



Optimal management of CHB patients under NUCs

Maria Butí, MD, PhD

Liver Unit, Internal Medicine Department

Vall d'Hebron Hospital



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

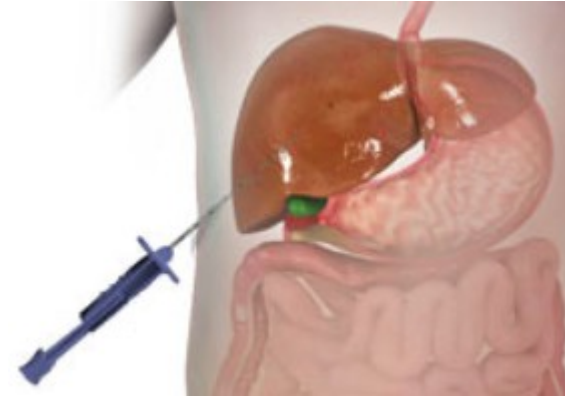
- Proper assessment before starting therapy
- Selection of NUCs
- Monitoring during therapy: Surveillance of HCC
- Finite therapy duration

Assessment Prior NUCs therapy

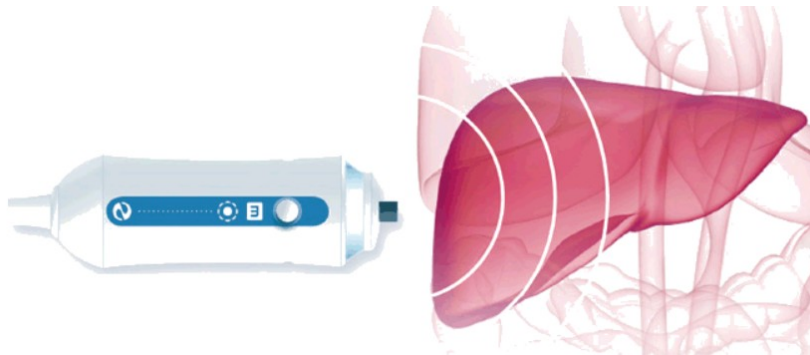
Virus	Liver Disease	Others
HBsAg	ALT, AST	Previous HBV therapy
HBeAg	Biochemistry (Renal function)	HCV, HIV and HDV coinfection
HBV DNA	Fibrosis assessment	HAV vaccination
HBV Genotype	HCC screening	Women planning family
HBcrAg		Comorbidities
HBV RNA		Alcohol

Cirrhosis has significant implications for the management of CHB

- Changes treatment criteria
- Requires 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

Biochemical markers for ruling out cirrhosis

Conventional cutoffs for APRI and FIB-4 misclassified as having no cirrhosis a 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.

Which Nucleos(t)ide?

- Tenofovir based regimen
 - Tenofovir disproxil fumarate
 - Tenofovir Alafenamide

- Entecavir



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

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

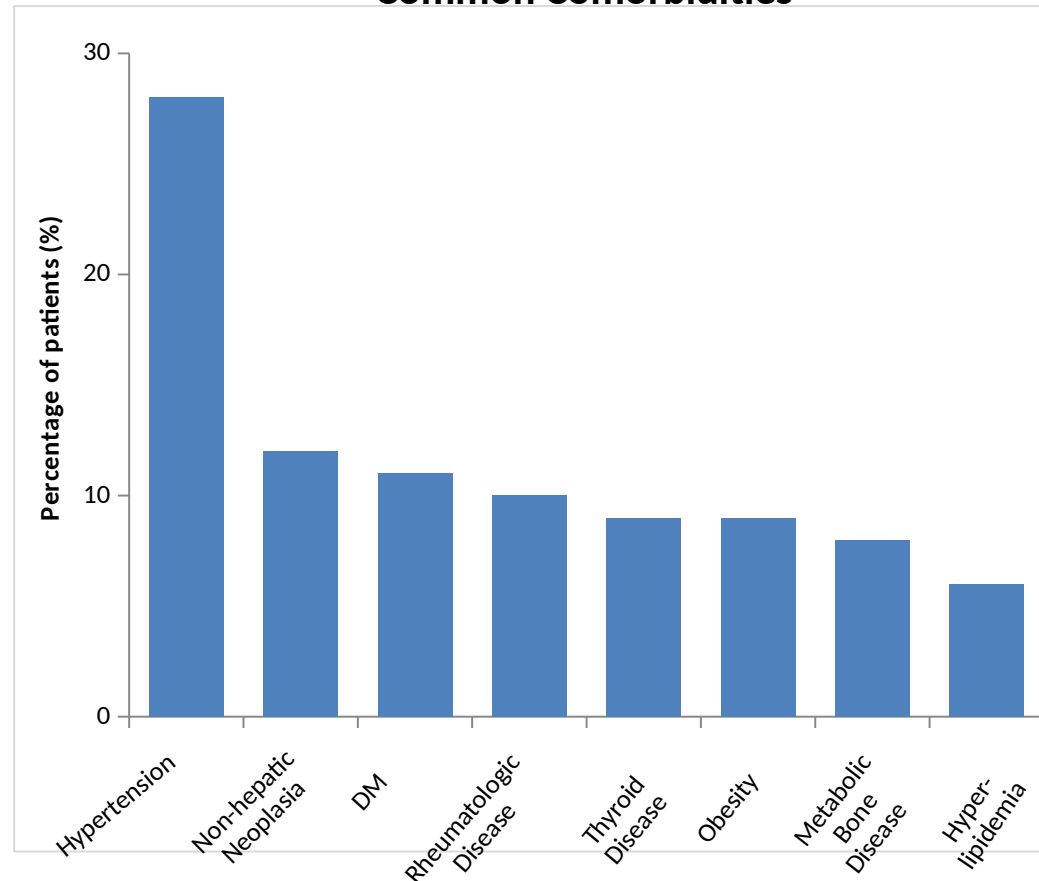
Comorbidities in CHB Patients Currently Treated with NUCs

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	301 (60)
ETV	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

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

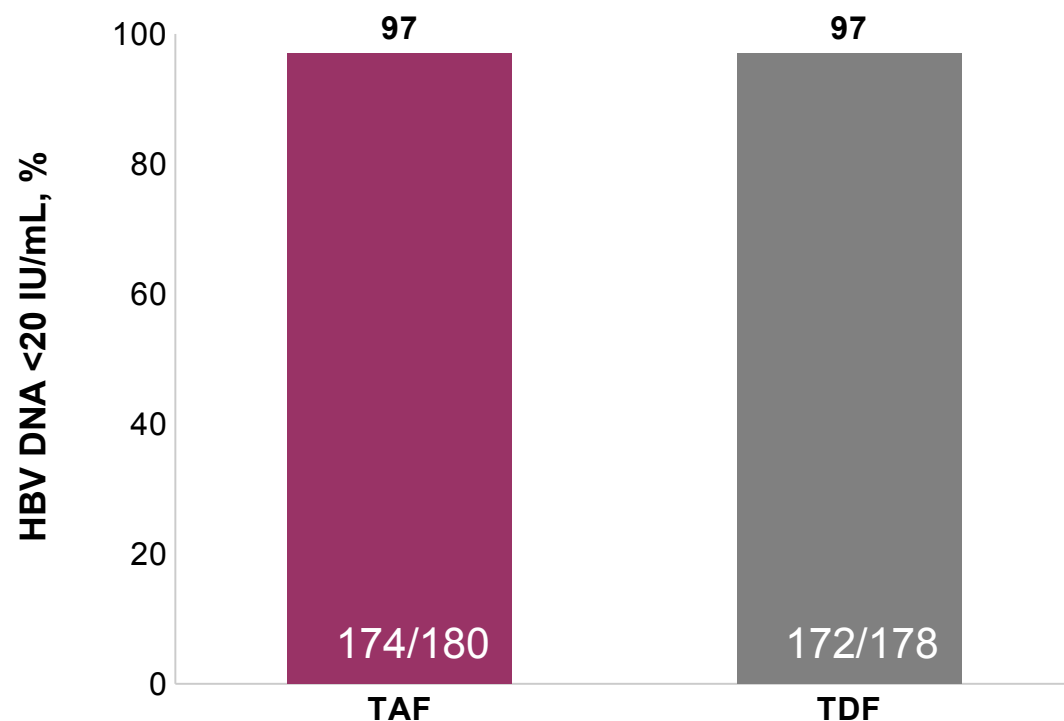
(eGFR <60 mL/min/1.73 m²; albuminuria; low phosphate; haemodialysis)

- 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

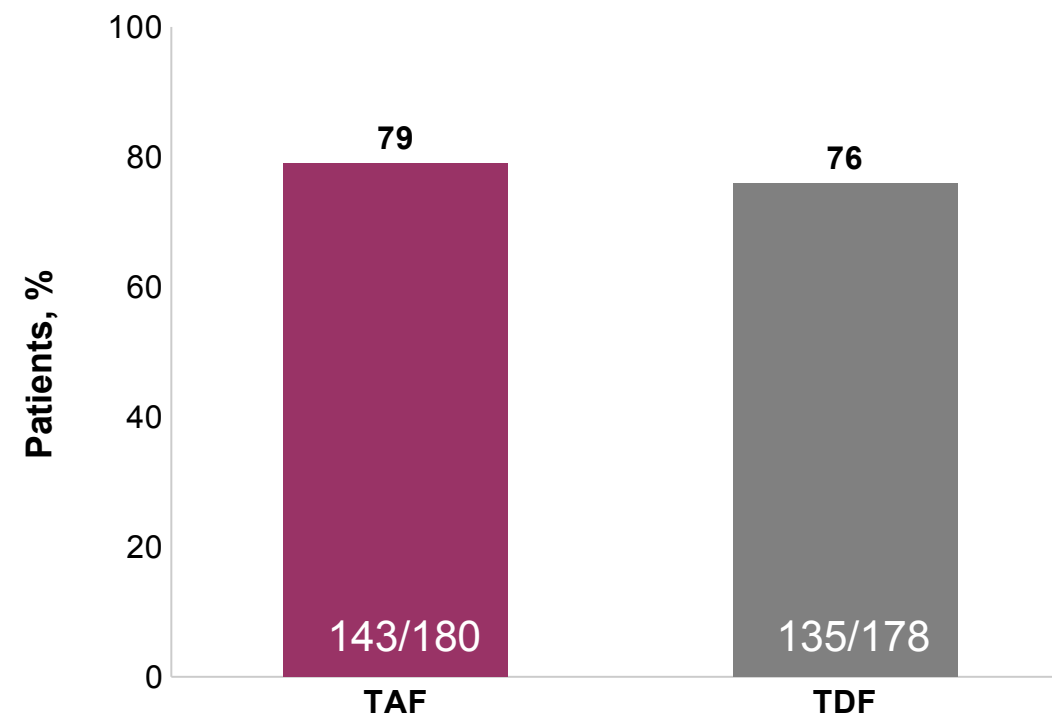
TAF preferred to ETV in patients with previous NA exposure

TAF in CHB Patients Switched from TDF with Risk Factors

Efficacy in Patients with ≥ 1 TDF Risk Factor



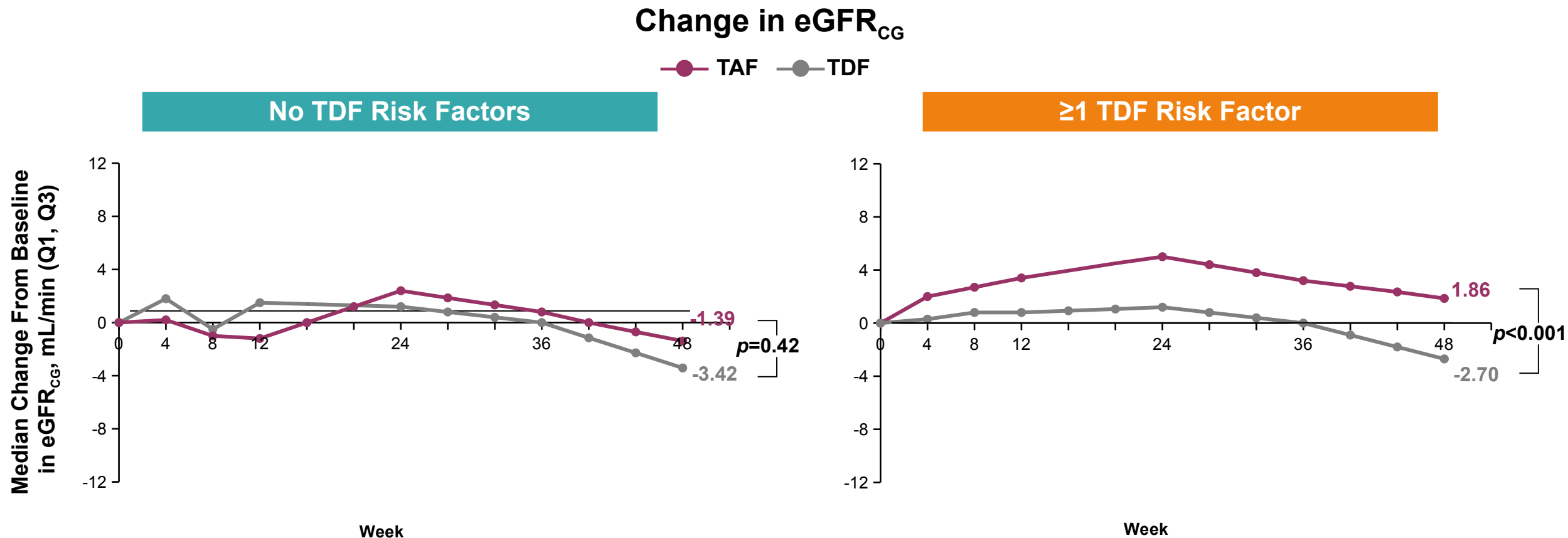
**Normal ALT in Patients with ≥ 1 TDF Risk Factor
*AASLD criteria***



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

TAF in CHB Patients Switched from TDF with Risk Factors

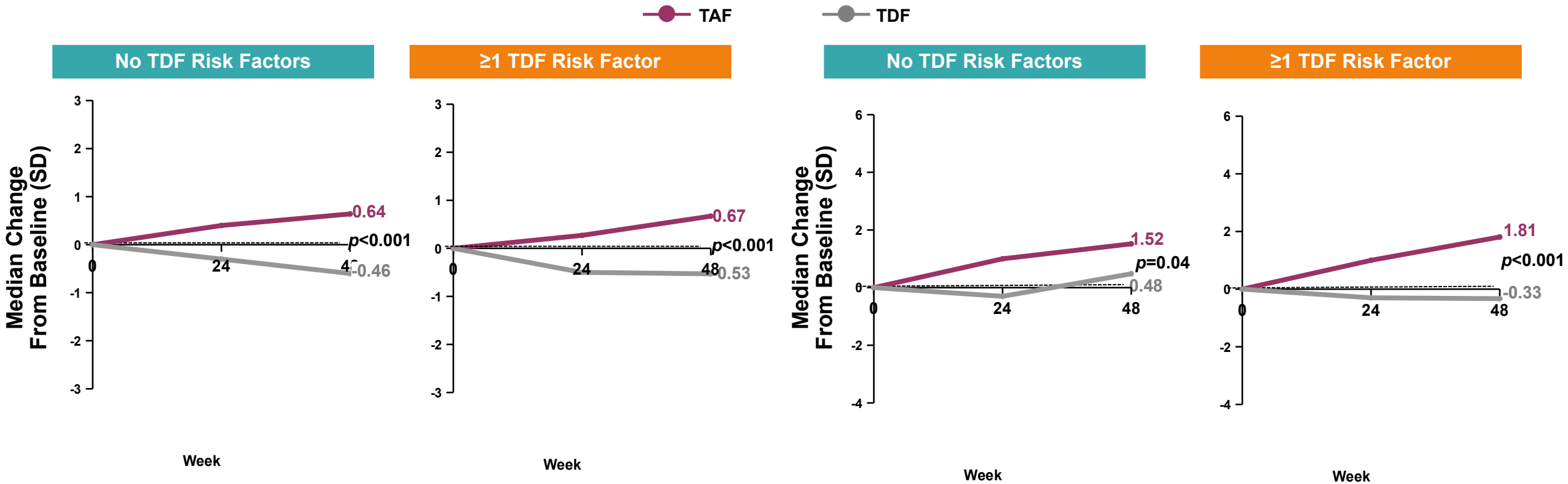


Switching TDF to TAF demonstrated improvements in renal function in patients with ≥1 risk factors

TAF in CHB Patients Switched from TDF with Risk Factors

Changes in Hip BMD

Changes in Spine BMD

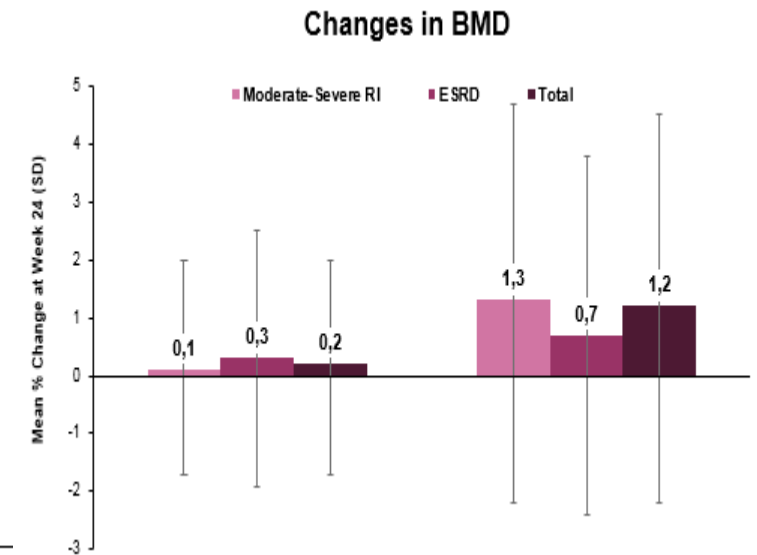
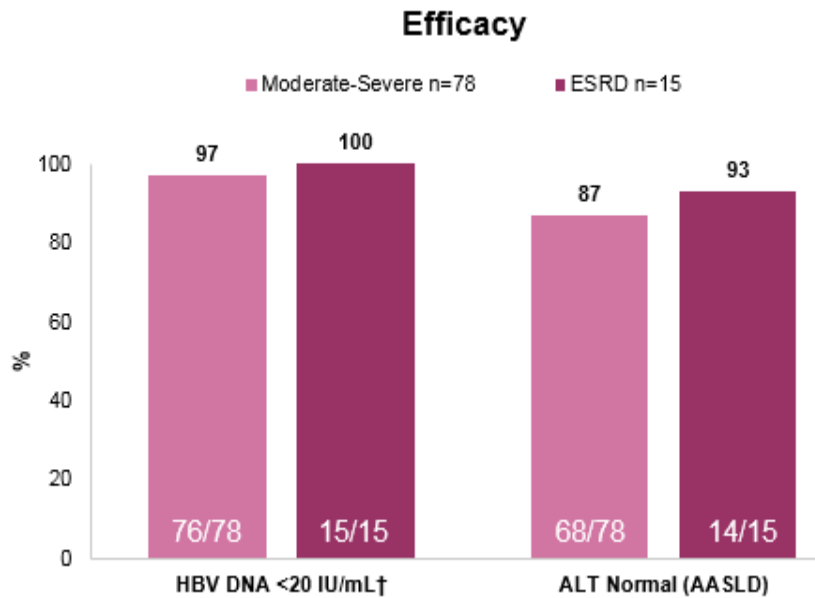


Switching from TDF to TAF demonstrated significant improvements in BMD

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

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

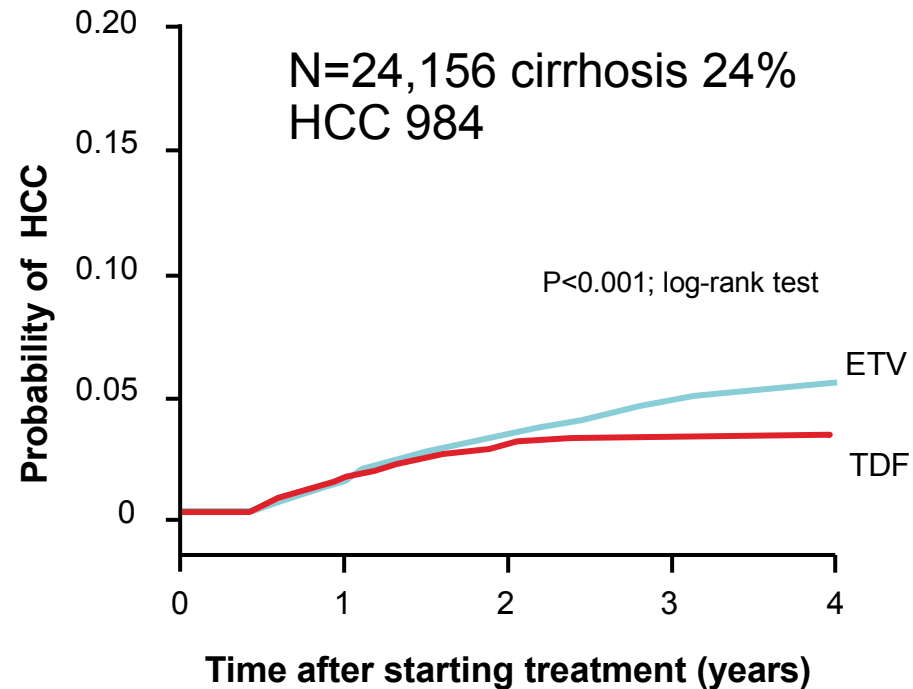
Jonggi Choi, MD; Hyo Jeong Kim, MPH; Jayoun Lee, PhD; Songhee Cho, MPH;
Min Jung Ko, PhD; Young-Suk Lim, MD, PhD

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.

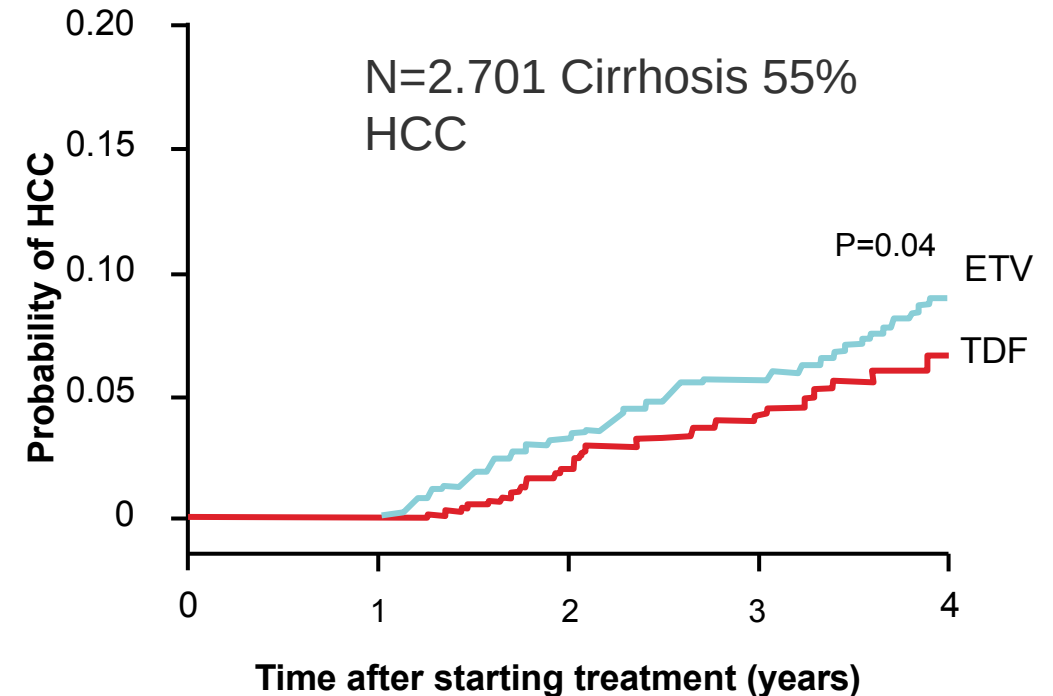
Korean Nationwide Cohort Study: Lower HCC risk with TDF vs. ETV; propensity score-matched analyses

Nationwide cohort



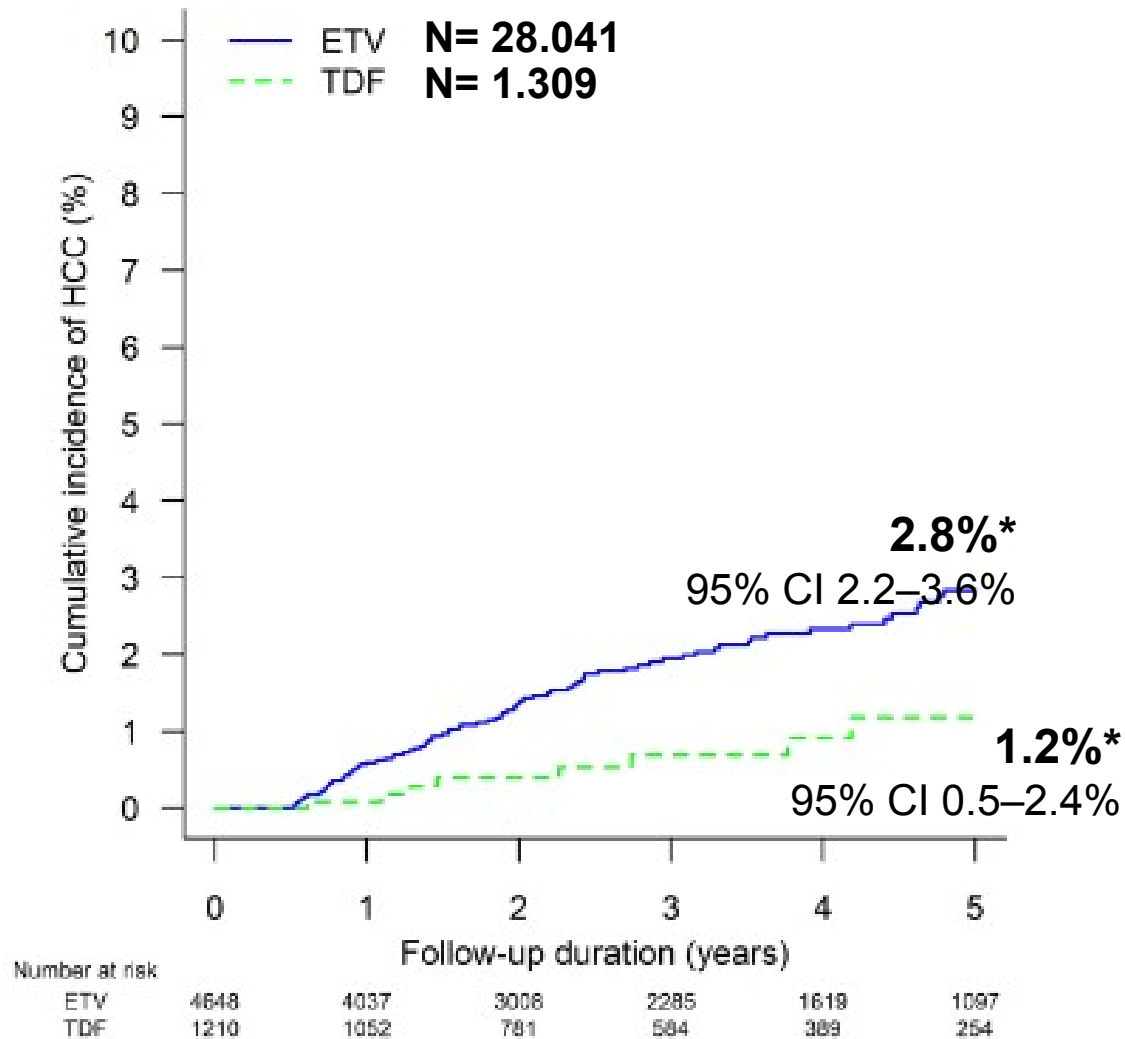
	Events n	Events/100 patient-years	HR	P-value
ETV	567	1.07	Reference	<0.001
TDF	350	0.66	0.62 (0.54-0.70)	

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)	

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



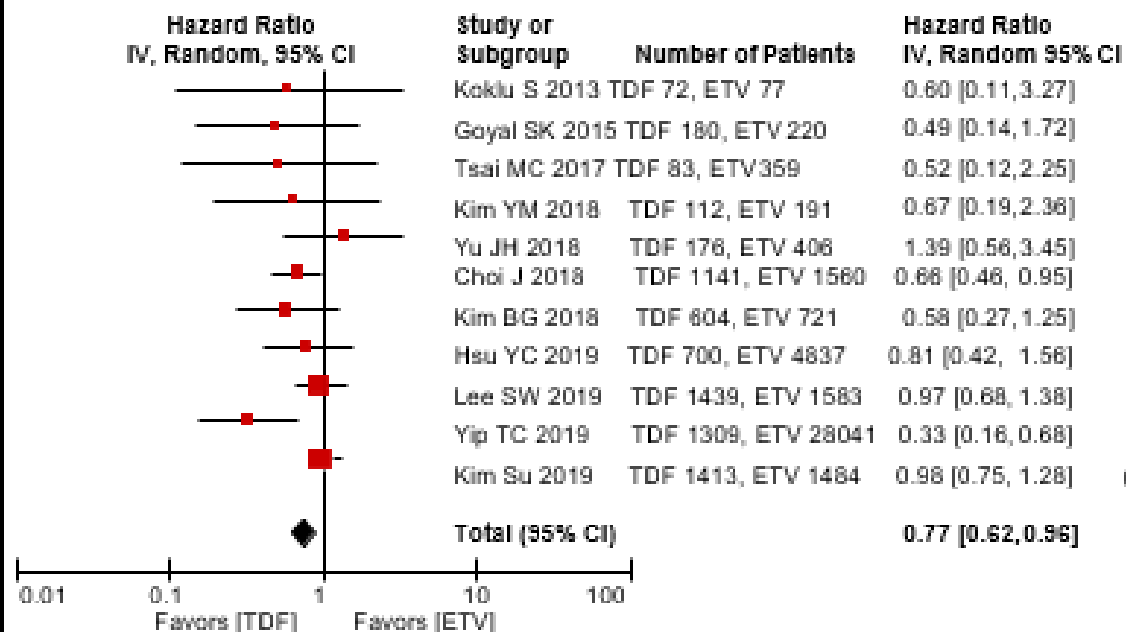
Parameters	Propensity score weighting analysis		
	Weighted SHR	95% CI	P value
TDF vs. ETV	0.36	0.16–0.80	0.013

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

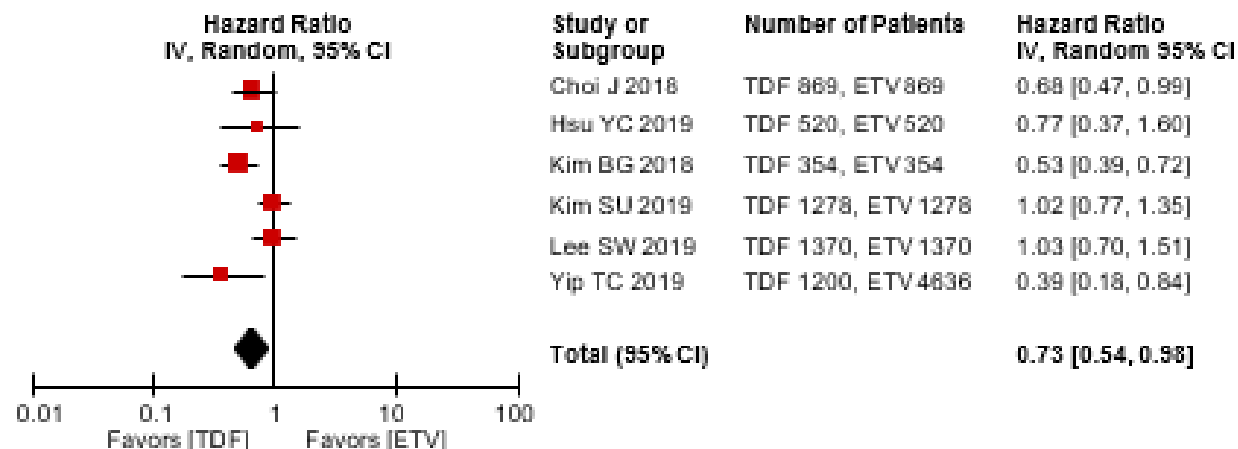
SHR = subdistribution hazard ratio

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



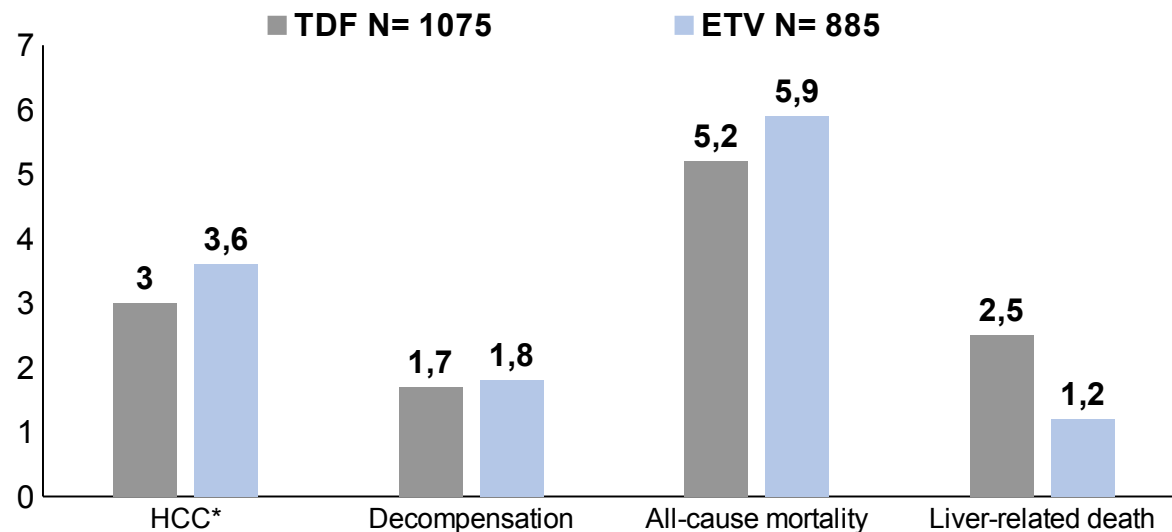
TDF therapy was associated with a significantly lower risk of HCC in patients with CHB compared with ETV therapy. This effect was observed even in patients with cirrhosis and in PSM cohorts

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

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.

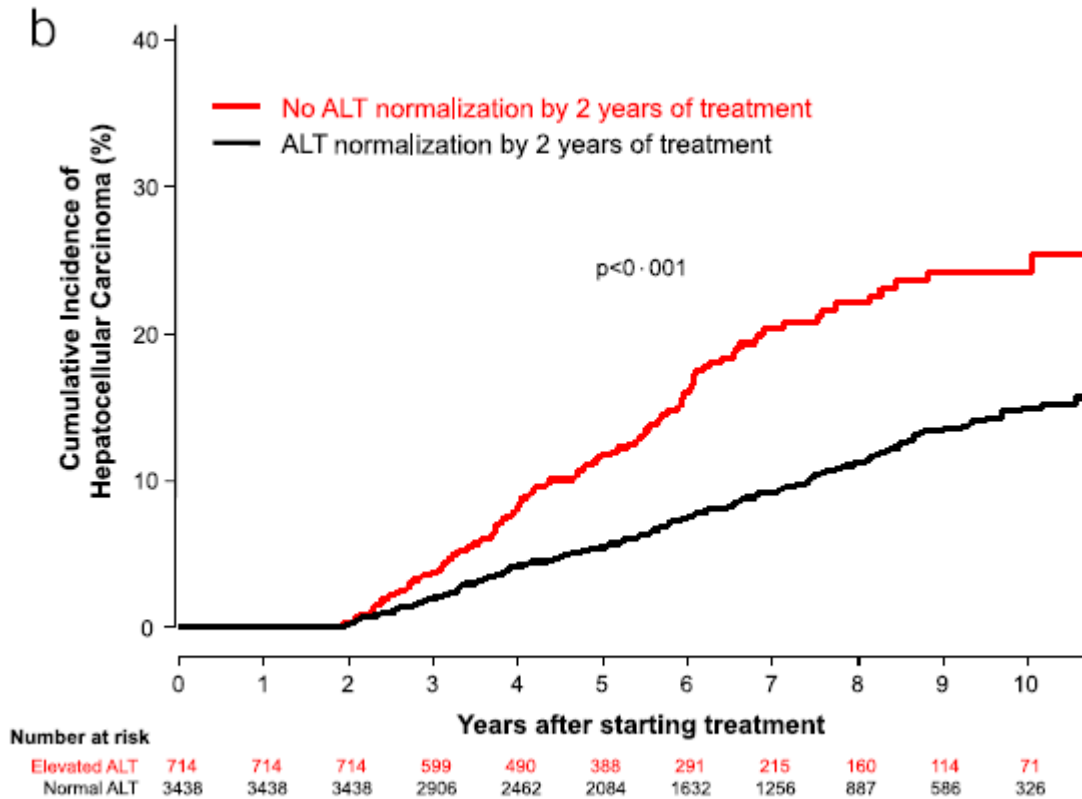
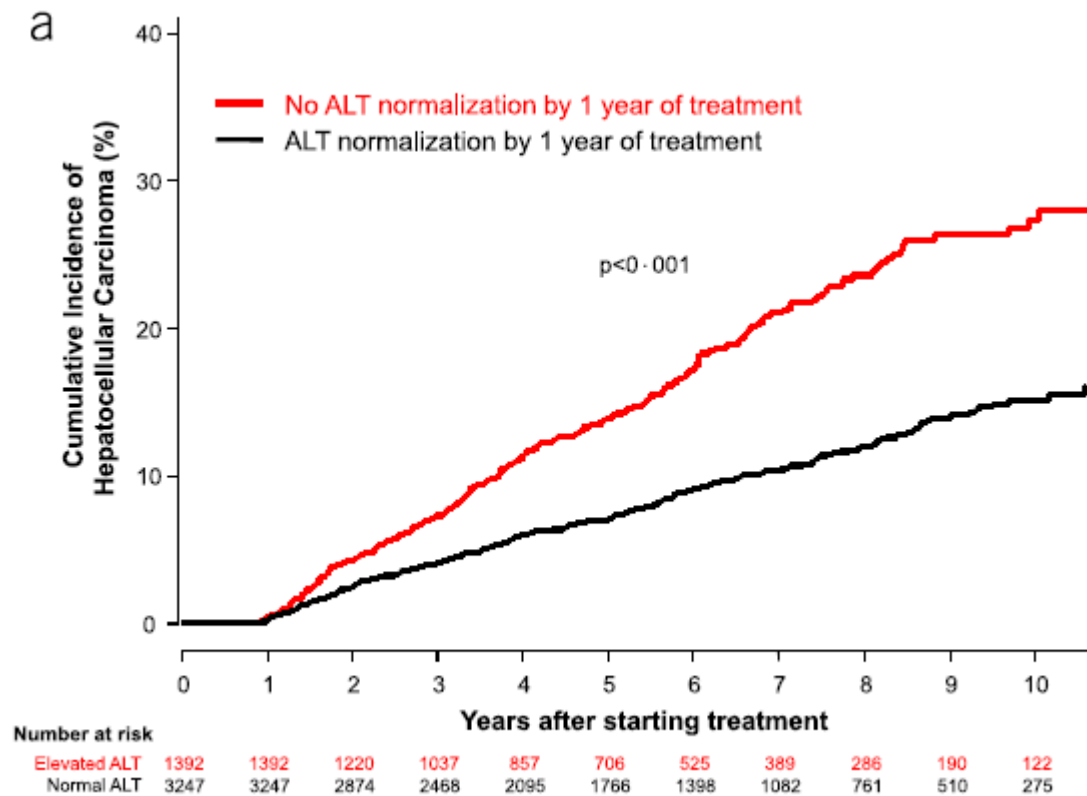
Pol S, et al. AASLD 2019. 197

Why may TDF have a lower risk of HCC?.

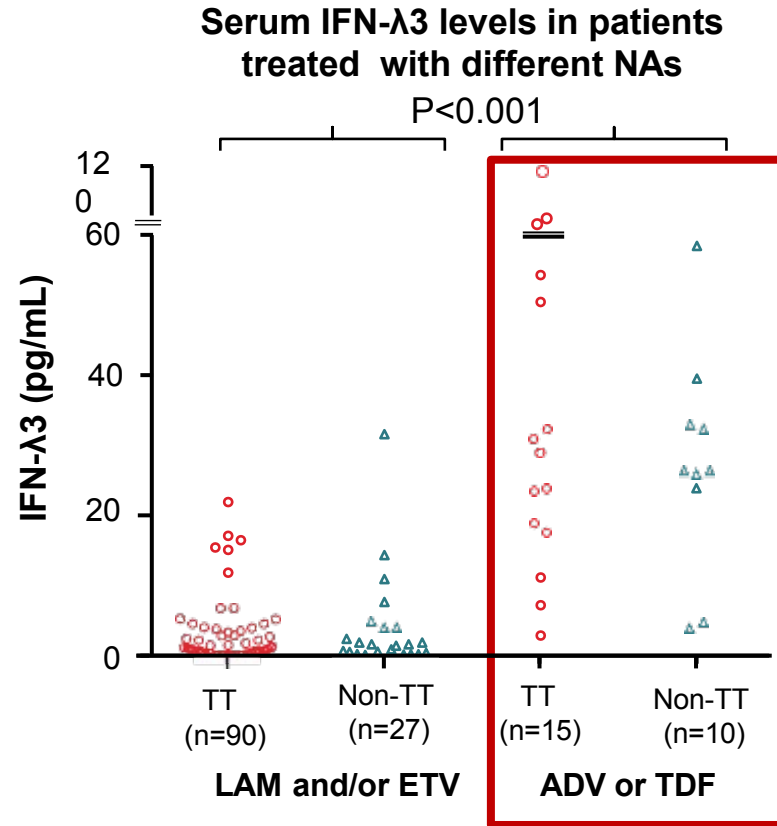
Entecavir	Tenofovir
Cohort with more severe liver disease more comorbidities	Better virological response
Procarcinogenic in rats (high-dose ETV)	Higher rates of normal ALT
	Higher levels of IFN Lambda Antitumoral activity

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

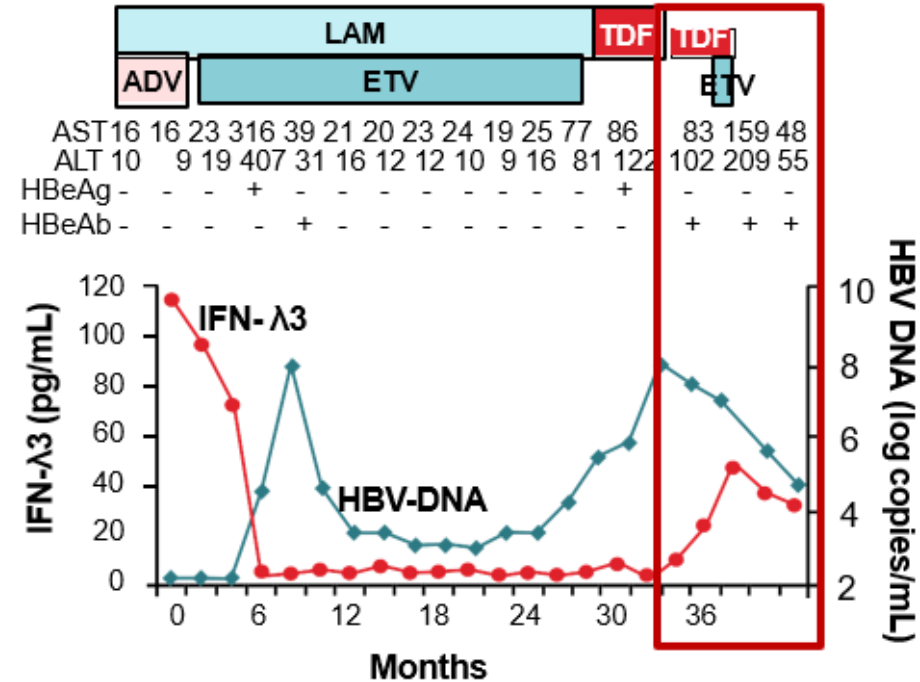
4,639 patients with CHB who initiated treatment with ETV or TDF During a median 5.6 years of treatment, 509 (11.0%) patients developed HCC



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

Concerns about Indefinite NUCs therapy

Financial burden

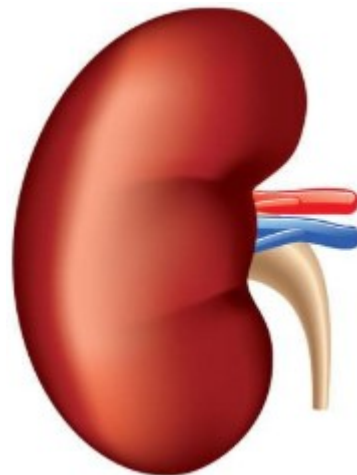


Adherence and willingness

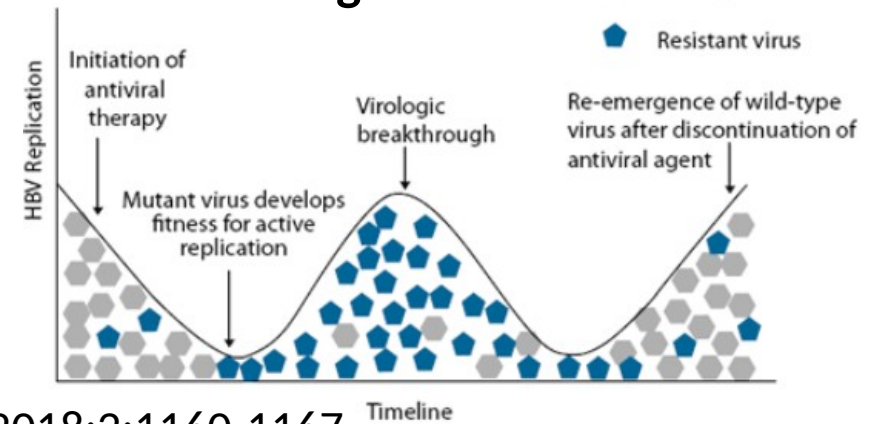


Systematic review 23,823 patients
Overall adherence 74%

Adverse Events



HBV Drug Resistance



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

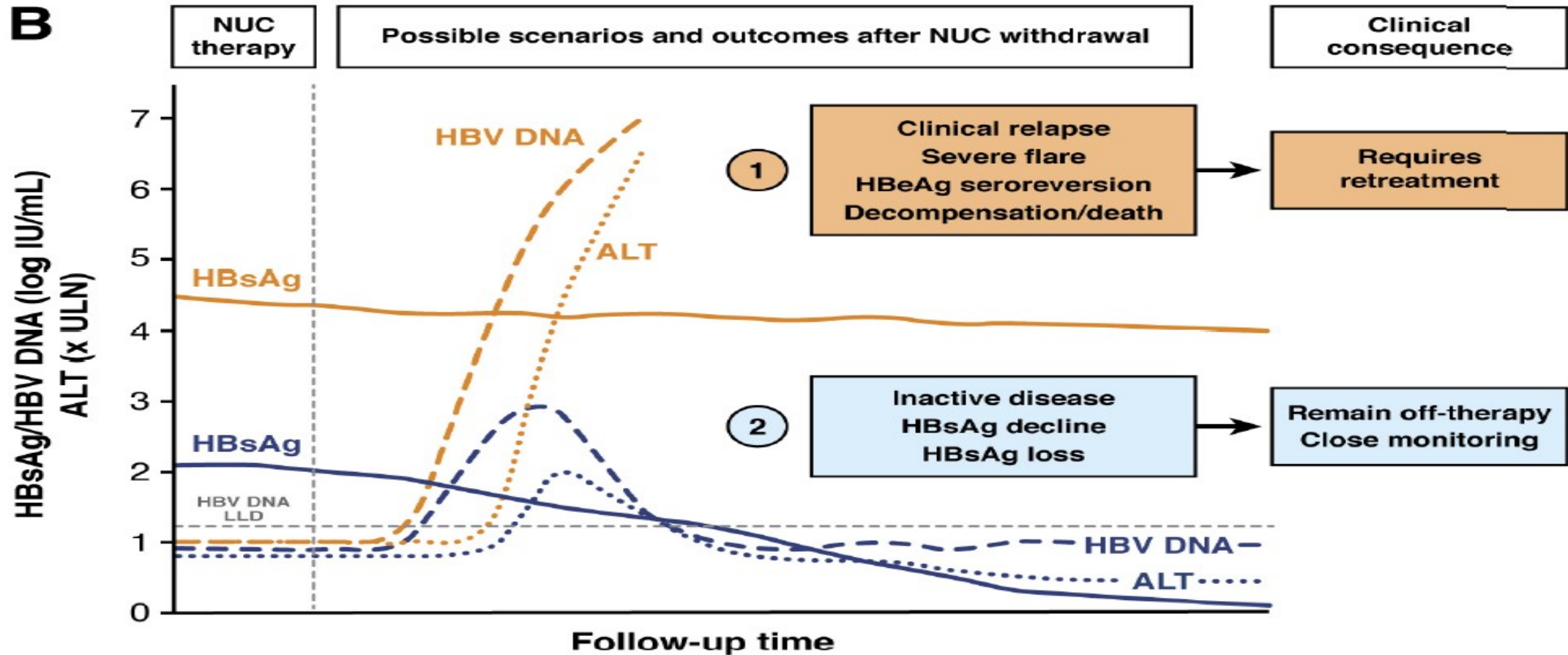
Quality and Certainty of Evidence: Low

Strength of Recommendation: Conditional

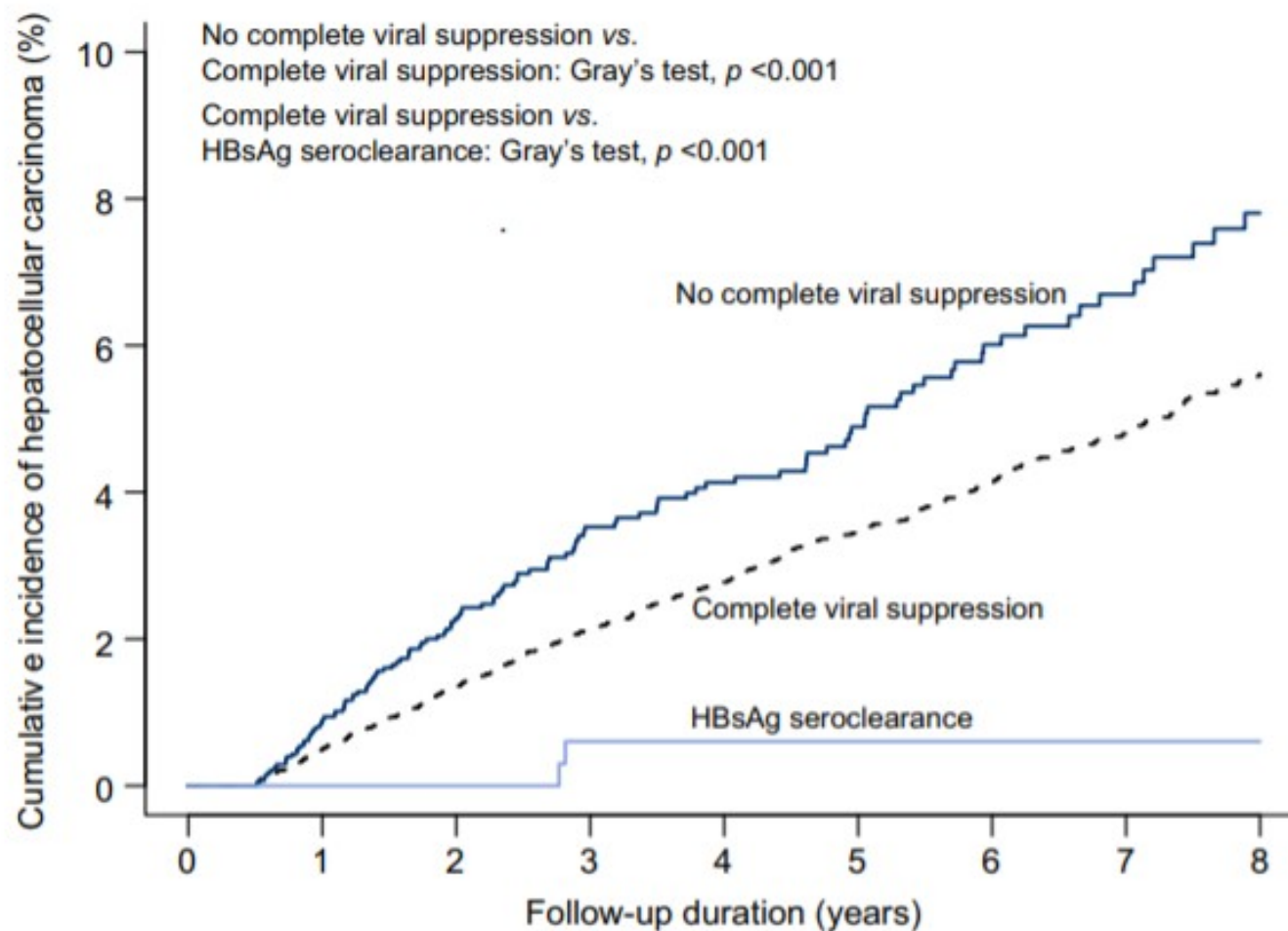
The optimal duration of NA therapy is unknown in patients with HBeAg-negative CHB. In patients without liver cirrhosis, the treatment can be withdrawn (1) after HBsAg loss following either anti-HBs seroconversion or at least 12 months of a post-HBsAg clearance consolidation period (B1), or (2) after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

APASL

Scenarios after NUCs withdrawal in CHB patients



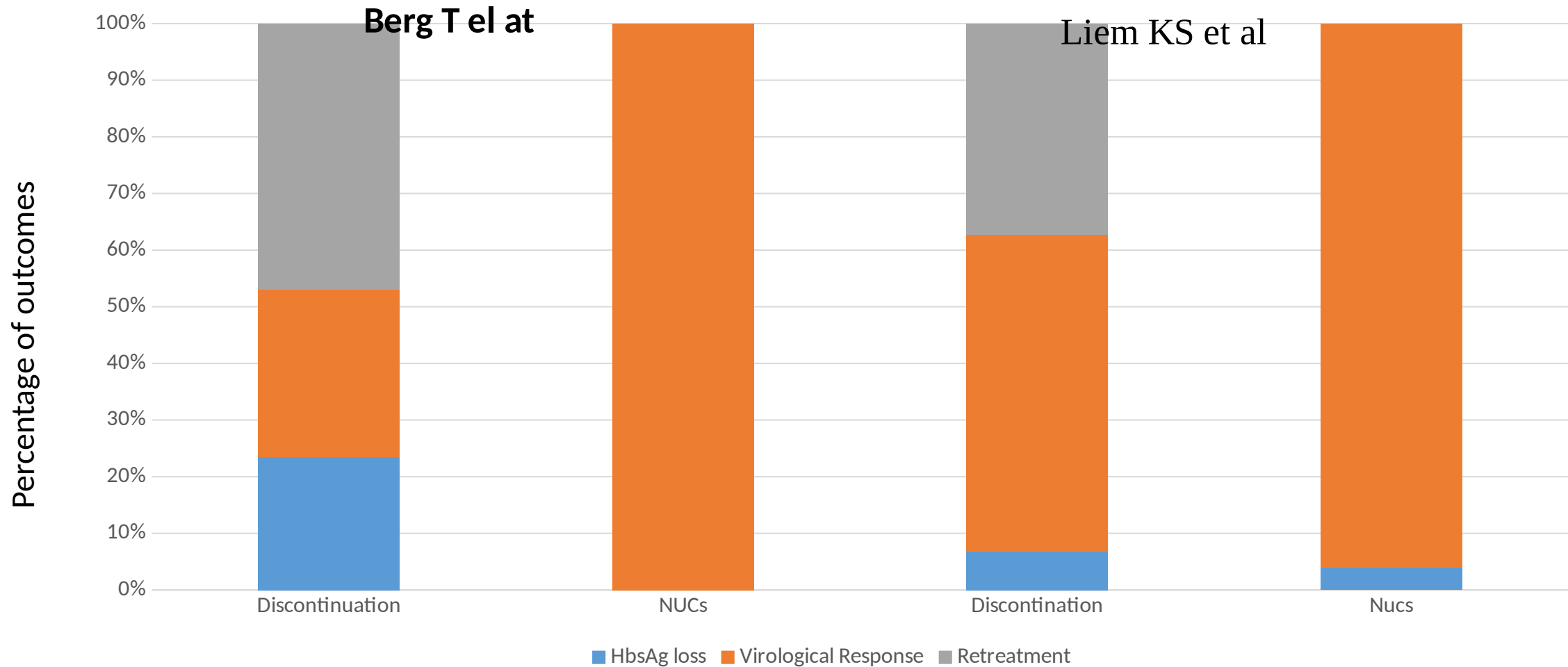
HBsAg seroclearance reduces HCC risk after complete viral suppression with nucleos(t)ide analogues



[Yip TC¹, 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



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

	No Cases	HBsAg loss	Sustained Response	Clinical Relapse	Re treatment
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%
<i>Liu, China</i>	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%

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 undetectable 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	

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