (2.1%)

CHeCS and Choi et al. studies

			All-cause mortality	
		p-value	HR (95% CI*)	p-value
		0.17		0.30
TDF vs ETV Asian	0.70 (0.29, 1.68)		0.86 (0.48, 1.53)	
TDF vs ETV Non-Asian	1.87 (0.60, 5.87)		1.25 (0.81, 1.92)	
CHeCS treatment naïve subgroup: Treatment x Race interaction		0.50		0.58
TDF vs ETV Asian	0.73 (0.29, 1.84)		0.94 (0.51, 1.73)	
TDF vs ETV Non-Asian	1.21 (0.37, 3.98)		1.17 (0.72, 1.90)	
Choi et al (national cohort)	0.61 (0.54, 0.70)	<0.01	n/a	n/a

Risk of HCC among patients treated with TDF compared to those treated ETV may vary with race. Among Asian patients, an adjusted hazard ratio=0.70 (TDF vs. ETV) suggests a trend toward HCC reduction, a consistent finding with the Choi findings.

Gordon et al. CHeCS. EASL 2019. LBP13

Summary of some key studies comparing HCC risk with TDF vs ETV

Study	Regions / Countries	Study Type	N (% Male)	Age, years	FU, months	No. (%) of HCC and HR of TDF vs. ETV
Liaw 2011	Multi-continents	Phase 2, double-blind, RCT	TDF: 45 (82.2) ETV: 22 (77.3)	52 (48-57) 54 (47-58)	48 weeks 48 weeks	TDF = 3 (6.7%) vs. ETV = 1 (4.5%); HR, N.A.
Koklu 2013	Turkey	Observational	TDF 72 (75.0) ETV: 77 (77.9)	54.2 ± 10.5 52.4 ± 11.2	21.4 ± 9.7 24.0 ± 13.3	TDF = 2 (2.8%) vs. ETV = 4 (5.2%); HR, 0.60; 95% CI, 0.11-3.28
Batirel 2014	Turkey	Observational	TDF: 90 (65.6) ETV: 105 (78.1)	43.3 ± 12.9 42.0 ± 11.2	27.2 ± 15.4 33.0 ± 15.4	TDF = 0 vs. ETV = 0 HR, N.A.
Goyal 2015	India	Observational	TDF: 220 ETV: 180	47.3 (24-65) 48.1 (26-65)	45 (12-68) 36 (11-60)	TDF = 6 (2.7%) vs. ETV = 4 (2.2%); HR, 0.49; 95% CI, 0.14-1.72
Wu 2017	Taiwan	Observational	TDF: 106 (69.8) ETV: 313 (73.5)	47.1 ± 12.1 47.0 ± 12.3	37.9 ± 7.2 49 ± 19.1	TDF = 7.7% at 48 months vs. ETV = 6.7% at 48 months HR, 0.73; 95% CI, 0.26-2.05
Kayaaslan 2018	Turkey	Observational	TDF: 86 (55.8) ETV: 166 (71.0)	42 (range, 18-71) 43 (range, 18-81)	18 (range, 12-72) 48 (range, 12-72)	TDF = 0 vs. ETV = 0 HR, N.A.
Kim 2018	South Korea	Observational	TDF: 112 (62.5) ETV: 191 (60.7)	49.3 ± 10.9 47.7 ± 12.3	38.5 ± 9.2 66.6 ± 26.8	TDF = 3 (2.7%) vs. ETV = 13 (6.8%); HR, 0.67; 95% CI, 0.19-2.35
Yu 2018	South Korea	Observational	TDF: 176 (59.1) ETV: 406 (67.0)	49 (range 20-84) 53 (range 18-84)	33.6 (range, 6.3-60.5) 69.9 (range, 6-119.4)	TDF = 7 (4.0%) vs. ETV = 31 (7.6%); HR, 1.39; 95% CI, 0.56-3.45
Kim 2018	South Korea	Observational	TDF: 604 (60.1) ETV: 721 (65.3)	50 ± 11 52 ± 11	33 (21-46) 66 (36-88)	TDF = 14 (2.3%) vs. ETV = 40 (5.5%); HR, 0.74; 95% CI, 0.39-1.39 aHR, 0.60; 95% CI, 0.28-1.30

Yip TC, Lai JC, Wong GL. J Gastroenterol 2020; Yip TC, Wong GL, J Gastroenterol Hepatol 2020

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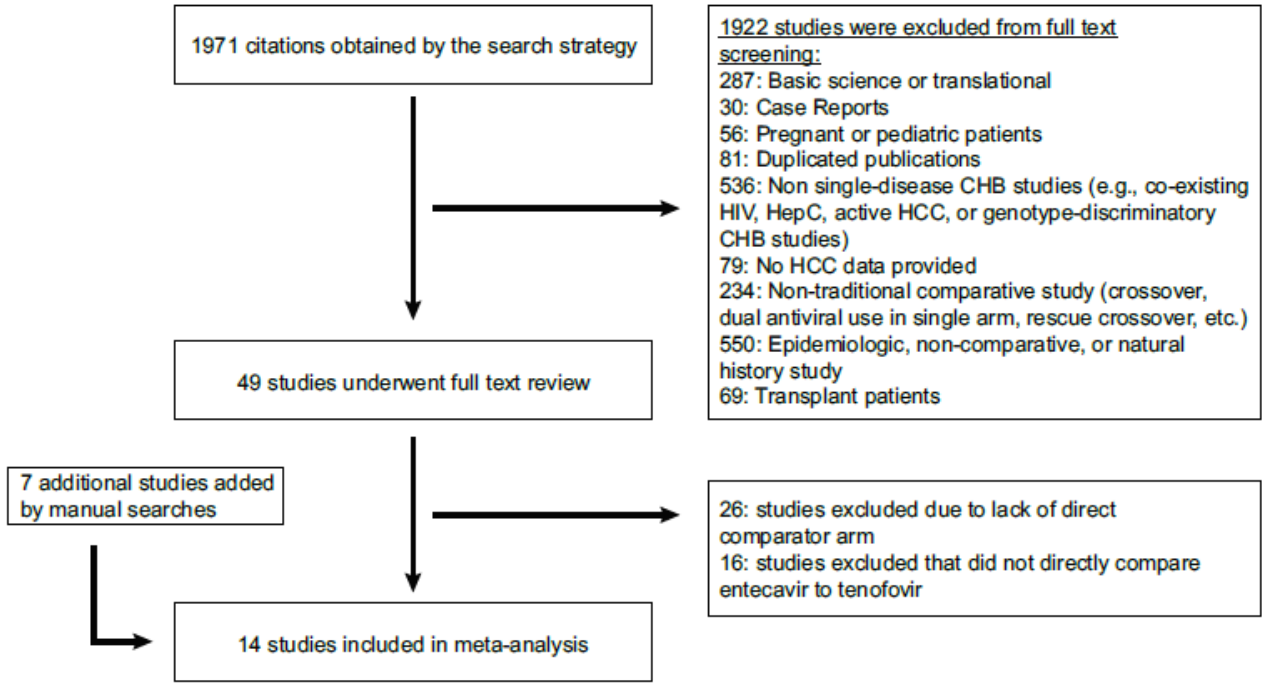
Study	Regions / Countries	Study Type	N (% Male)	Age, years	FU, months	No. (%) of HCC and HR of TDF vs. ETV
Choi 2019	South Korea	Observational	TDF: 1141 (60.6) ETV: 1560 (61.9)	48.1 ± 10.5 49.2 ± 10.5	32.0 (23-40) 48.0 (36-48)	TDF = 39 (3.4%) vs. ETV = 115 (7.4%); HR, 0.64; 95% CI, 0.45-0.93; aHR, 0.66; 95% CI, 0.46-0.96
Cai 2019	China	RCT	TDF: 157 (75.8) ETV: 158 (76.6)	30.8 ± 8.8 31.0 ± 8.4	36 36	TDF = 0 vs. ETV = 0 HR, N.A.
Kim 2019	South Korea	Observational	TDF: 1413 (64.6) ETV: 1484 (59.9)	48.8 ± 12.0 48.2 ± 11.5	N.A. N.A.	TDF = 102 (7.2%) vs. ETV = 138 (9.3%); aHR, 0.98; 95% CI, 0.75-1.27
Gordon 2019	United States	Observational	TDF: 407 ETV: 415	48 51	48 66	TDF = 13 (3.2%) vs. ETV = 18 (4.3%); aHR for Asian, 0.70; 95% CI, 0.29-1.68 aHR for Non-Asian, 1.87; 95% CI, 0.60-5.87
Yip 2020	Hong Kong	Observational	TDF: 1309 (45.1) ETV: 28041 (64.5)	43.2 ± 13.1 53.4 ± 13.0	33.6 (16.8-54) 44.4 (20.4-60)	TDF = 13 (1.9%) vs. ETV = 285 (5.9%) aHR, 0.36; 95% CI, 0.16-0.80
Hsu 2019	Multi-continents	Observational	DF: 700 (65.1) ETV: 4837 (68.8)	45.7 ± 0.5 50.2 ± 0.2	38.7 (23.8-56.2) 60 (39.6-60)	TDF = 13 (1.9%) vs. ETV = 285 (5.9%) aHR, 0.81; 95% CI, 0.42-1.56
Lee 2019	South Korea	Observational	TDF: 1439 (58.4) ETV: 1583 (58.5)	47.3 ± 11.2 46.7 ± 11.8	36.4 (N.A.-N.A.) 60 (N.A.-N.A.)	TDF = 50 (3.5%) vs. ETV = 84 (5.3%) aHR, 0.97; 95% CI, 0.68-1.4
Kim 2019	United States	Observational	TDF: 5903 (56.0) ETV: 3819 (63.1)	N.A. N.A.	17.9 (7.9-34.7) 17.0 (8.0-32.2)	TDF = 39 (0.7%) vs. ETV = 46 (1.2%); aHR, 0.61; 95% CI, 0.39-0.94
Lee 2019	Taiwan	Observational	TDF: 288 (61.8) ETV: 452 (65.7)	54.1 (24.0-94.1) 53.0 (23.4-89.7)	33.6 (8.4-124.8) 37.2 (6-145.2)	TDF = 8 (2.8%) vs. ETV = 31 (6.9%); HR, 0.86; 95% CI, 0.39-1.91

Yip TC, Lai JC, Wong GL. J Gastroenterol 2020; Yip TC, Wong GL, J Gastroenterol Hepatol 2020

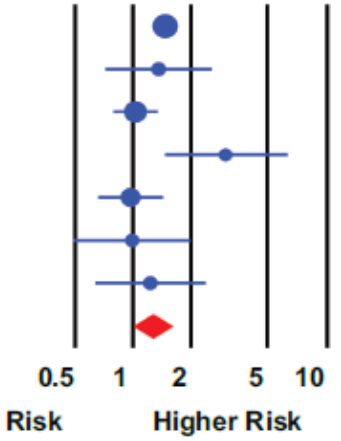
ETV vs TDF in HCC risk: A Systematic Review and Meta-analysis



Adjusted data (multivariate or propensity-matched data), HCC risk in ETV-treated patients 27% higher than TDF-treated patients (7 studies; 95% CI, 1.01-1.60, p=0.04)

Risk of HCC in CHB patients - Entecavir vs. Tenofovir, Adjusted Analysis

Study name	Hazard ratio	Lower limit	Upper limit	p-Value
Choi 2018	1.47	1.29	1.68	0.00
Kim 2018	1.36	0.72	2.56	0.34
Kim 2019	1.03	0.79	1.34	0.82
Yip 2019	3.03	1.48	6.21	0.00
Lee 2019	0.97	0.66	1.42	0.88
Gordon 2019	0.99	0.49	1.99	0.98
Hsu 2019	1.23	0.64	2.37	0.54
Entecavir vs. Tenofovir	**1.27**	**1.01**	**1.60**	**0.04**



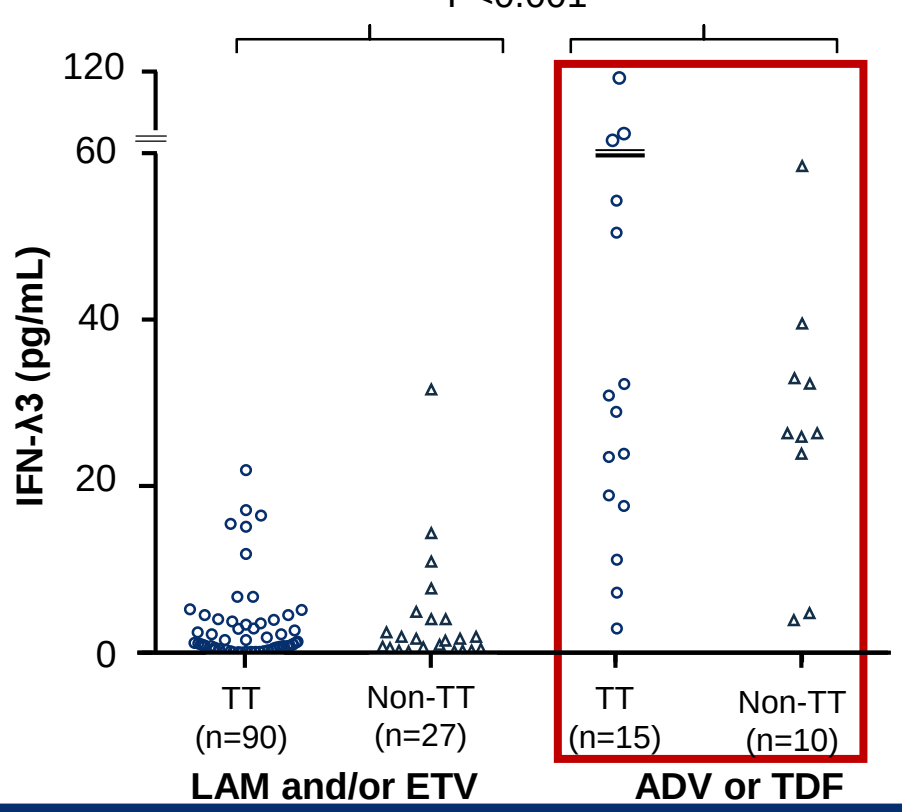
香港中文大學
The Chinese University of Hong Kong

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

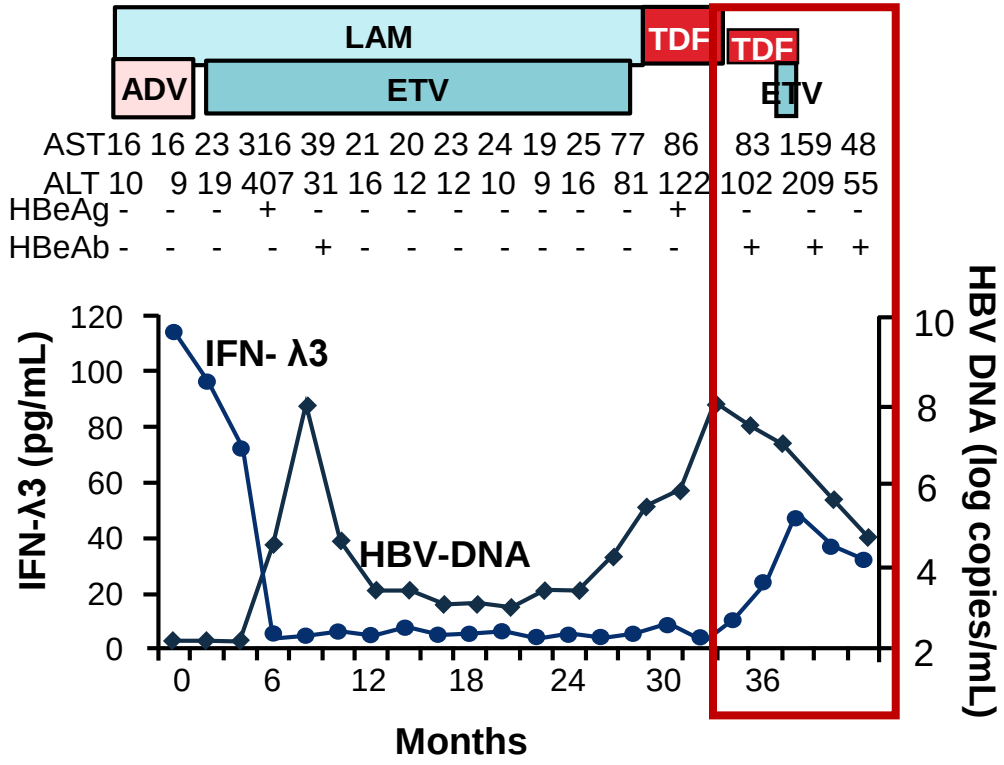
Dave S, et al. Hepatology 2020.

Possible mechanism: variable induction of IFN-lambda expression by different antivirals

Serum IFN-λ3 levels in patients treated with different NAs



Serum IFN-λ3 levels in a 78-year old man treated with different NAs



TDF, but not ETV, induces IFN-λ3 expression. IFN-λ directly inhibits the replication of HBV and induces ISGs, which contribute to inhibition of viral mRNA translation, as well as to RNA degradation and synthesis in cell lines

IFN: interferon; ISG: IFN-stimulated genes; TT: major homozygous genotype of IL-28B

Murata K, et al. Gut 2018;67:362–71

Does antiviral therapy reduce HCC in chronic hepatitis B?

Yes!

Is one NA better than the other?

TDF is likely associated with lower risk of HCC compared to ETV

Future studies

Biochemical basis

- ALT normalization

Virological basis

- HBV DNA suppression
- HBeAg seroclearance
- HBsAg level reduction
- cccDNA or transcriptional activity of HBV
- Serum HBcrAg / HBV RNA levels

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong