Optimal management of CHB patients under NUCs

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CONFLICT OF INTEREST

I have financial relationships to disclose within the past 12 months relevant to my presentation:

Consultant and Speaker Bureau
Abbvie, Arbutus, BMS, Gilead, Merck/MSD, Roche

Management of CHB patients under NUCs

- Proper assessment before starting therapy
- Selection of NUCs
- Monitoring during therapy: Surveillance of HCC
- Finite therapy duration

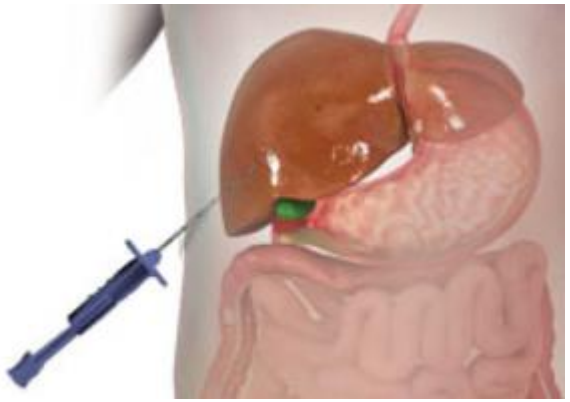
Assessment Prior NUCs therapy

Virus	Liver Disease	Others
HBsAg	ALT, AST	Previous HBV therapy
HBeAg	Biochemistry (Renal function)	HCV, HIV and HDV coinfection
HBV DNA	Fibrosis assessment	HAV vaccination
HBV Genotype	HCC screening	Women planning family
HBcrAg		Comorbidities
HBV RNA		Alcohol

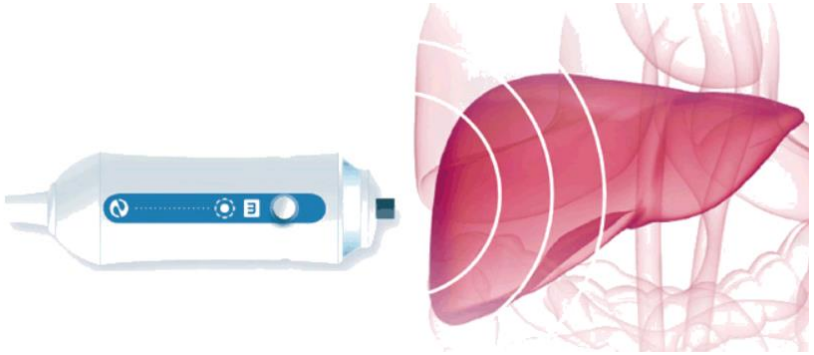
EASL Guidelines. J Hepatol 2019, Terraulth N et al. Hepatology 2018; Sarin SK et al. Hepatol Int. 2016

Cirrhosis has significant implications for the management of CHB

- Changes treatment criteria
- Requieres HCC surveillance
- Precludes stopping therapy until HBsAg loss



Liver Biopsy Gold Standard



Fibroscan not always available

Current treatment guidelines, EASL, AASLD, APASL and WHO support the use of biochemical indices to assess the extent hepatic fibrosis

EASL Guidelines. J Hepatol 2019, Terraulth N et al. Hepatology 2018; Sarin SK et al. Hepatol Int. 2016

Biochemical markers for ruling out cirrhosis

Conventional cutoffs for APRI and FIB-4 misclassified as having no cirrhosisa large proportion of patients with cirrhosis

APRI					
Dataset	**Cut-off**	**N identified**	**Cirrhosis**	**NPV**	**Misclassification***
Derivation	**< 0.45**	627 (21.4%)	29 (4.6%)	95.4%	29/340 (8.5%)
Validation	**< 0.45**	407 (39.4%)	22 (5%)	94.6%	22/155 (14.2%)

FIB-4					
Dataset	**Cut-off**	**N identified**	**Cirrhosis**	**NPV**	**Misclassification***
Derivation	**< 0.70**	925 (31.6%)	31 (3.4%)	96.6%	31/340 (9.1%)
Validation	**< 0.70**	337 (32.6%)	9 (2.7%)	97.3%	9/155 (5.8%)

. *Number of patients with score below the cut-off who did have cirrhosis on liver biopsy.

A cutoff for FIB-4 (≤0·70) can be used to exclude cirrhosis in patients over 30 years of age.

Sonneveld M et al Lancet Gastrro 2019

Which Nucleos(t)ide?

- Tenofovir based regimen
  - Tenfovir disproxil fumarate
  - Tenofovir Alafenamide

- Entecavir

EASL Guidelines. J Hepatol 2019, Terraulth N et al. Hepatology 2018; Sarin SK et al. Hepatol Int. 2016

Efficacy and Safety of the recommended NUCs

	TDF	TAF	Entecavir
Antiviral Efficacy	**+++**	**+++**	**+++**
HBsAg loss	**Rare**	**Rare**	**Rare**
Drug resistance	**No**	**No**	**Naive 1.2% at year 6 Previously treated +++**
Dose adjusted to renal function	**Yes**	**No**	**Yes**
Bone alterations	**+**	**No**	**No**
Cost	**Generics**	**++**	**Generics**

EASL Guidelines. J Hepatol 2019, Terraulth N et al. Hepatology 2018; Sarin SK et al. Hepatol Int. 2016

Efficacy and Safety of the Recommended NUCs in Special Populations

	TDF	TAF	ETV
Decompensated Cirrhosis	**YES**	**On going studies**	**YES Lactic acidosis????**
Renal Alterations	**Adjusted to eGFR**	**Yes**	**Adjusted to eGFR**
HIV Coinfection	**YES**	**YES**	**No Monotherapy**
Children	**> 2 years**	**On going studies**	**> 2 years**
Women planning family	**YES**	**YES**	**NO**

EASL Guidelines. J Hepatol 2019, Terraulth N et al. Hepatology 2018; SK et al. Hepatol Int. 2016

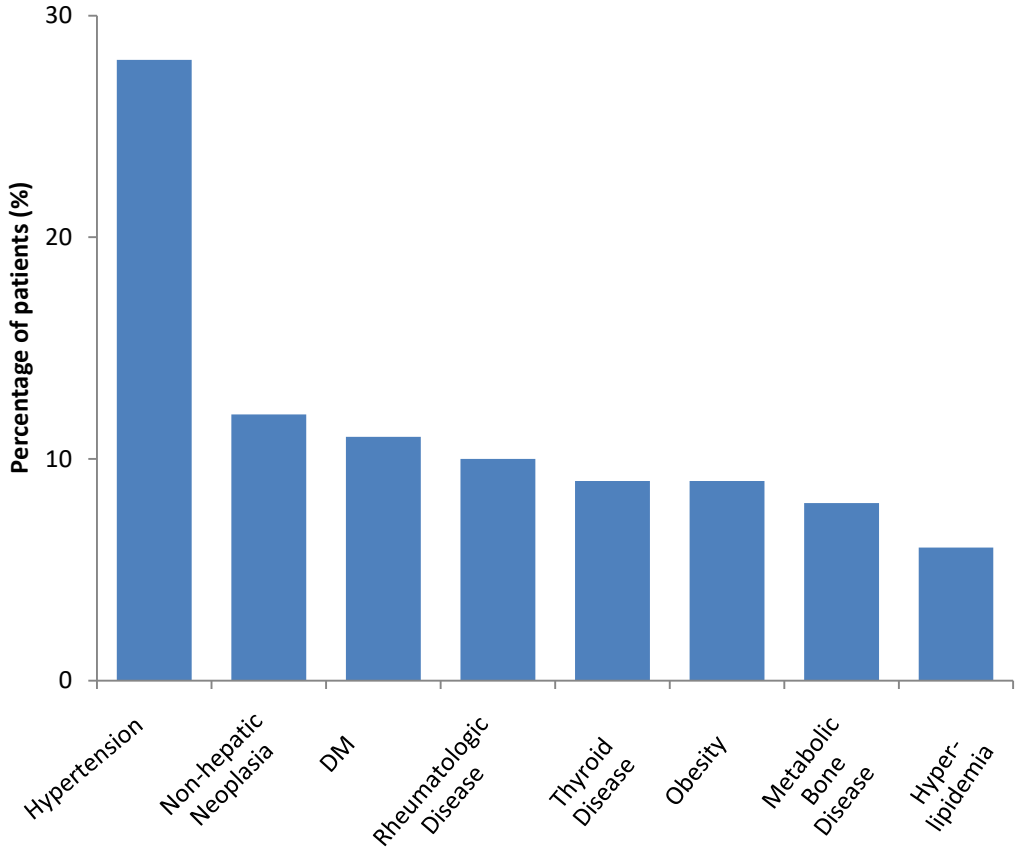
Comorbidities in CHB Patients Currently Treated with NUCs

Multicenter assessment of 500 consecutive CHB patients receiving long-term NUCs in 2016 at outpatient liver clinics of 5 tertiary Greek hepatology centers

Patient Characteristics

	N=500
Age, years	57.7±14.9
Male, n (%)	329 (66)
Alcohol abuse, n (%)	20 (4)
Former or current smoker, n (%)	147 (29)
Current NUC, n (%) TDF ETV	 301 (60) 185 (37)
HCC development under treatment, n (%)	21 (4)
Decompensated cirrhosis, n (%)	48 (10)
Previous antiviral treatment	213 (43)
Total Rx duration, mean±SD (range), months	72 ± 58 (1-212)
LAM-experienced, n (%)	156 (31.1)
LAM-resistant, n (%)	104 (21)

Common Comorbidities



CHB patients treated with NUCs are of older age, LAM-exposed, have multiple comorbidities and require careful management

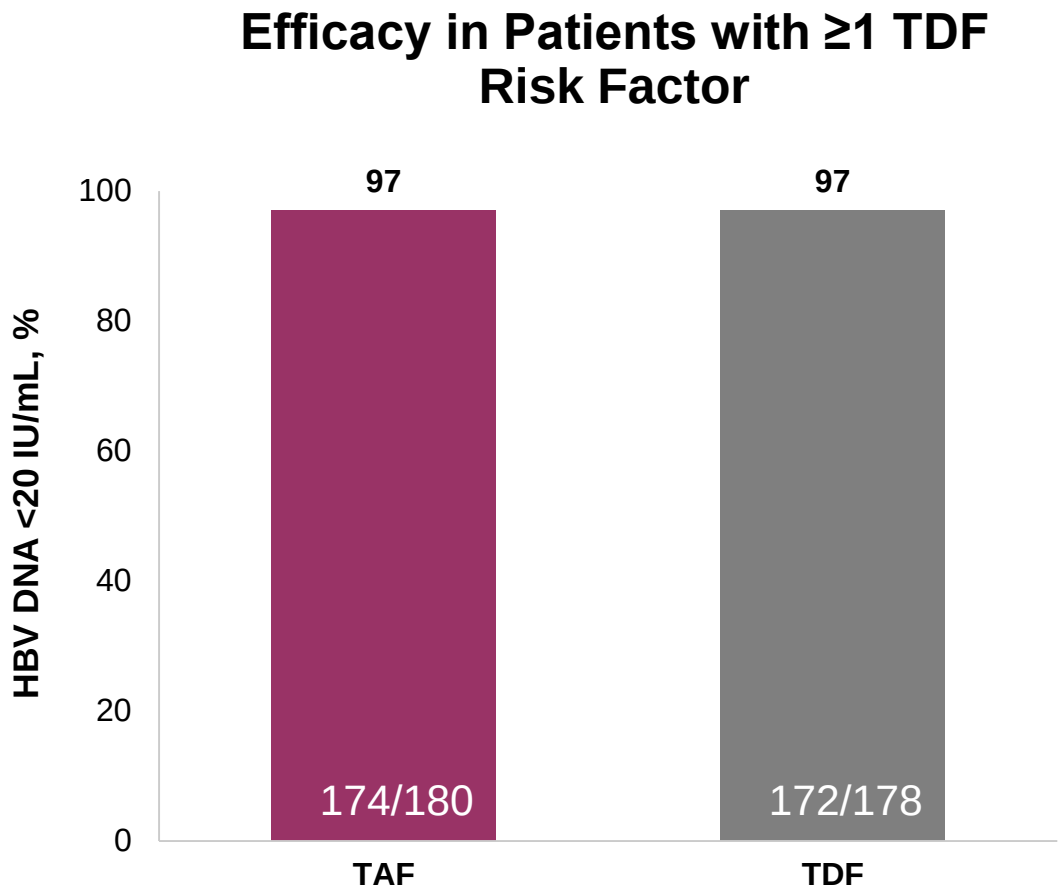
Siakavellas, EASL2018, FRI-292

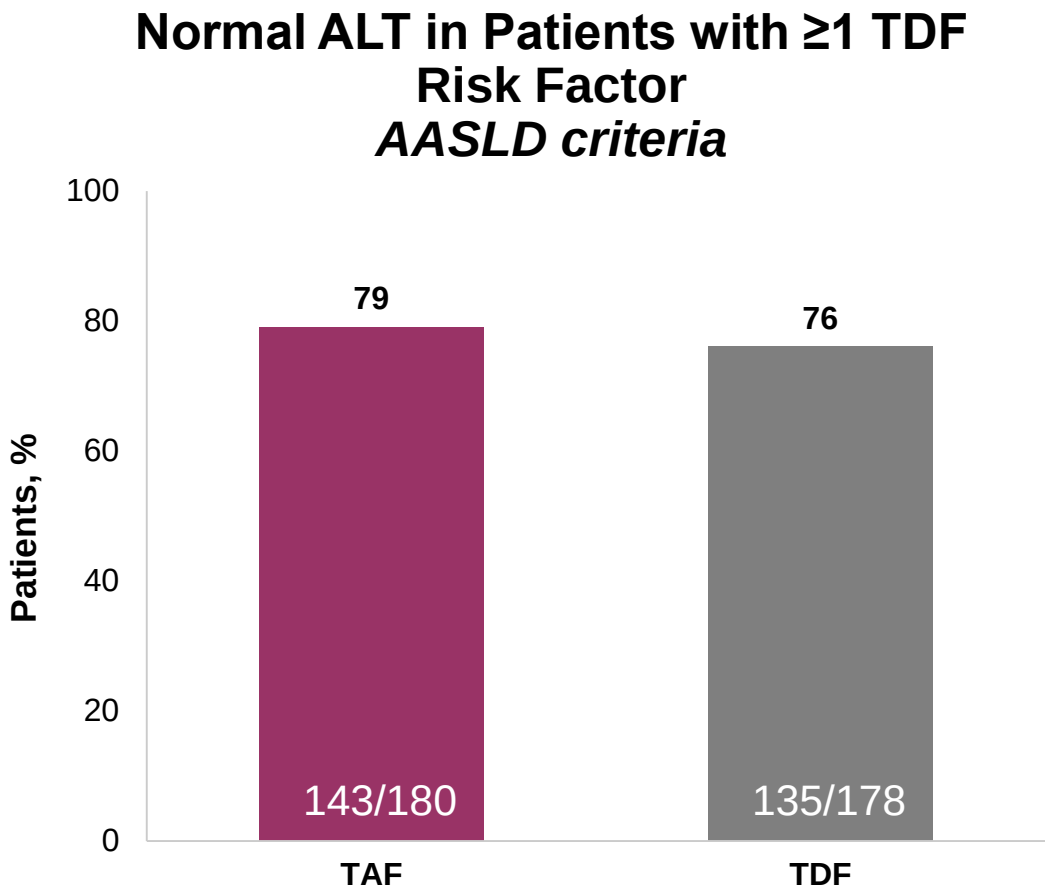
EASL Clinical Practice Guidelines on the management of HBV infection

Indications for selecting TAF or ETV over TDF
Age >60 years
Bone disease Chronic steroid use or use of other medications that worsen bone density, history of fragility fracture, osteoporosis
Renal alteration (eGFR <60 min/mL/1.73 m^2; albuminuria; low phosphate; haemodialysis) • ETV dose adjusted if eGFR <50 mL/min • No dose adjustment of TAF is required in adults or adolescents* with estimated CrCl ≥15 mL/min or in patients with CrCl <15 mL/min who are receiving haemodialysis
TAF preferred to ETV in patients with previous NA exposure

EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017

TAF in CHB Patients Switched from TDF with Risk Factors

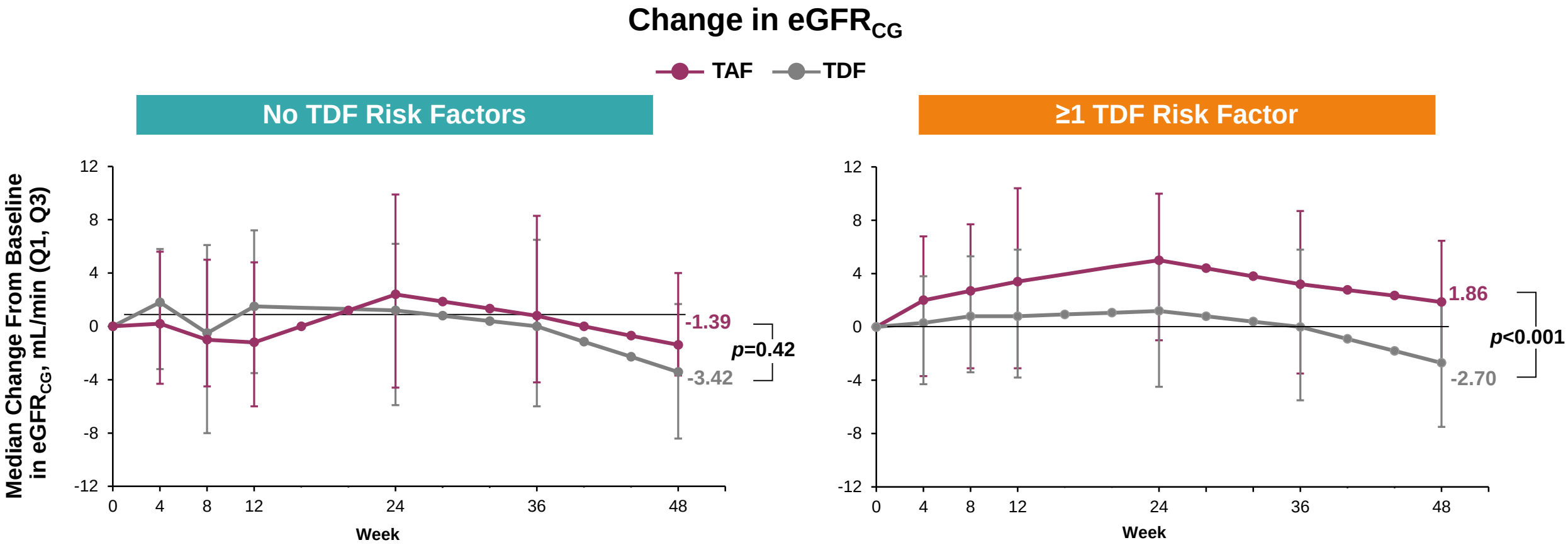




In CHB patients with risk factors to TDF, viral suppression was maintained with numerically higher rates of normal ALT in those switching from TDF to TAF at Week 48

Buti M, et al. AASLD 2019. 476

TAF in CHB Patients Switched from TDF with Risk Factors



Switching TDF to TAF demonstrated improvements in renal function in patients with ≥1 risk factors

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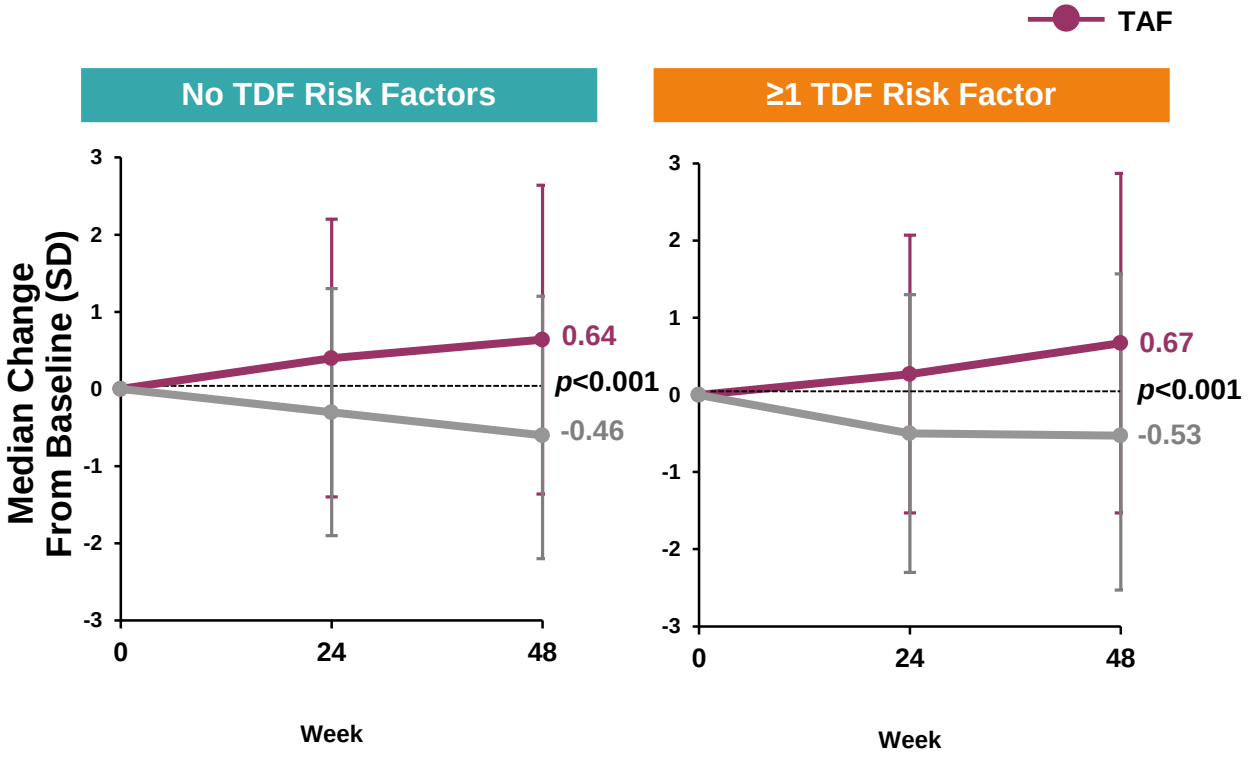
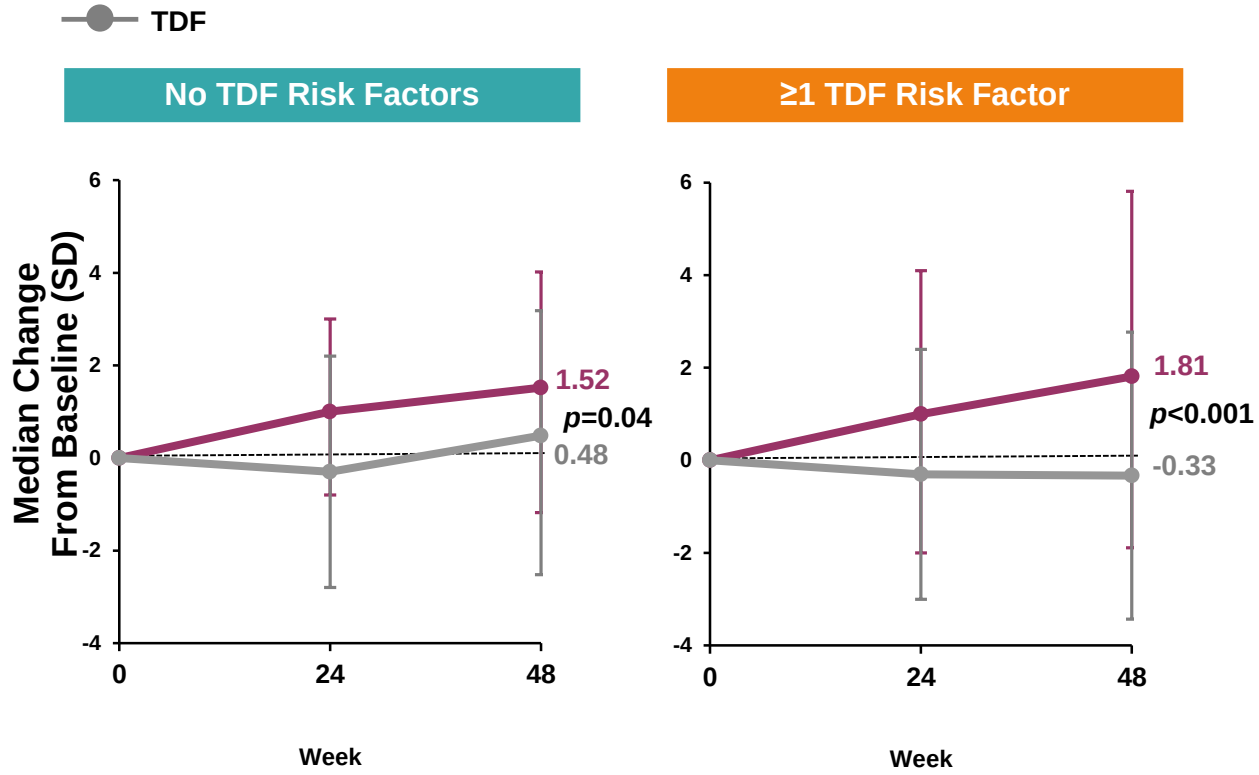
TAF in CHB Patients Switched from TDF with Risk Factors

Changes in Hip BMD



Changes in Spine BMD

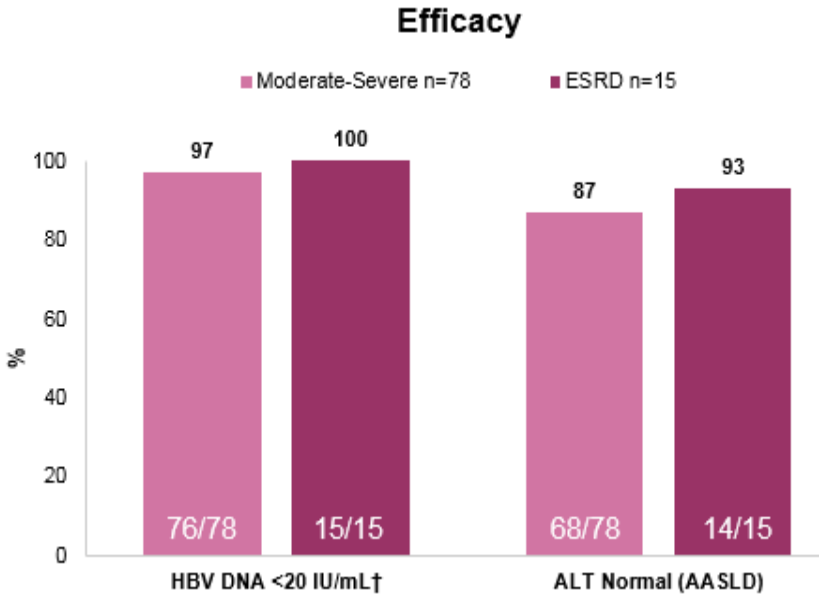


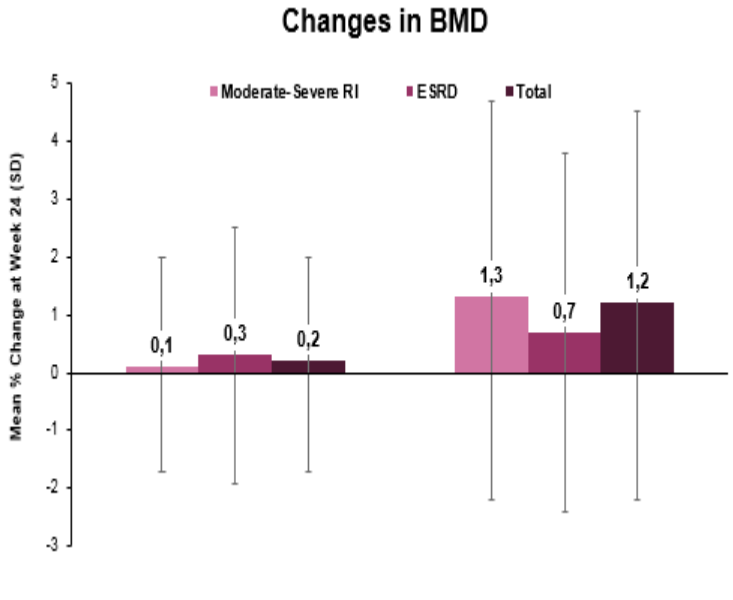
Switching from TDF to TAF demonstrated significant improvements in BMD

TAF in CHB Patients with Renal Impairment

Phase 2 CHB Switch to TAF: Week 24 Analysis

Open-label study of switching to TAF in 93 patients with moderate-severe renal impairment or ESRD





Switching to TAF in CHB patients with renal impairment maintained viral suppression with high rate of normal ALT and resulted in stable or improved renal and bone safety at Week 24

Janssen H, et al. AASLD 2019. 483

Antiviral Therapy reduces the risk of Hepatocellular Carcinoma Risk in patients with Chronic Hepatitis B

JAMA Oncology | Original Investigation

Risk of Hepatocellular Carcinoma in Patients Treated With Entecavir vs Tenofovir for Chronic Hepatitis B

A Korean Nationwide Cohort Study

Jonggi Choi, MD; Hyo Jeong Kim, MPH; Jayoun Lee, PhD; Songhee Cho, MPH; Min Jung Ko, PhD; Young-Suk Lim, MD, PhD

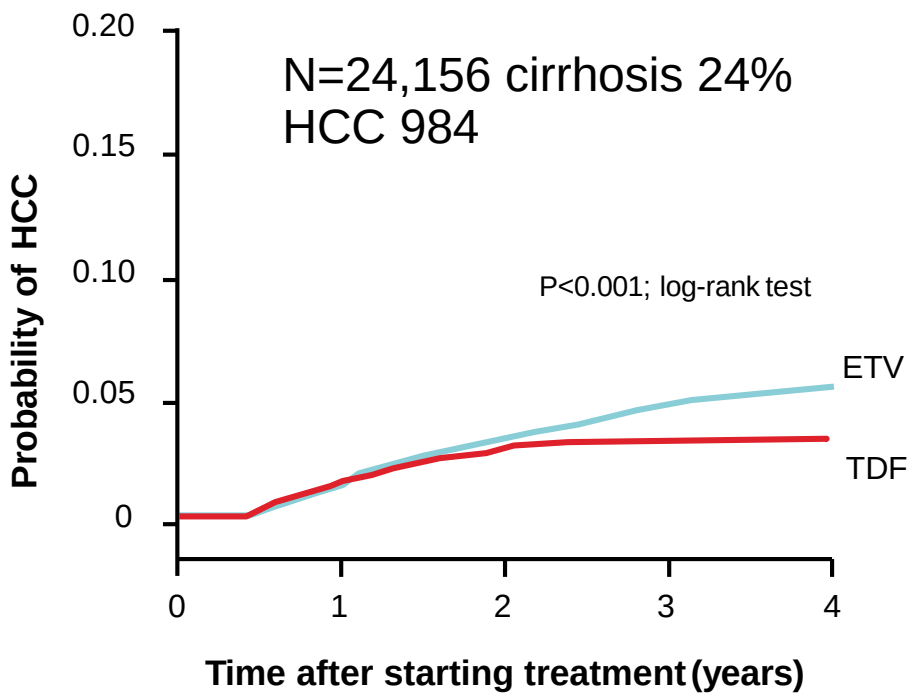
DESIGN, SETTING, AND PARTICIPANTS A nationwide historical population cohort study involving treatment-naive adult patients with CHB who started treatment with entecavir (n = 11 464) or tenofovir disoproxil fumarate (n = 12 692) between January 1, 2012, and December 31, 2014, using data from the Korean National Health Insurance Service database. As validation, a hospital cohort of patients with CHB treated with entecavir (n = 1560) or tenofovir (n = 1141) in a tertiary referral center between January 1, 2010, and December 31, 2016, were analyzed. Nationwide cohort data were retrieved from January 1, 2010, to

CONCLUSIONS AND RELEVANCE This study suggests that tenofovir treatment was associated with a significantly lower risk of HCC compared with entecavir treatment in a population-based cohort of adults with CHB; these findings were validated in a hospital cohort. Given the poor prognosis of patients with HCC, these findings may have considerable clinical implications in prevention of this cancer in patients with CHB infection.

10.1001/jamaoncol.2019.0576

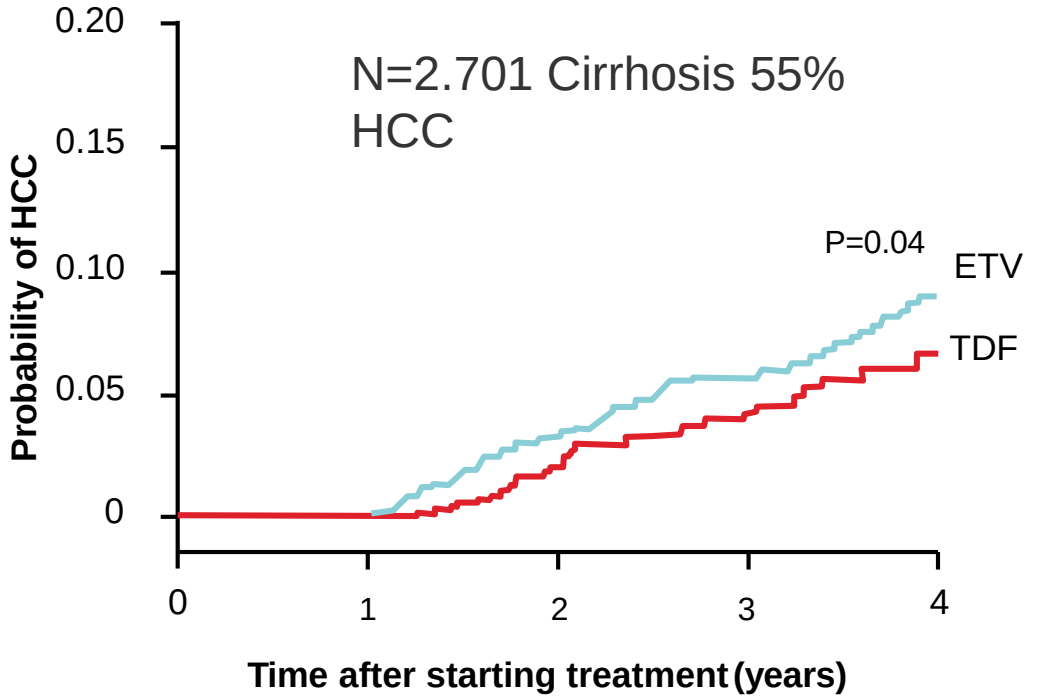
Korean Nationwide Cohort Study: Lower HCC risk with TDF vs. ETV; propensity score-matched analyses

Nationwide cohort



	Events n	Events/100 patient-years	HR	P-value
ETV	567	1.07	Reference	<0.001
TDF	350	0.66	0.62 (0.54-0.70)	

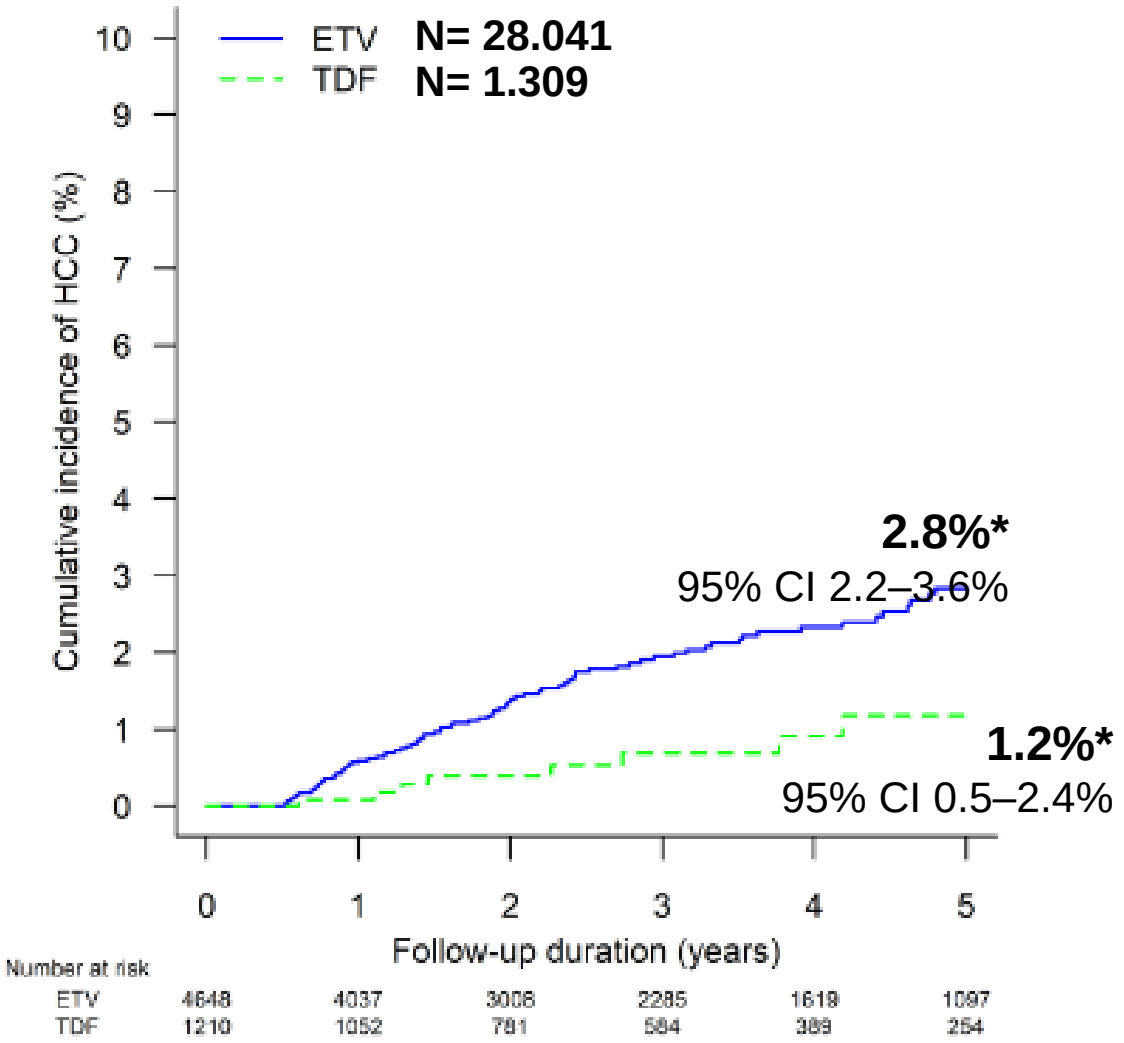
Hospital validation cohort



	Events n	Events/100 patient-years	HR	P-value
ETV	61	2.17	Reference	<0.04
TDF	31	1.37	0.68 (0.46–0.99)	

Choi J, et al. JAMA Oncol 2019;5:30–36.

TDF lowers HCC risk compared to ETV – PS weighting / matching



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

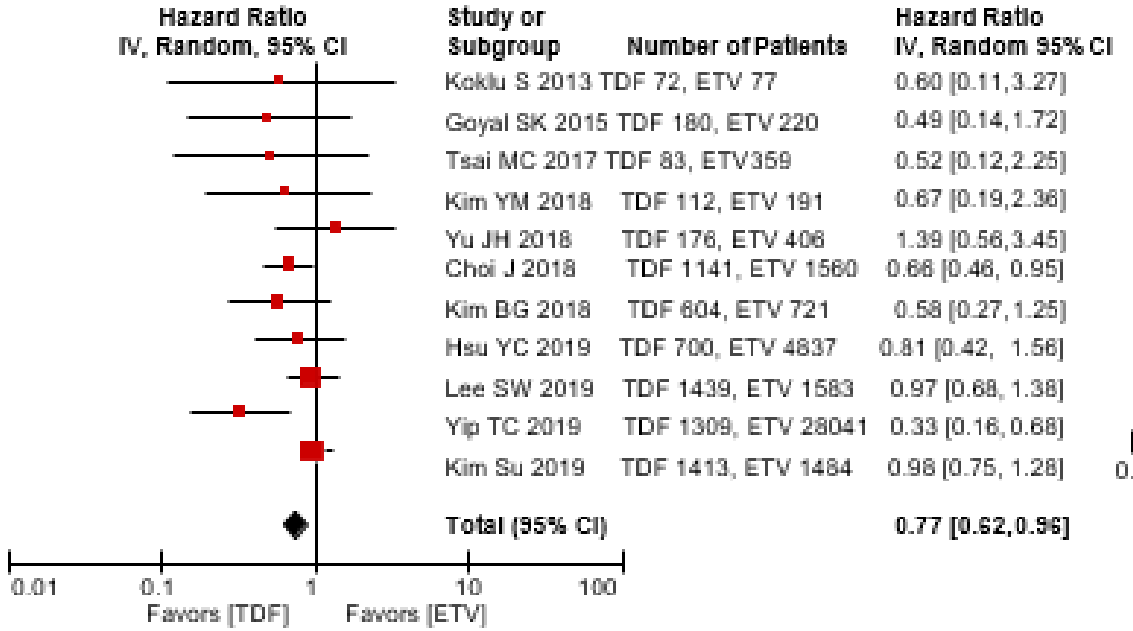
Parameters	Propensity score matching analysis		
	SHR	95% CI	*P* value
TDF *vs.* ETV	0.42	0.17–1.04	*0.060*

SHR = subdistribution hazard ratio

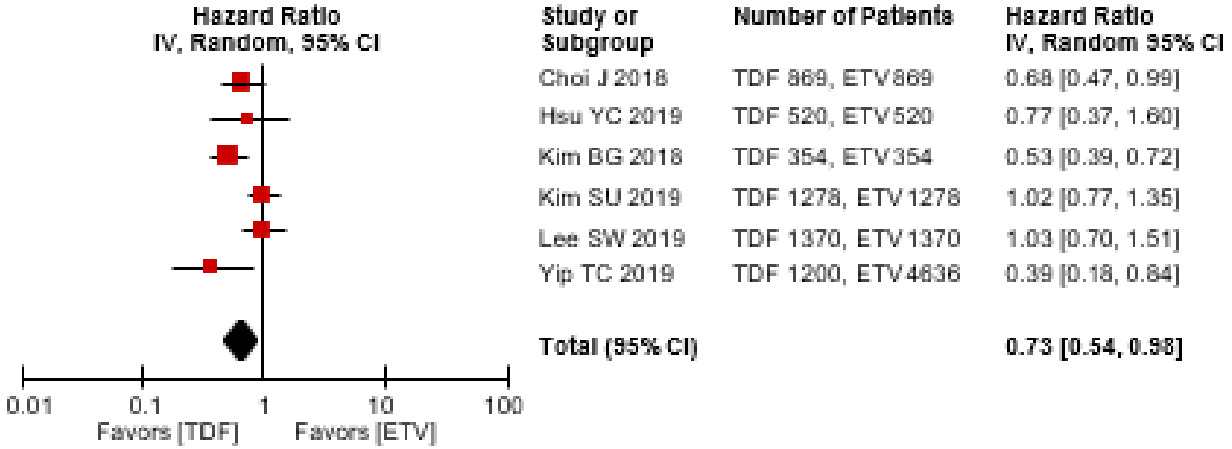
Yip TC et al . Gastroenterol 2020 158(1):215-225.e6.

TDF vs ETV on Risk of HCC in Patients with CHB

Forest plot of pooled HR for HCC between TDF and ETV



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



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 patients with cirrhosis and in PSM cohorts

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

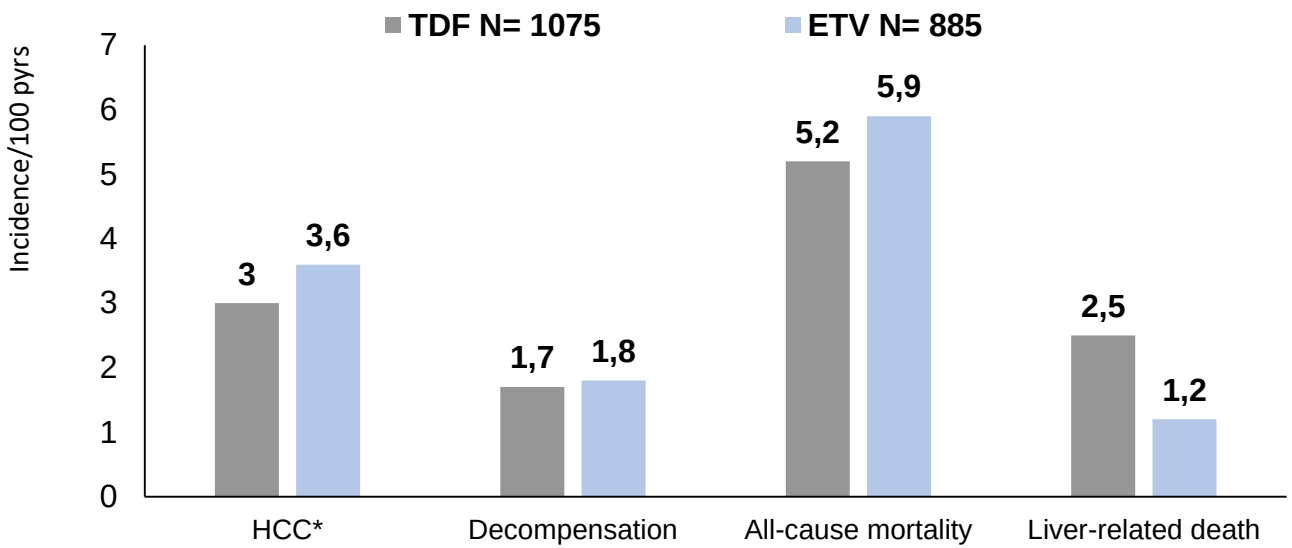
PSM propensity score matched

‡

TDF vs ETV Impact on HCC and Liver-Related Complications

Prospective cohort study of 1960 patients from a French cohort who received TDF or ETV with a mean follow-up of 45 months (IQR 26-53)

Event Incidence Rates



*Cases of HCC: 12/4039 in TDF group; 12/3345 in ETV group

Hazard Ratio (TDF vs ETV)

	Multivariate** HR (95% CI)	IPW HR (95% CI)
HCC	1.1 (0.5-2.5)	1.1 (0.5-2.4)
Decompensation	1.1 (0.4-2.7)	0.8 (0.4-1.8)
All-cause mortality	1.1 (0.6-1.9)	1.2 (0.7-1.9)
Liver-related death	1.3 (0.6-2.8)	1.5 (0.8-3.0)

**adjusted for: age, gender, geographic origin, prior cirrhosis decompensation, fibrosis score, ALT, AST, platelet count, prothrombin time, diabetes, arterial hypertension, time from first treatment, time from start of treatment

In this cohort, multivariable-adjusted hazard ratio showed no evidence of an association between NUCs type and HCC, or other liver complications

IPW=inverse of probability weighting analysis.

Pol S, et al. AASLD 2019. 197

Why may TDF have a lower risk of HCC?.

Entecavir	Tenofovir
Cohort with more severe liver disease more comorbidities	Better virological response
Procarcinogenic in rats (high-dose ETV)	Higher rates of normal ALT
	Higher levels of IFN Lambda Antitumoral activity

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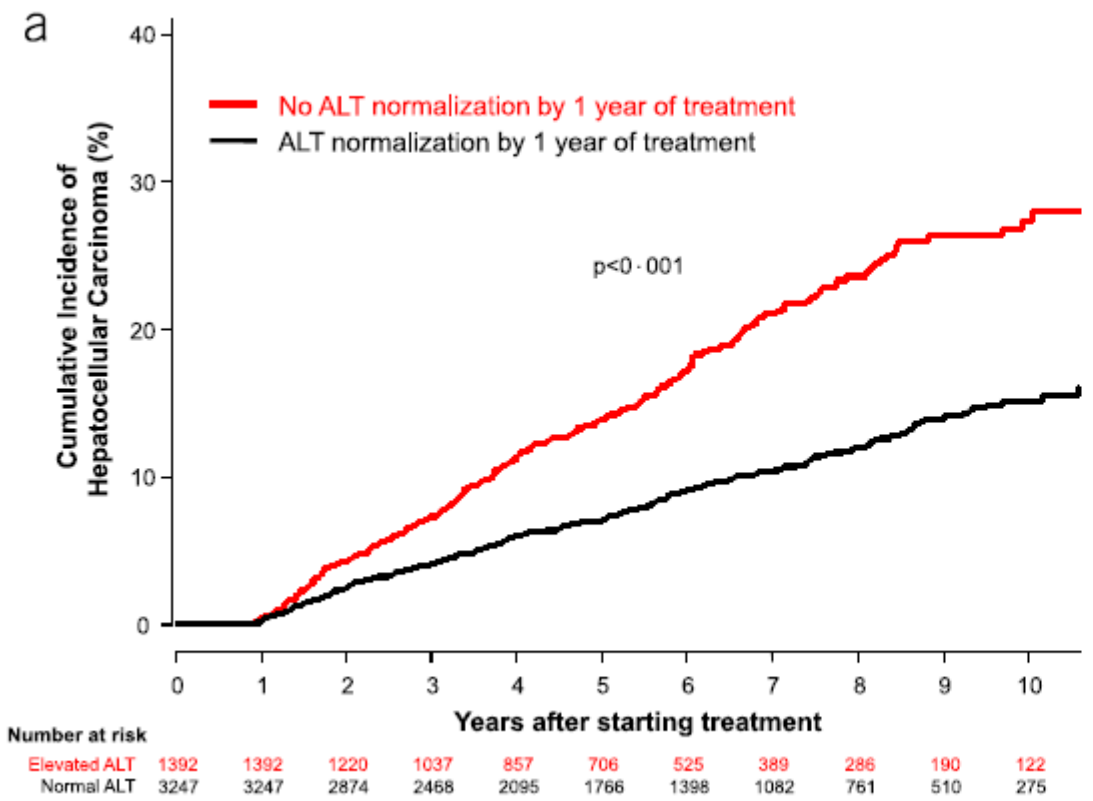
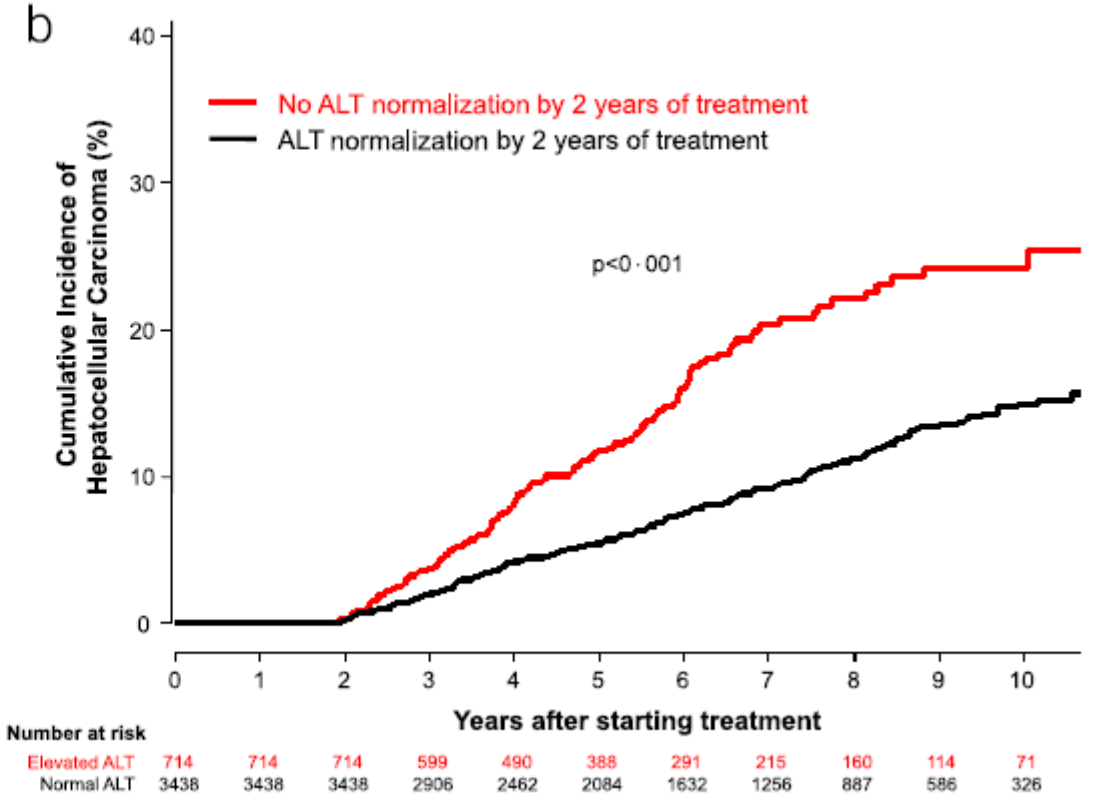
Kim S, et al. AASLD 2019. 488. Choi J, et al. JAMA Oncol 2019;5:30–36. Murata K, et al. Gut 2018;67:362–71

Earlier ALT Normalization During Antiviral Treatment Is Independently Associated With Lower Risk of HCC

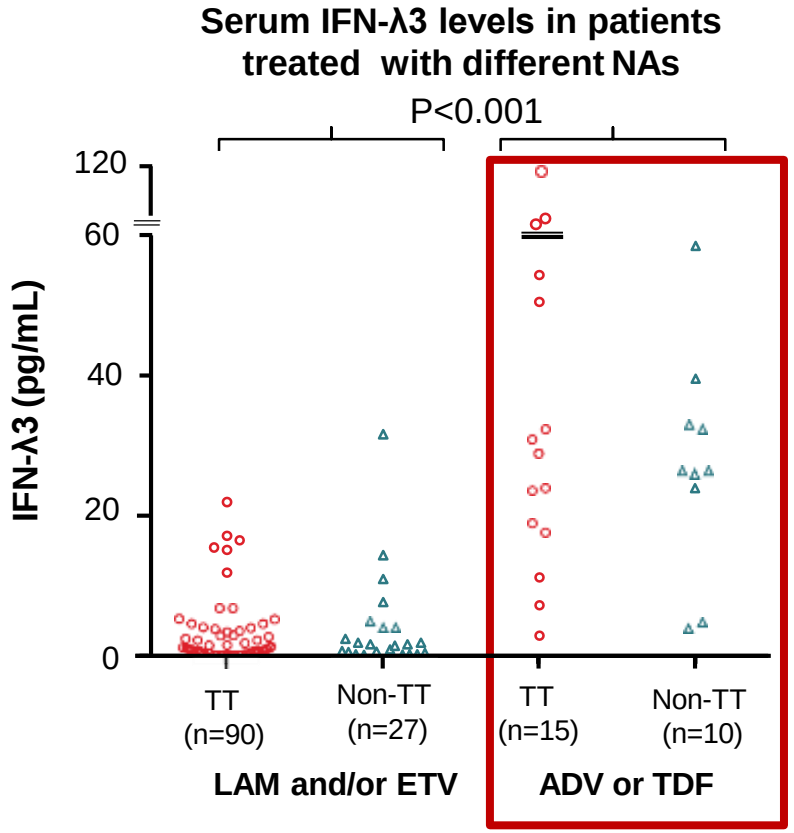
4,639 patients with CHB who initiated treatment with ETV or TDF During a median 5.6 years of treatment, 509 (11.0%) patients developed HCC

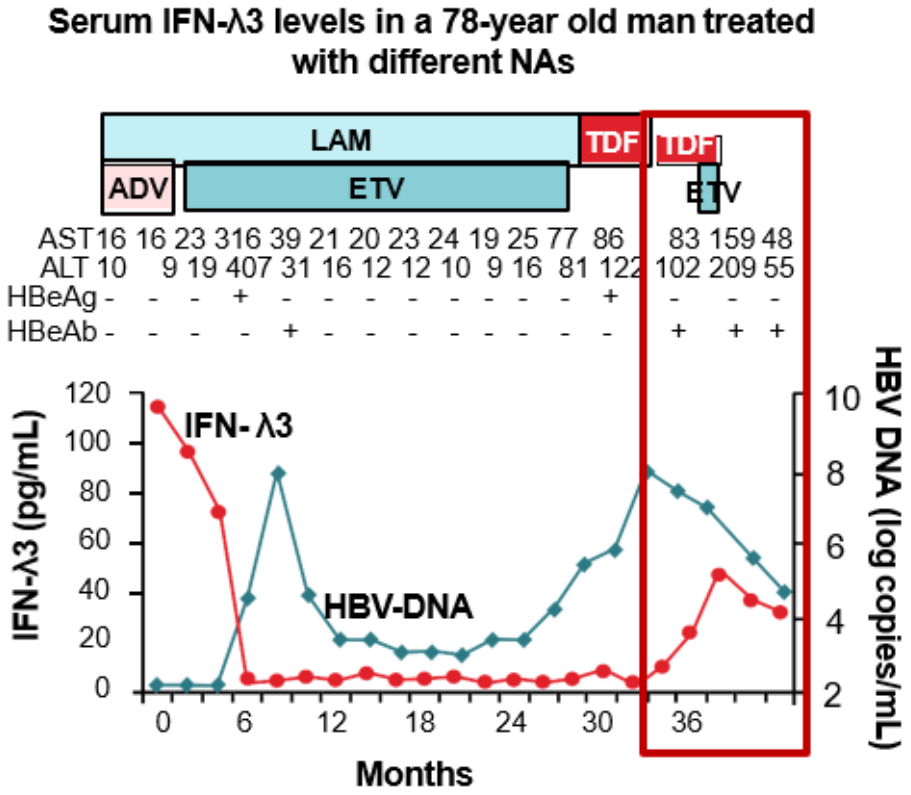




Choi et al. Am J Gastro2020

Possible mechanism may be the variable induction of IFN-λ expression by 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.

Murata K, et al. Gut 2018;67:362–71

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

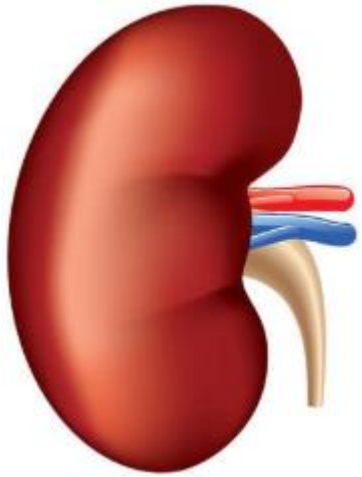
Concerns about Indefinite NUCs therapy

Financial burden

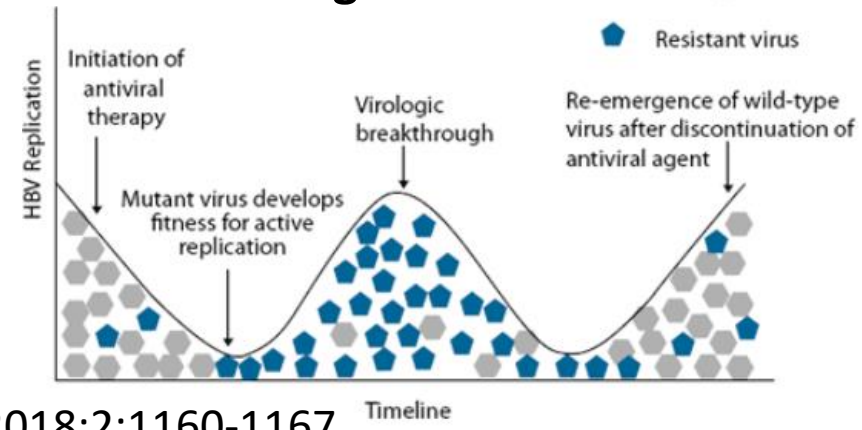
Adherence and willingness

Systematic review 23,823 patients
Overall adherence 74%

Adverse Events



HBV Drug Resistance



Liaw YF et al Hepatol International 2019; Ford N et al. Hepatol Commun 2018;2:1160-1167

Guidelines recommendations on Stopping NUCs in HBeAg negative patients

EASL

21. NAs should be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion.
Evidence level II-2, grade of recommendation 1.

22. NAs can be discontinued in non-cirrhotic HBeAg-positive CHB patients who achieve stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is warranted.
Evidence level II-2, grade of recommendation 2.

23. Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term (≥3 years) virological suppression under NA(s) may be considered if close post-NA monitoring can be guaranteed.
Evidence level II-2, grade of recommendation 2.

AASLD

4. The AASLD suggests indefinite antiviral therapy for adults with HBeAg-negative, immune-active CHB unless there is a compelling rationale for treatment discontinuation

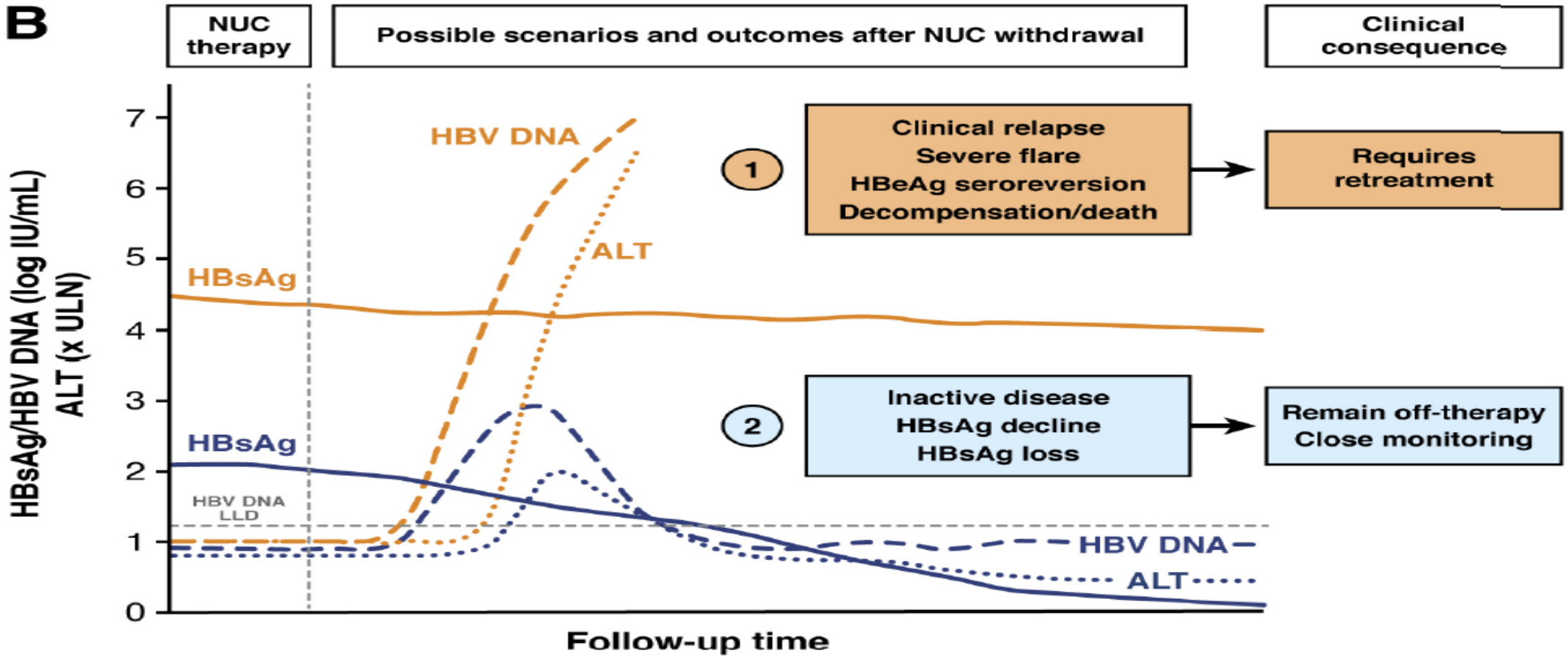
Quality and Certainty of Evidence: Low
Strength of Recommendation: Conditional

APASL

The optimal duration of NA therapy is unknown in patients with HBeAg-negative CHB. In patients without liver cirrhosis, the treatment can be withdrawn (1) after HBsAg loss following either anti-HBs seroconversion or at least 12 months of a post-HBsAg clearance consolidation period (B1), or (2) after treatment for at least 2 years with undetectable HBV DNA documented on three separate occasions, 6 months apart (B1).

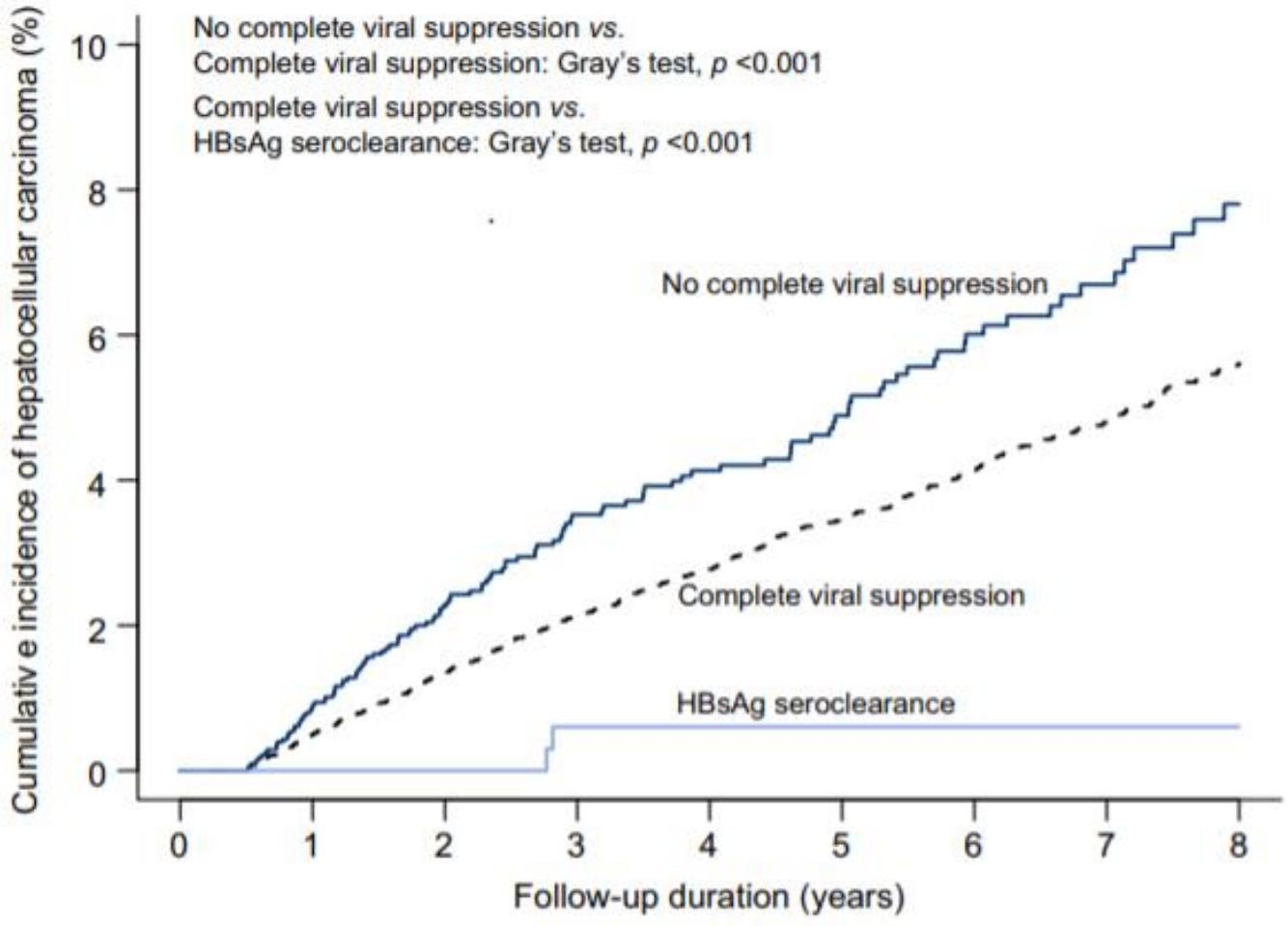
EASL Guidelines. J Hepatol 2019, Terraulth N et al. Hepatology 2018;
Sarin SK et al. Hepatol Int. 2016

Scenarios after NUCs withdrawal in CHB patients



Liem KS et al Gastroenterology in press

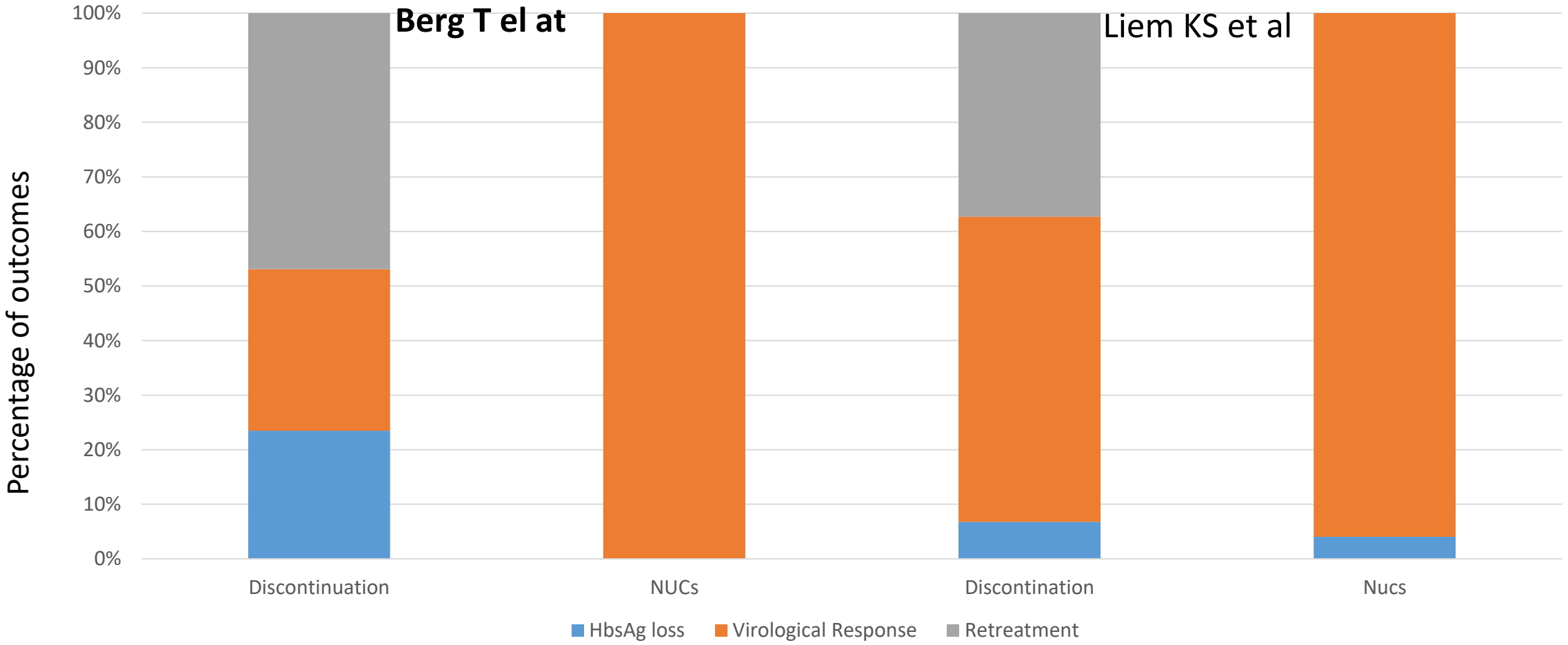
HBsAg seroclearance reduces HCC risk after complete viral suppression with nucleos(t)ide analogues



Yip TC[1],et al.

Yip T C-F et al. J Hepatol. 2019 Mar;70(3):361-370.

Randomized studies on NUCs discontinuation in HBeAg negative patients



Liem KS et al. Gut 2019 Berg T et al J Hepatol 2017

Beneficial and Adverse Outcomes after NUCs Discontinuation in HBeAg-ve Patients. Prospective studies

	No Cases	HBsAg loss	Sustained Response	Clinical Relapse	Re treatement
Buti, (33% Asians)	**106**	**5%**	**39%**	**49%**	**-**
Cao, China	**22**	**6%**	**29%**	**53%**	**53%**
Chi , China	**29**	**10%**	**-**	**59%**	**59%**
Jung, Korea	**68**	**-**	**-**	**18%**	**38%**
Liu, China	**85**	**14%**	**-**	**Vir 62%**	**28%**
Papatheodoridis, Greece	**57**	**25%**	**86%**	**33%**	**28%**
Papatheodoridis,Gre/Taiwan	**130**	**-**	**-**	**40%**	**33%**
Su , Taiwan	**72**	**0%**	**-**	**Vir 72%**	**40%**
Wong , Hong Kong	**20**	**0%**	**0%**	**50%**	**55%**

Liem KS et al Gastroenterology in press

Possible Factors Predictive of clinical relapse after stopping NUCs

Host Factor	Virus Factor	Treatment Factors
Age	**HBV genotype**	**Treatment or consolidation duration**
Genetic and Immune markers	**Baseline serum HBV DNA**	**Time to undetecatble serum HBV DNA**
	Baseline serum HBsAg	**Duration of Viral suppression under Nucs**
	HBsAg level at end of therapy	**Type of Nucs (ETV vs TDF)**
	HBcrAg levels at end of therapy	
	HBV RNA level at end of therapy	

Kao J-H et al. Gut 2019

In summary, optimal management of CHB patients receiving NUCs requires

- proper assessment before starting therapy
- selection of the most appropriate NUCs for treatment, particularly in special populations
- switching to TAF when there are risk factors for TDF use
- adequate HCC surveillance, regardless of the type of NUC
- further study investigating potential predictive factors of achieving HBsAg loss after stopping therapy