Hepatitis crónica B: retos en el paciente en respuesta con antivirales orales

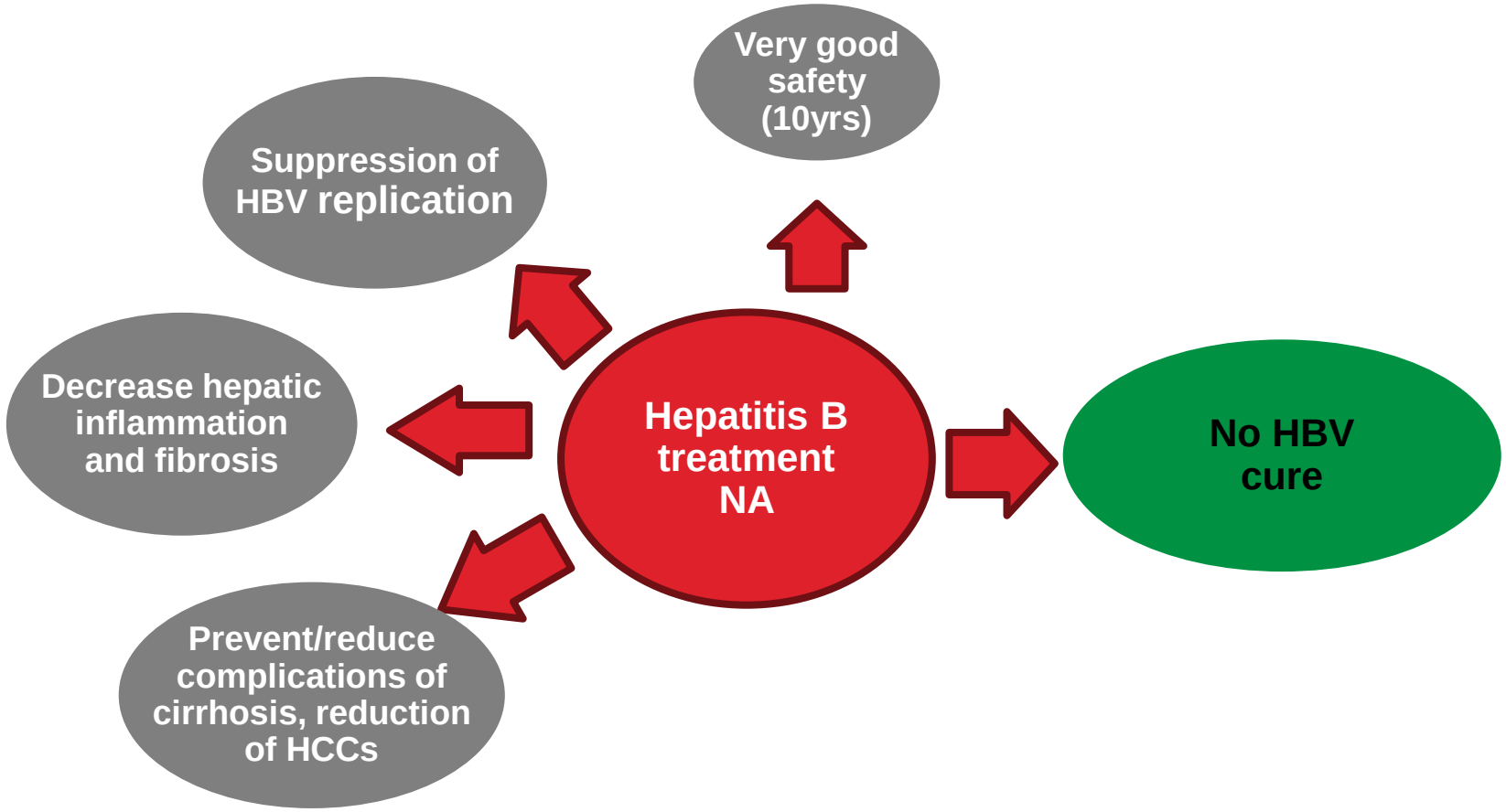
Maria Buti MD
Hospital Universitario Valle Hebron
Barcelona.

Disclosures

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

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

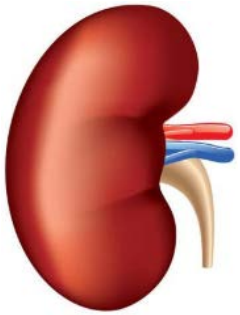
Achievements and ongoing challenges of Hepatitis B



Liaw YF, et al. N Engl J Med 2004;351:1521–31;
Marcellin P, et al. Lancet 2013;381:468–75
Dandri M, Petersen J. Clin Infect Dis 2016;62:281-8

Challenges in NUCs suppressed CHB patients

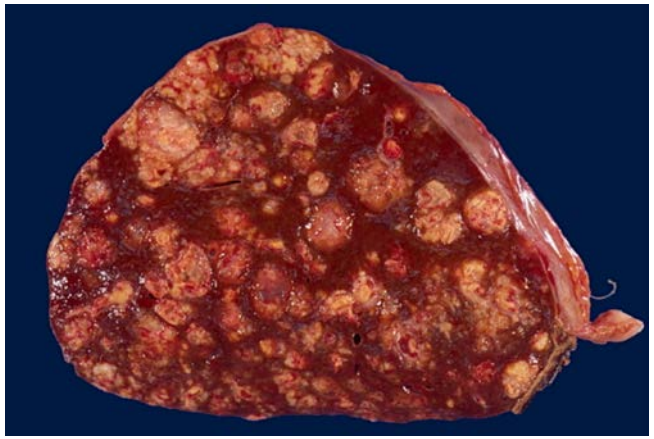
Adverse Events



Increase HBsAg loss and Viral suppression

Financial burden

Reduce HCC risk



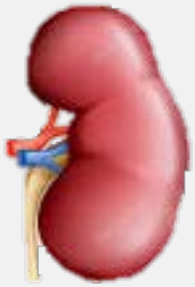
Liaw YF et al Hepatol International 2019; Ford N et al. Hepatol Commun 2018;2:1160-1167

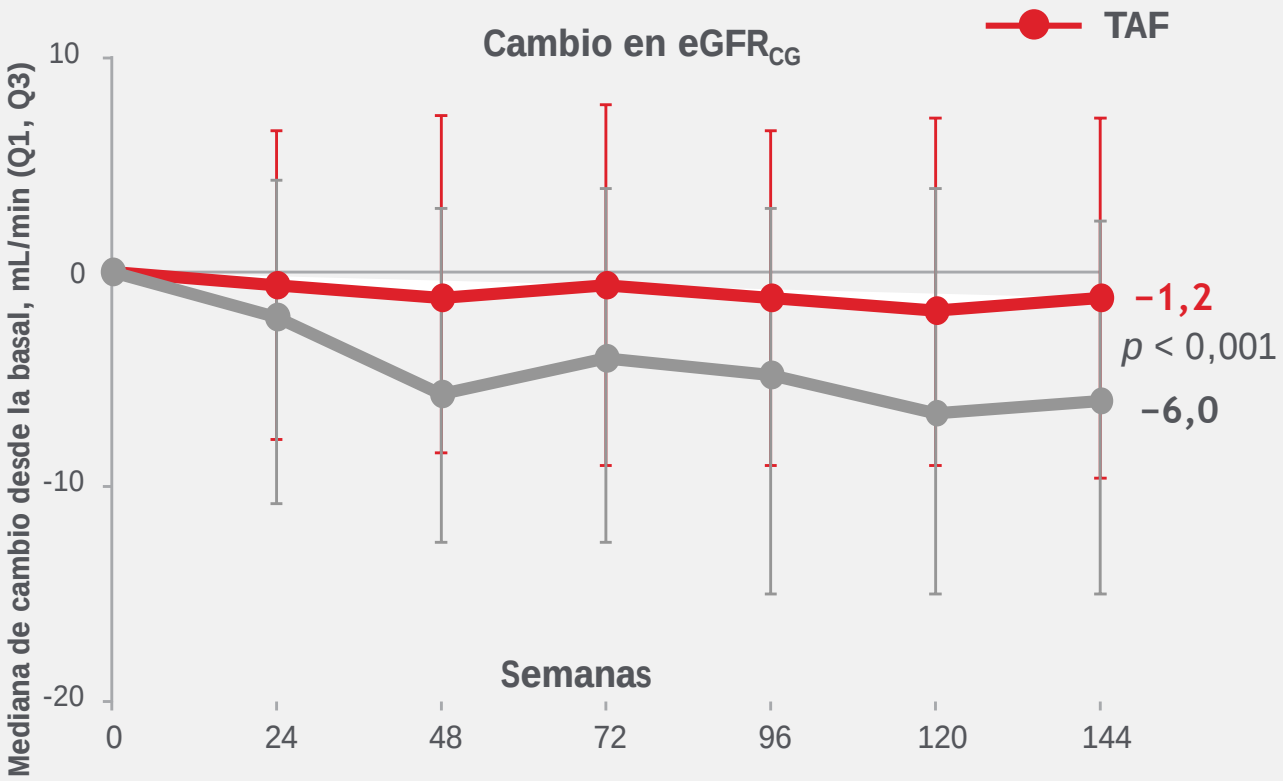
Efficacy and Safety of the recommended NUCs

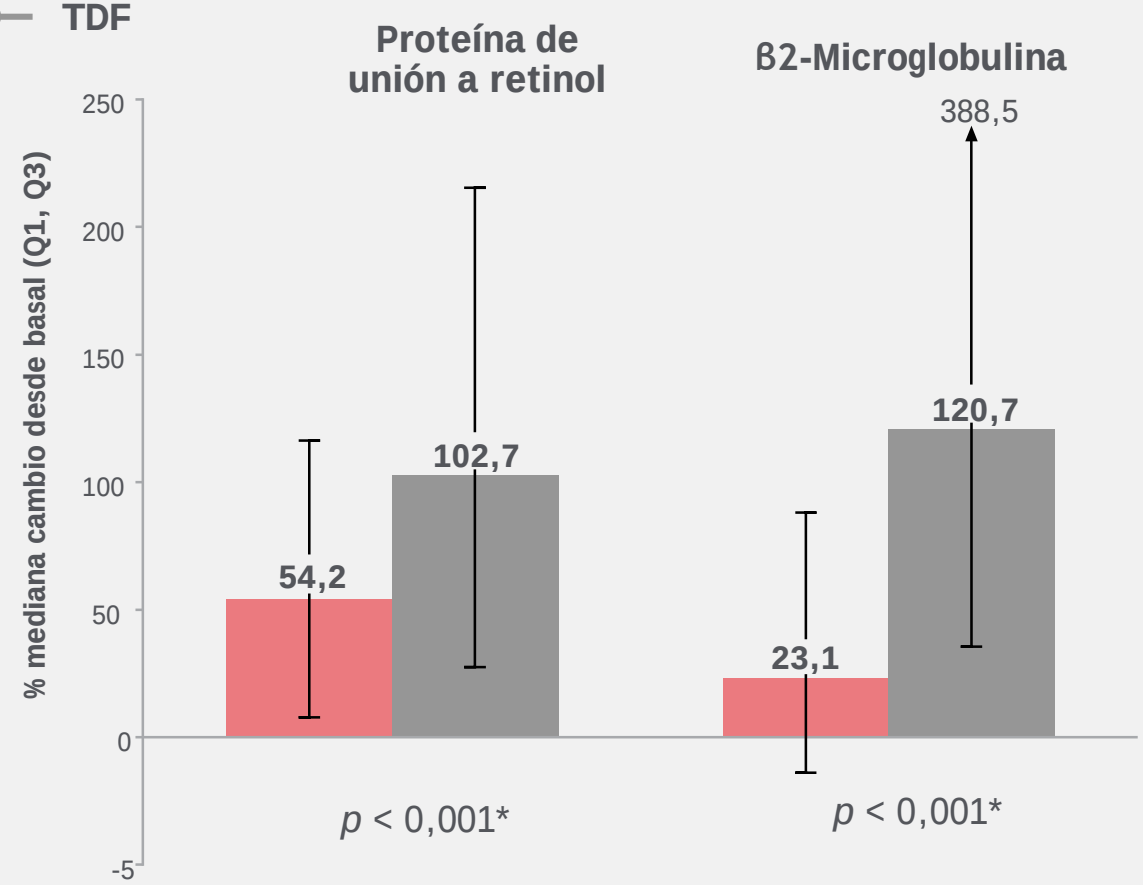
	TDF	TAF	Entecavir
Antiviral Efficacy	**+++**	**+++**	**+++**
HBsAg loss	**Rare**	**Rare**	**Rare**
Drug resistance	**No**	**No**	**Naive 1.2% at year 6 Previously treated +++**
Dose adjusted to renal function	**Yes**	**No**	**Yes**
Bone alterations	**+**	**No**	**No**
Cost	**Generics**	**++**	**Generics**

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

Seguridad renal: Cambio en parámetros renales durante + de 144 semanas





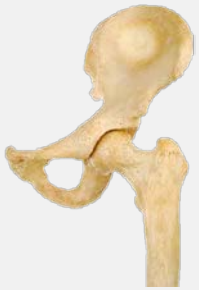


Hubo disminuciones significativamente menores en eGFR CG y cambios en marcadores tubulares proximales con TAF vs TDF a semana 144

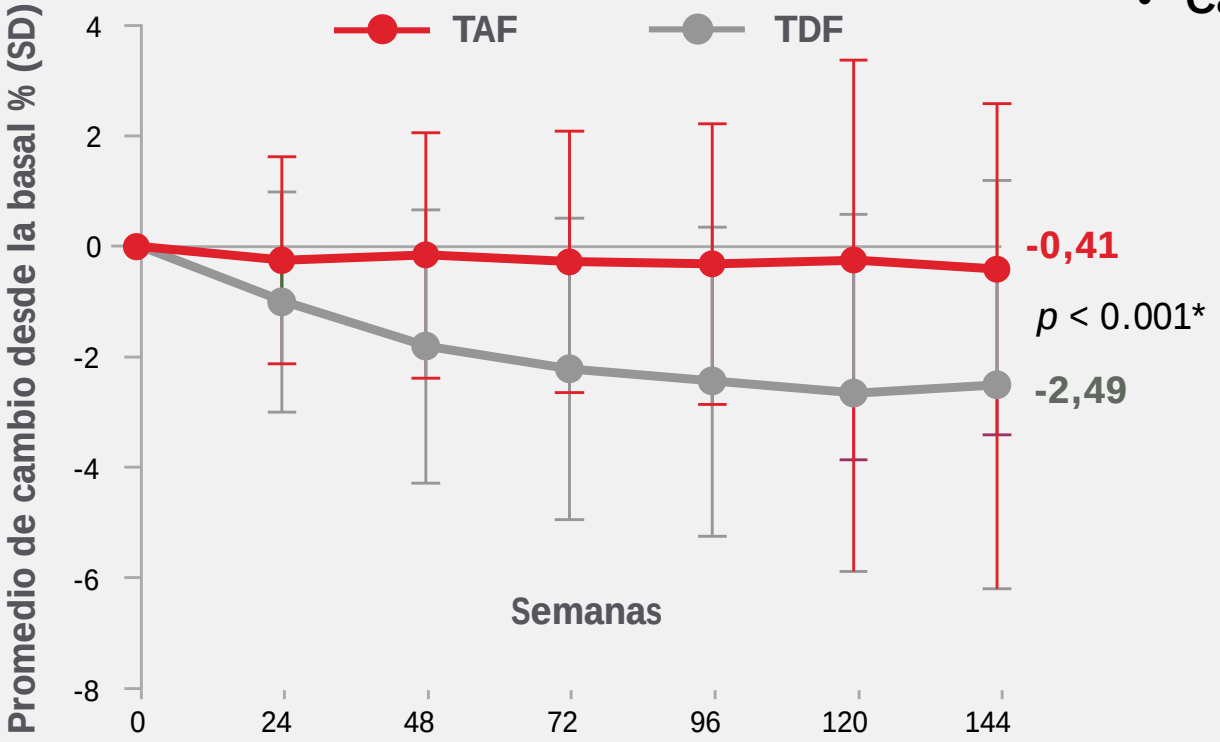
- *Prueba de suma de rangos de Wilcoxon de 2 lados

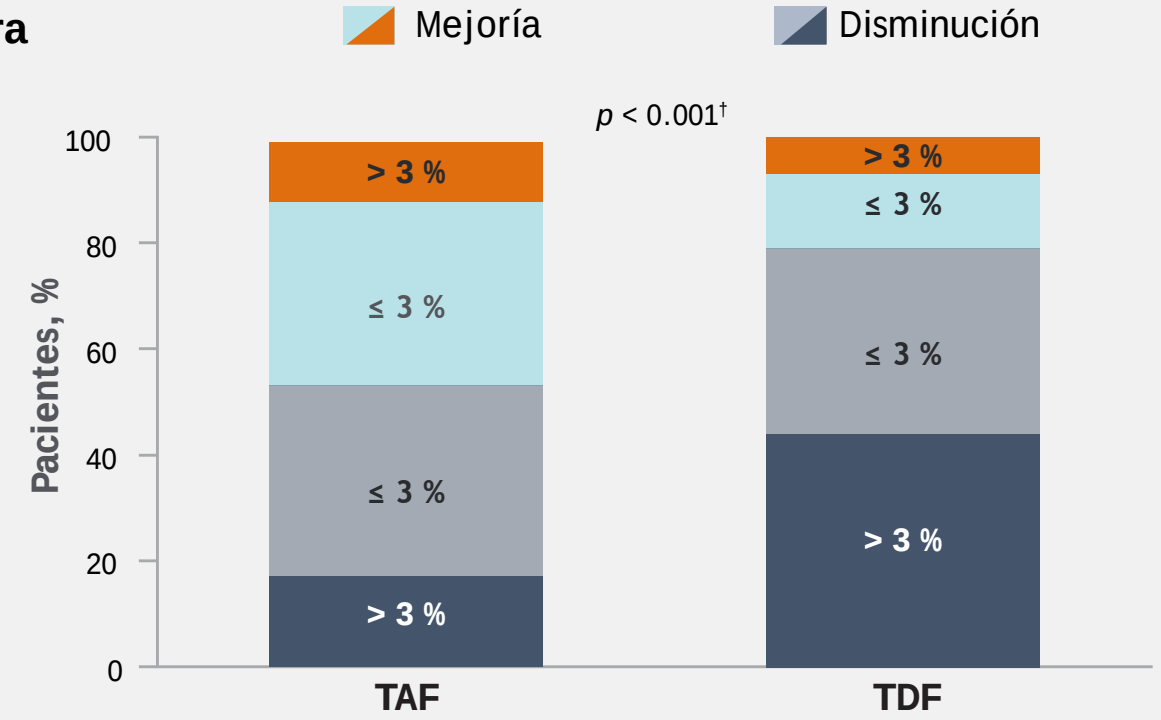
Chan, AASLD 2018, 0381

TAF vs. TDF para el VHB: Cambios en la densidad mineral ósea en pacientes de más de 144 semanas



- **Cadera**





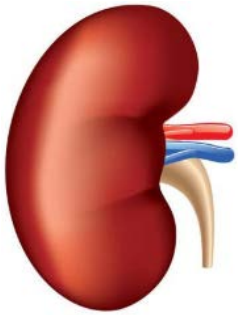
Disminución significativamente menor en la DMO de cadera con TAF vs TDF
La proporción con TAF con mejoría de la DMO fue significativamente mayor vs TDF

*analisis de varianza
†Cochran-Mantel-Haenszel test

Chan, AASLD 2018, 0381

Challenges in NUCs suppressed CHB patients

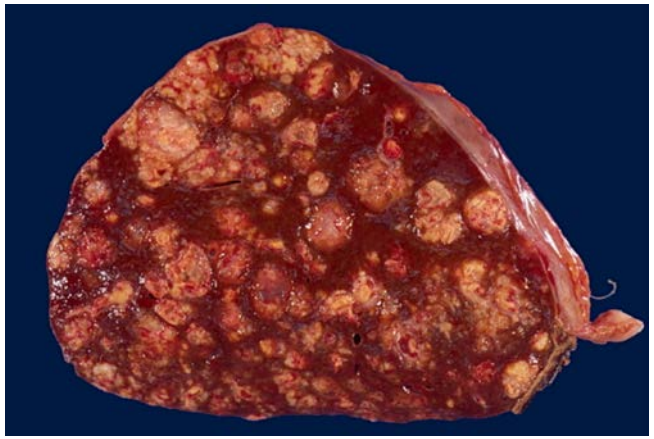
Adverse Events



Increase HBsAg loss and Viral suppression

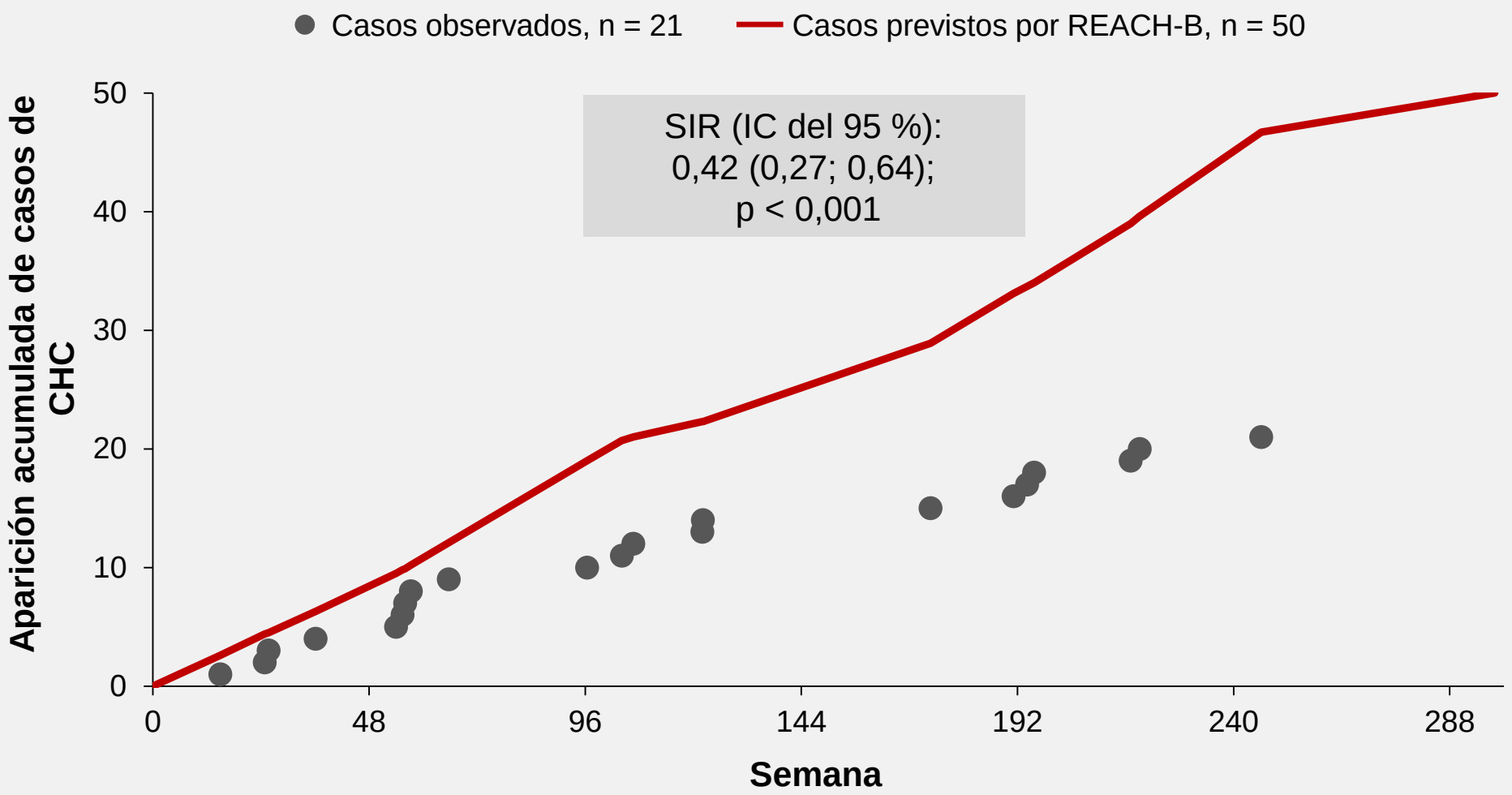
Financial burden

Reduce HCC risk



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

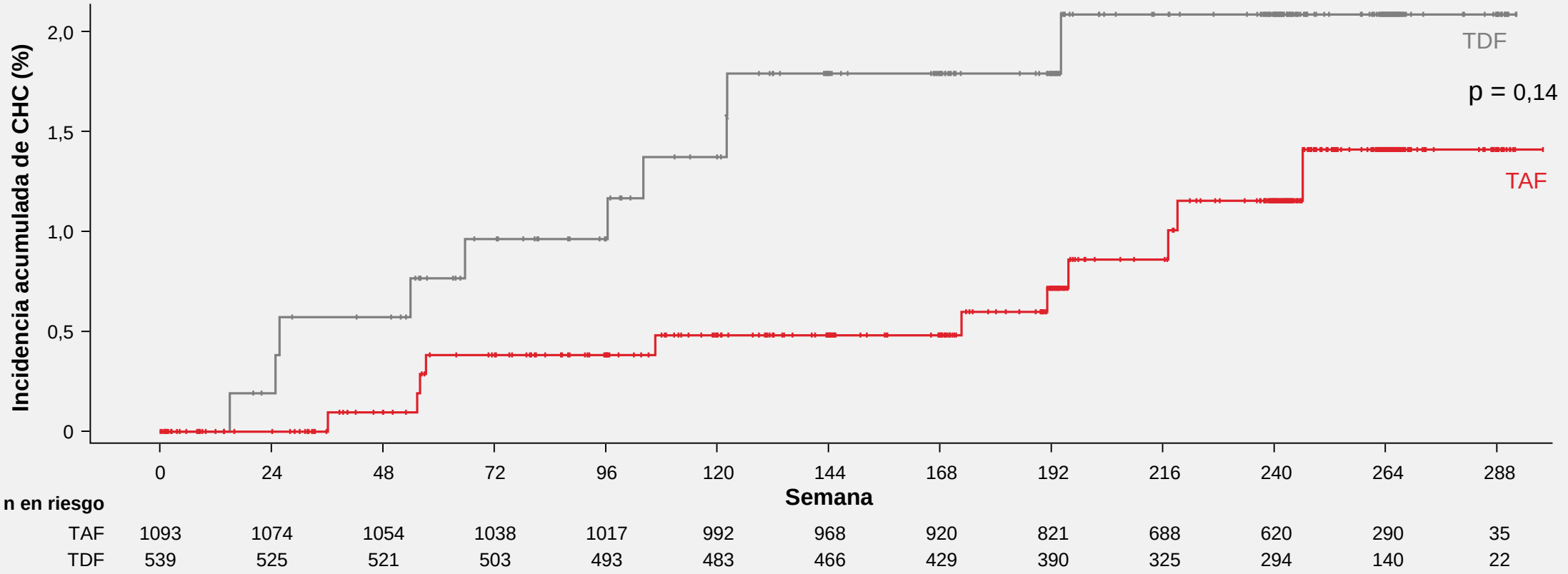
TAF vs TDF Resultados a 288 semanas
Casos observados vs. casos previstos de CHC
Todos los casos



SIR es cociente estandarizado de incidencia de los casos observados/casos previstos según lo determina REACH-B

Lim Y-S, et al. AASLD 2019.
194

Resultados: Aparición e incidencia de CHC

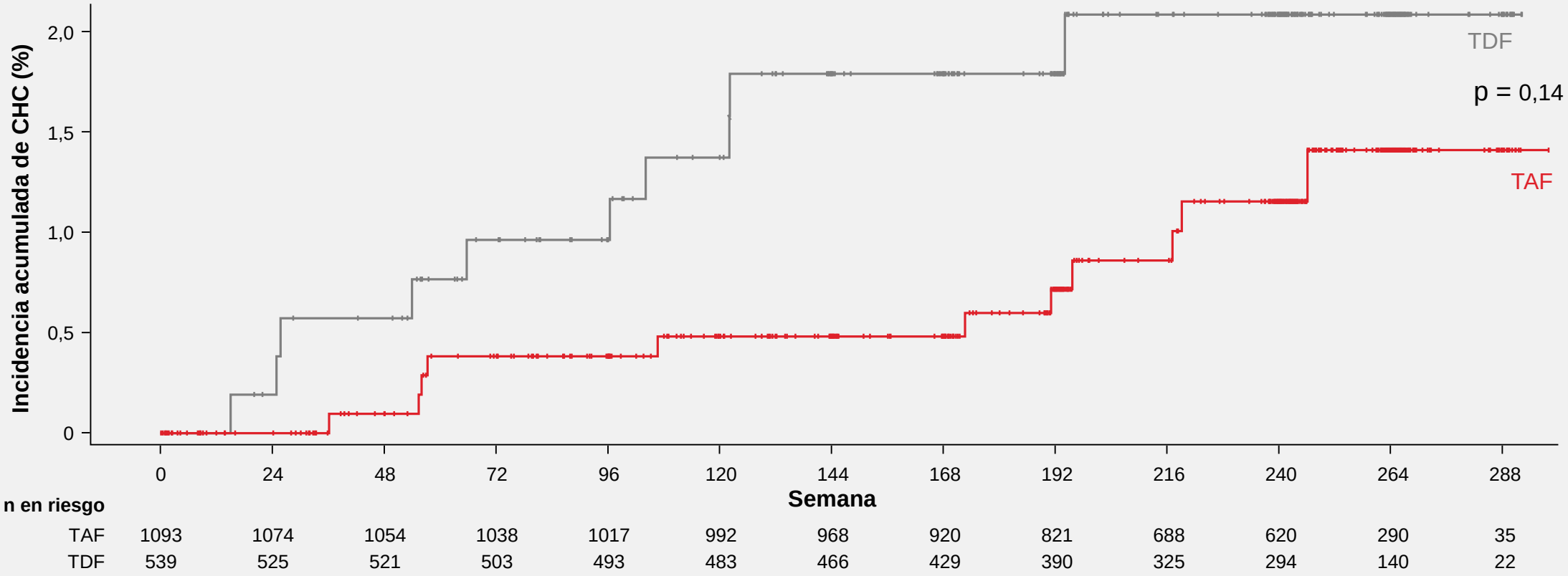


	TAF, n = 1093	TDF, n = 539	Total, n = 1632
Casos de CHC, n (%)*	11 (1,0)	10 (1,9)	21 (1,3)
Fase doble ciego, n (%)	5 (0,5)	6 (1,1)	11 (0,7)
Fase abierta de TAF, n (%)	6 (0,5)	4 (0,7)†	10 (0,6)
Mediana de tiempo hasta la aparición de CHC, semana (Q1, Q3)‡	173 (56; 217)	81 (26; 122)	104 (55; 191)

*p = 0,165; †Todos los casos OL ocurrieron dentro de las 48 semanas después de cambiar a TAF; ‡p = 0,085. Q, cuartil.

Lim Y-S, et al. AASLD 2019.
194

Resultados: Aparición e incidencia de CHC



n en riesgo													
TAF	1093	1074	1054	1038	1017	992	968	920	821	688	620	290	35
TDF	539	525	521	503	493	483	466	429	390	325	294	140	22

Predictores iniciales/durante el tratamiento de desarrollo de CHC según análisis MV:

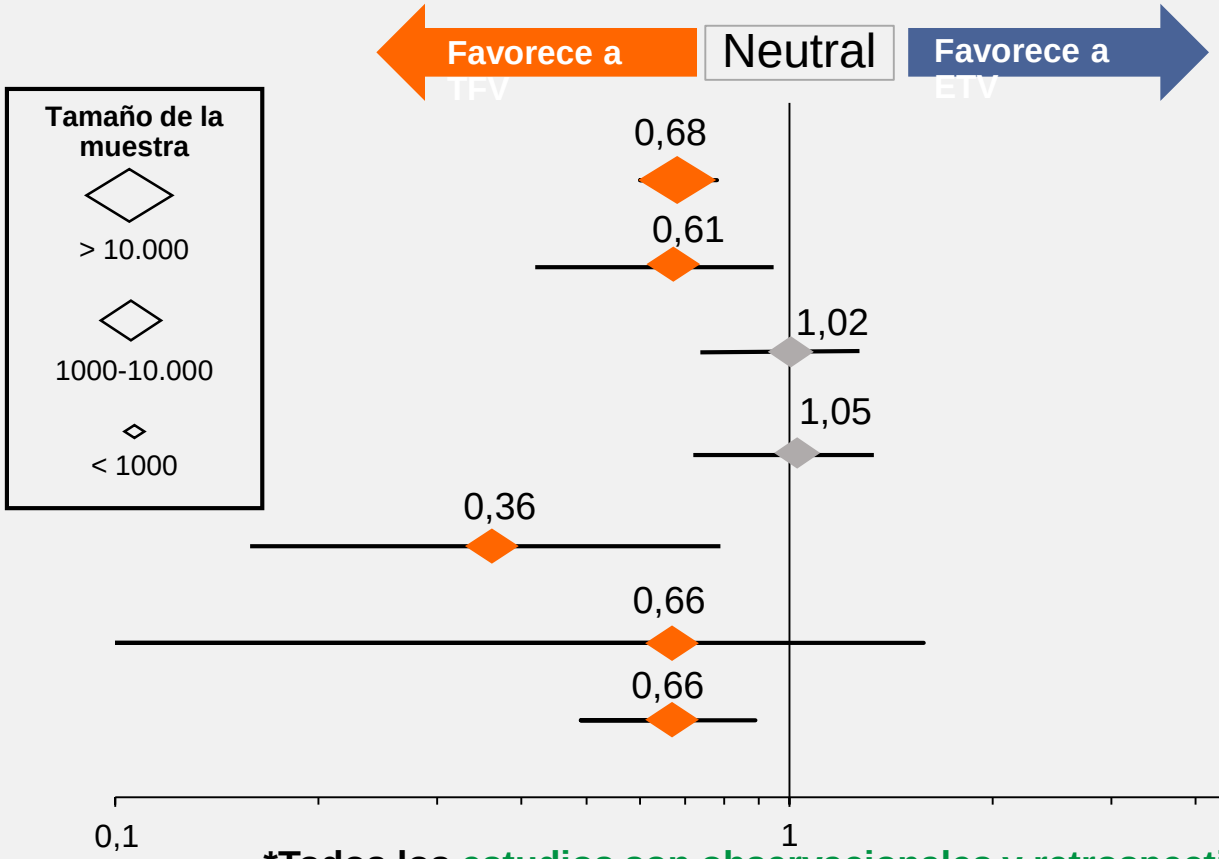
- **Falta de normalización de la ALT en la semana 24 (HR 6,90; p = 0,011), cirrosis (HR 4,18; p = 0,006), nivel inicial de HBsAg (HR 0,53; p = 0,006), e hipertensión al inicio (HR 5,55; p < 0,001)**

*p = 0,165; †Todos los casos OL ocurrieron dentro de las 48 semanas después de cambiar a TAF; ‡p = 0,085. Q, cuartil.

Lim Y-S, et al. AASLD 2019.
194

Resumen del efecto de TFV vs. ETV en la incidencia de CHC en pacientes con hepatitis B crónica

Reducción del riesgo de CHC (índices de riesgo)



Estudio*	TFV/ETV (n)	Método	Valor P
Choi J 2019	10923/10923	PS Matched	< 0,001
Kim R 2019	5903/3819†	PS IPTW	Se esperan
Kim SU 2019	1413/1484	PS IPTW	0,516
Lee SW 2019	1857/1857	PS IPTW	0,758
Yip TC 2019	1309/1249	PS IPTW	0,013
Wang X 2019∞	2384/2430	Índice de riesgo de metaanálisis*	> 0,05
Zhang Z 2019	1574/2124	Índice de tasa de metaanálisis*	0,008

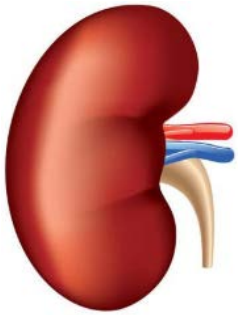
***Todos los estudios son observacionales y retrospectivos y esta información no pretende establecer comparaciones entre la seguridad o eficacia de los productos descritos**

Choi J et al. *Jama Oncology*. 2019;5(1):30-36; Kim WR, et al. AASLD 2019. 478; Kim SU et al. *J Hepatol* 2019;71:456-464; Lee SW et al. EASL 2019:FRI-187; Yip T CF, et al. *Gastroenterol.* 2019 Sep 28. pii: S0016-5085(19)41367-X. doi: 10.1053/j.gastro.2019.09.025. [Publicación electrónica anterior a la impresión; Wang X, et al. *Gut Liver*. 3 de junio de 2019. doi: 10.5009/gnl18546. [publicación electrónica anterior a la impresión]; Zhang Z, et al. *BMC Cancer.* 2019;19(1):511. doi: 10.1186/s12885-019-5735-9

PS, Puntuación de propensión; IPTW, Probabilidad inversa de ponderación del tratamiento; ∞HR calculado desde 1/1,52 = 0,66; *sin índices de riesgo, † total de la población

Challenges in NUCs suppressed CHB patients

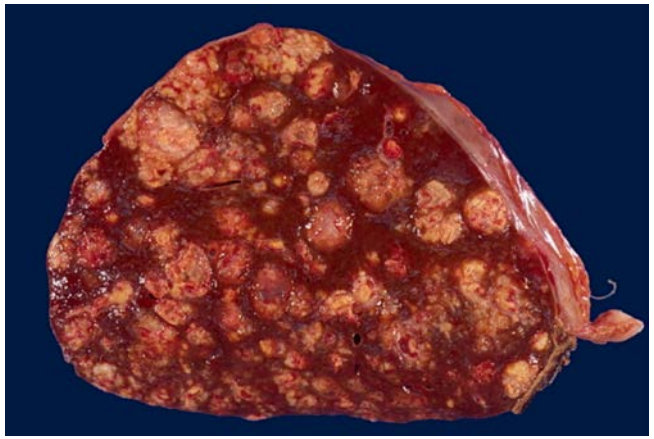
Adverse Events



Increase HBsAg loss and Viral suppression

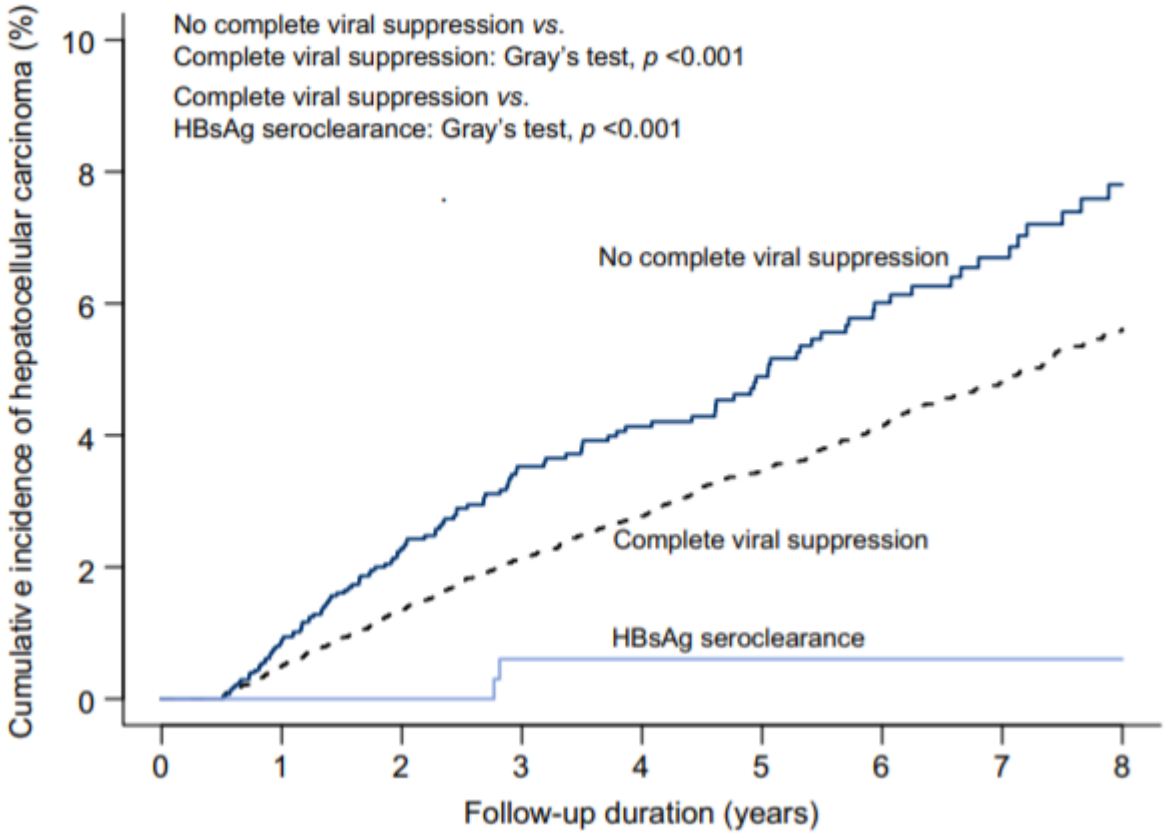
Financial burden

Reduce HCC risk



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

HBsAg seroclearance further reduces hepatocellular carcinoma risk after complete viral suppression with nucleos(t)ide analogues

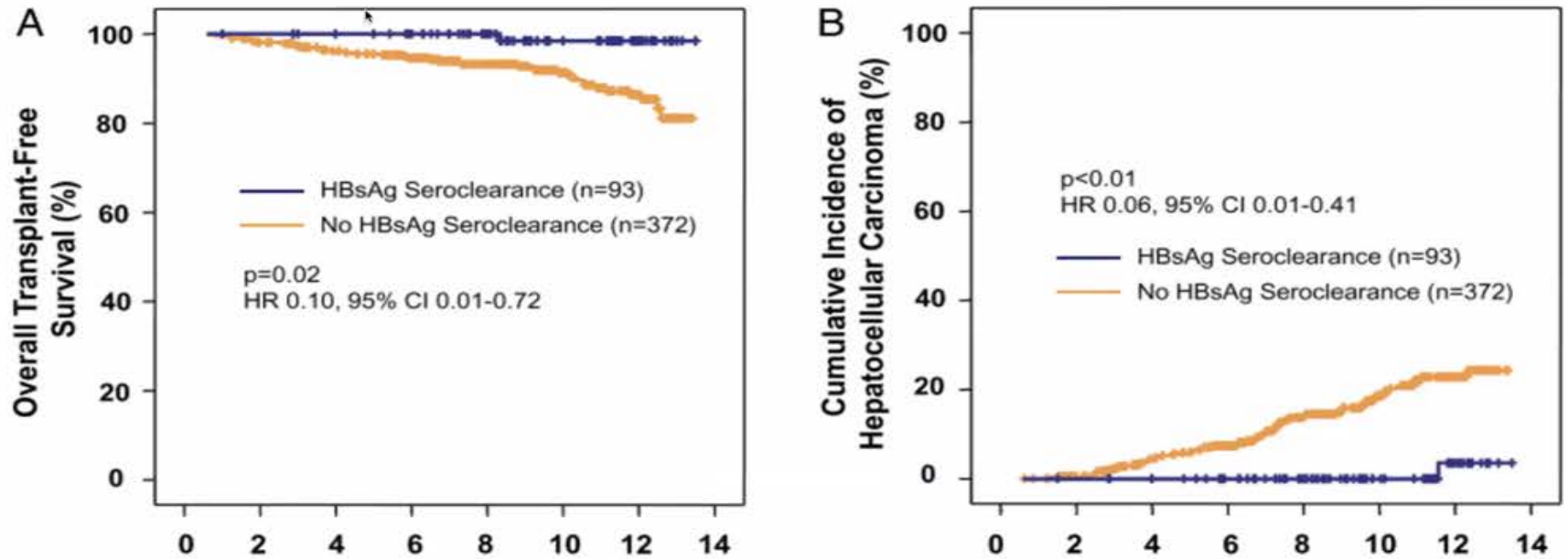


Yip TC[1],et al.

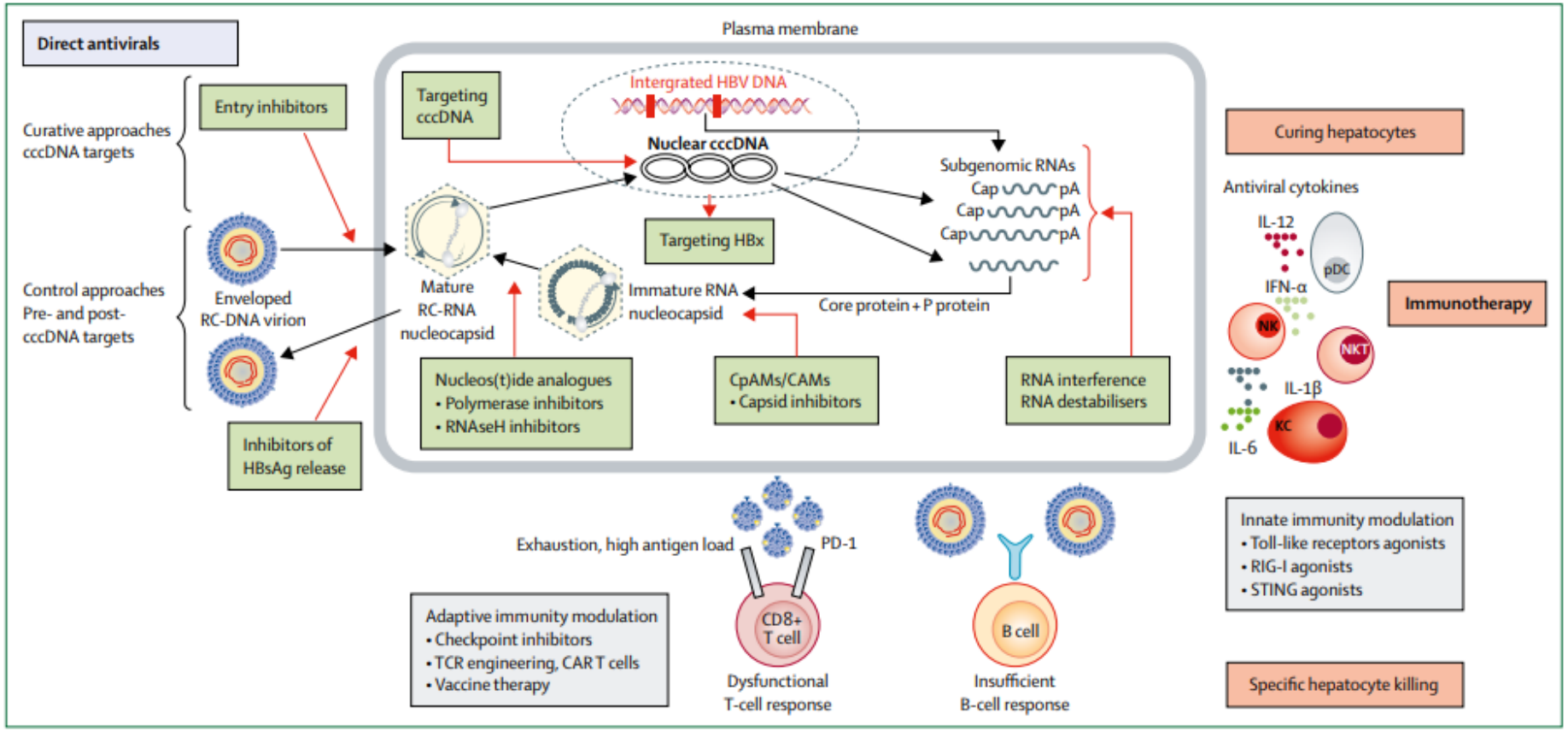
Yip T C-F et al. J Hepatol. 2019 Mar;70(3):361-370.

HBsAg Clearance Reduces Mortality Risk in NA-Treated Patients

- **Propensity score-matched cohort from Korea, CHB on NA therapy (92 with seroclearance and 372 without) with at least 6.77 years follow-up**
- **HBsAg seroclearance was durable in 90% at 3 years**



HBV virological and immunological targets that will be necessary for treatment and cure of chronic hepatitis B



Revill P et al Lancet Gastro Hepatol 2019

Pathways to Achieving Functional Cure

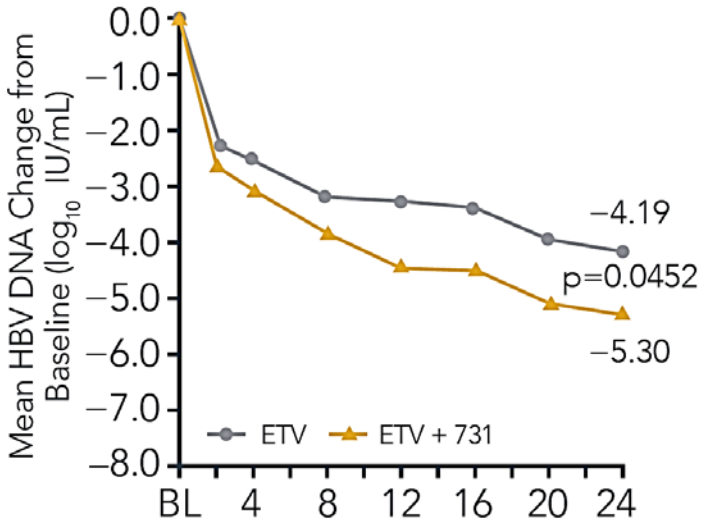
Inhibit replication	Reduce Antigens	Enhance immune response
Interferon	RNAi	TLR7/TLR8 agonist
Polymerase (NUCs)	Nucleic Acid Polymers	RIG-I agonist
Entry	Oligonucleotide	Anti-PD1/PDL1
Capside assembly		Therapeutic vaccine
cccDNA		Interferon

ABI-H0731+ NUCs results in sequential reduction/loss of HBV DNA, HBV RNA, HBeAg, HBcrAg and HBsAg in HBeAg positive patients

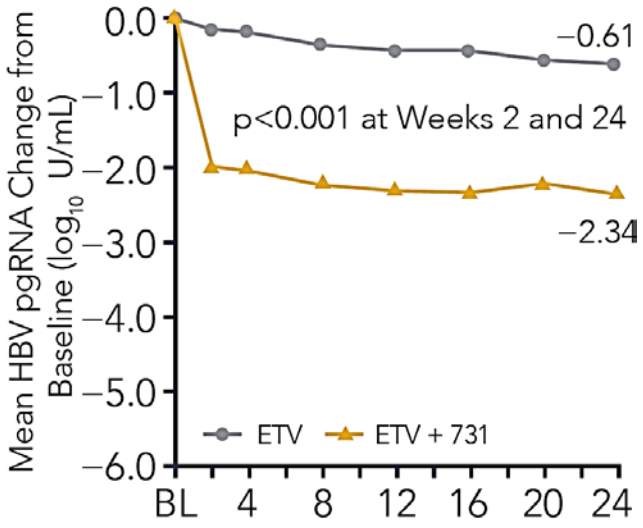
DNA/pgRNA reductions with ABI-H0731 + ETV combination

Study 202: HBeAg+, Rx-naïve

HBV DNA



pgRNA

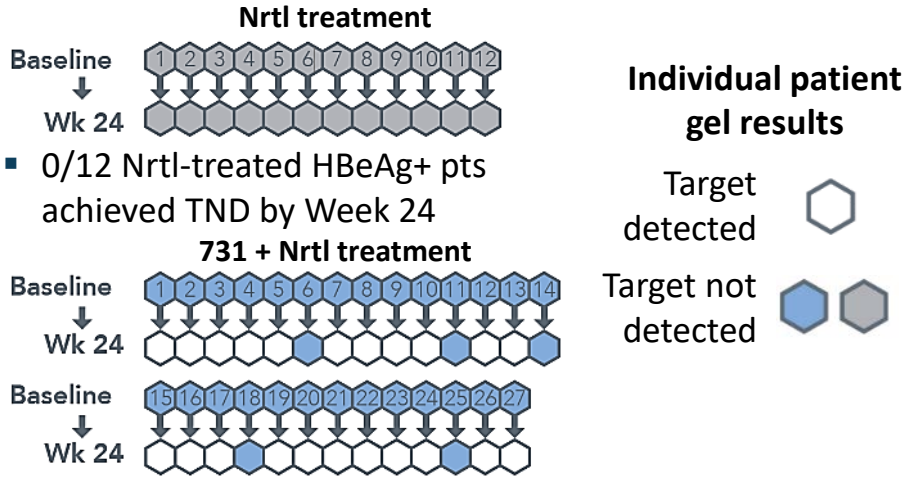


- Faster and greater HBV DNA declines with combo than ETV alone
- Rapid 2 log reductions in pgRNA by Week 2, only with combo
- Reduction of HBsAg >9.4 log
- Initial rapid phase decline of pgRNA thought to be mechanism-based inhibition, second phase thought to reflect reduction in cccDNA pools
- Rash in 1 cases

Sulkowski MS, et al. AASLD 2019, Boston, USA. #LP1

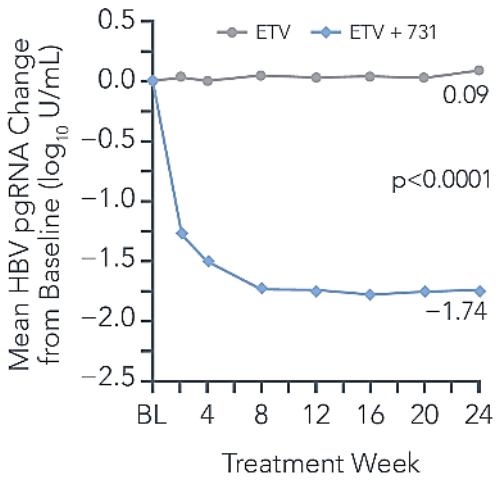
DNA/pgRNA declines in NUCs Suppressed, HBeAg+ patients

Study 201



- 0/12 Nrtl-treated HBeAg+ pts achieved TND by Week 24
- 22/27 (81%) of combo HBeAg+ patients achieved TND by Week 24

pgRNA



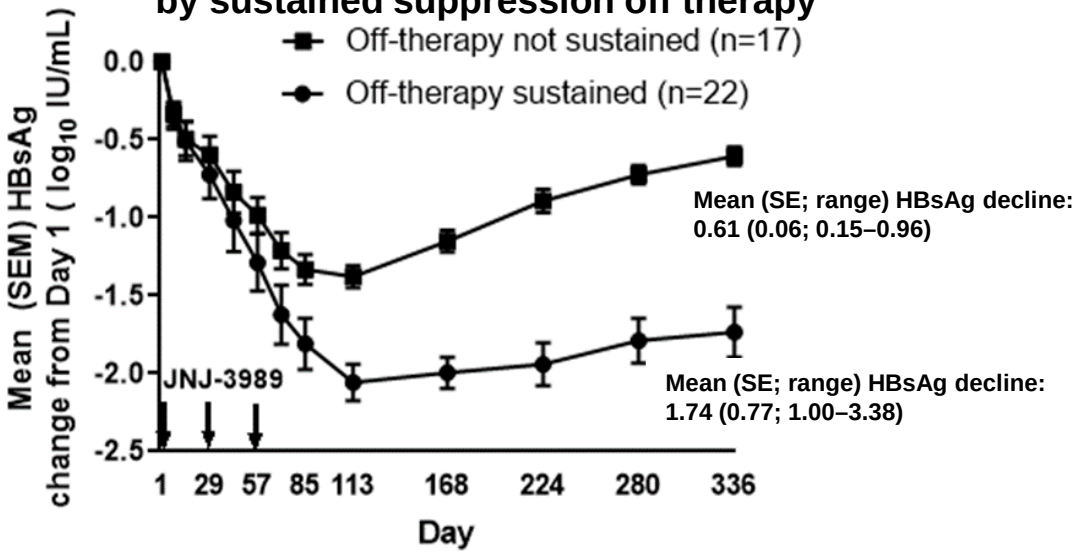
Short-term treatment with RNAi therapy, JNJ-3989, results in sustained HBsAg suppression in patients with chronic hepatitis B receiving nucleos(t)ide analogue treatment

RESULTS

- Patient demographics:
  - 73% male; 85% Asian; median age 45 years*; 65% HBeAg-; 80% NA-experienced
- No deaths, treatment discontinuations or drug-related SAEs
  - Most common drug-related AEs were mild injection site AEs (17.5%)

JNJ-3989	100 mg	200 mg	300 mg	400 mg
Mean (SE) HBsAg nadir	1.72 (0.18)	1.79 (0.14)	2.04 (0.20)	1.90 (0.18)
≥1.0 $\log_{10}$ HBsAg reduction at nadir from Day 1, n (%)	39 (98) (range 1.11–3.77)			

Mean change in HBsAg by sustained suppression off therapy



- Sustained suppression of HBV RNA, HBeAg and HBcrAg was seen in 58%, 64% and 42% of patients with available data, respectively

CONCLUSION

- JNJ-3989 (100–400 mg) with an NA was well tolerated in patients with CHB
- A ≥1.0 $\log_{10}$ reduction in HBsAg at nadir was achieved in 98% of patients
- A subset of patients had sustained HBsAg suppression ~9 months after the last RNAi dose
  - Studies of longer term dual therapy and triple therapy including a CAM are underway

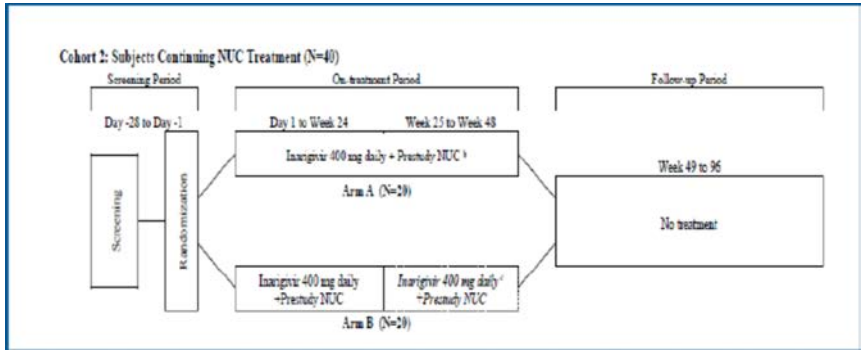
*Range 26–66 years

Gane EJ, et al. DILC 2020; GS10

Stimulation of IFN gene agonists : RNA Sensor RIG-I Dually Functions as an Innate Sensor and Direct Antiviral Factor for HBV

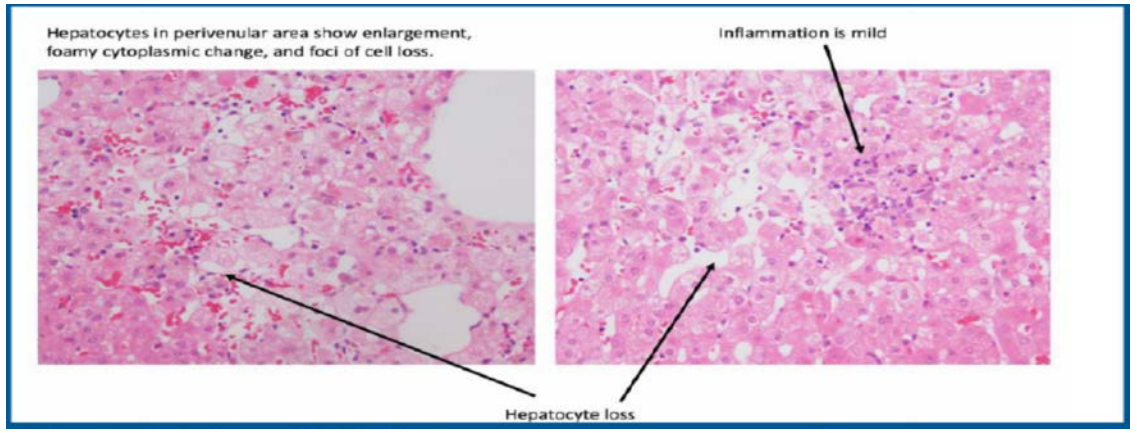
Inarigivir phase 2 study

Open-label,randomized, multiple dose, varied administration regimen study with 2 parts (Parts A and B) in Subjects Infected with Chronic Hepatitis B Virus



42 HBeAg-negative non-cirrhotic long-term NUC suppressed patients with normal ALT and HBV DNA<20 IU/ml in 7 sites in the UK and Canada were randomised to treatment with inarigivir 400mg daily in ARM 2

Seven (17%) presented with an SAE after a mean of 16 weeks treatment (range 13-21 weeks). All 7 had elevated ALT (maximal elevation mean 212 IU/L; range 116-412 IU/l), 4 had associated hyperbilirubinemia > 2 ULN and 3 had abdominal pain. All patients were contacted and stopped therapy on 19th December 2019



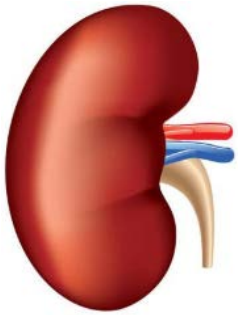
Spring Bank Stops Dosing of Inarigivir Patients in Phase 2 Program

RIG I: Retinoic Acid Inducible protein I

Sato et al., 2015, Cell Immunity 42, 123–132

Challenges in NUCs suppressed CHB patients

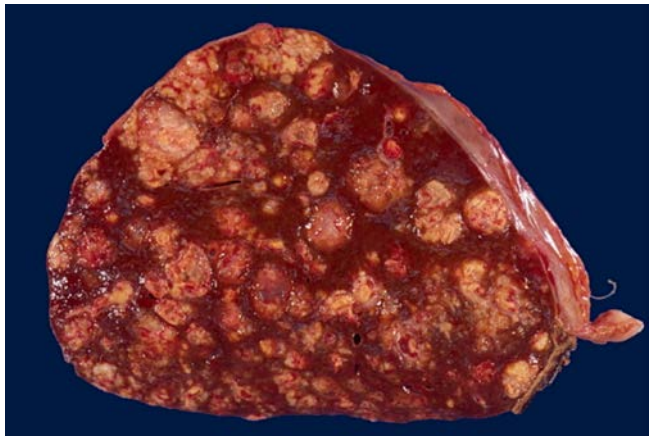
Adverse Events



Increase HBsAg loss and Viral suppression

Financial burden

Reduce HCC risk



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

Guidelines recommendations on Stoping 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

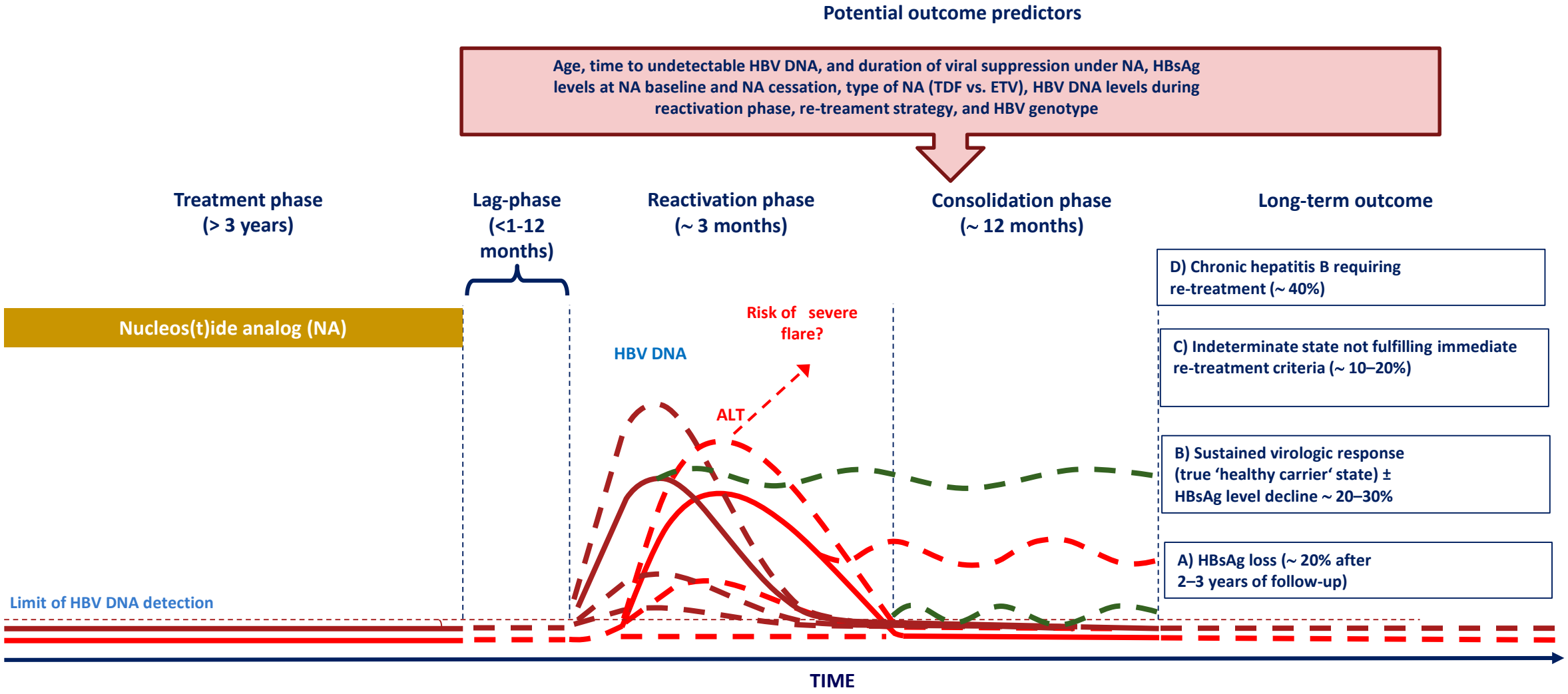
4. The AASLD suggests indefinite antiviral therapy for adults with HBeAg-negative, immune-active CHB unless there is a compelling rationale for treatment discontinuation

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).

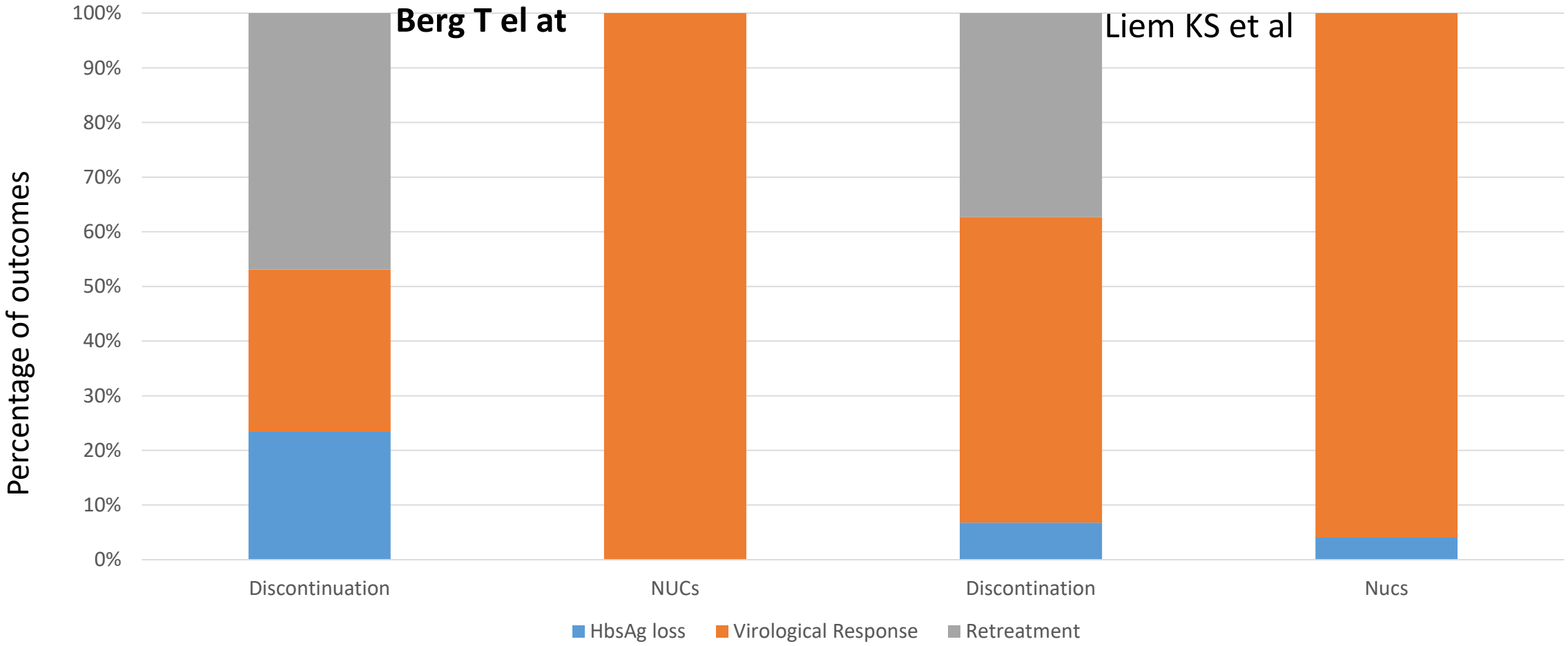
Parada de tratamiento con análogos en pacientes HBeAg negativo sin pérdida del HBsAg



HBsAg: hepatitis B surface antigen

Lampertico P, Berg T. Hepatology 2018; 10.1002/hep.29821

Randomized studies on NUCs discontinuation in HBeAg negative patients



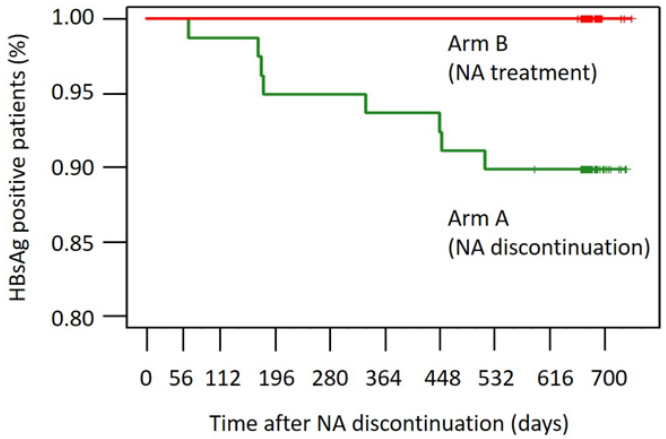
Liem KS et al. Gut 2019 Berg T et al J Hepatol 2017

Response to discontinuation of long-term nucleos(t)ide analogue treatment in HBeAg-negative patients: Results of the Stop-NUC trial

RESULTS

- Full analysis set: 79 patients in each arm*
- HBsAg loss at Week 96 post-NA discontinuation
  - ARM A: 8/79 (10%)
  - ARM B: 0/79

  p=0.006



- HBsAg loss at Week 96 post-NA discontinuation
  - ARM A: 6/79 (8%)
  - ARM B: 0/79

  p=0.006

*Eight patients who dropped out immediately after randomization were excluded;
†According to EASL recommendations
van Bömmel F, et al. DILC 2020; LBO06

Predictive value of HBsAg levels at discontinuation

HBsAg loss	Baseline HBsAg <1,000 U/mL	Baseline HBsAg ≥1,000 U/mL	p value
No	18 (72%)	53 (98.1%)	0.001
Yes	7 (28%)	1 (1.9%)	

- All patients in ARM A but none in ARM B experienced an HBV DNA flare >20 IU/mL after NA discontinuation

Parameter at Week 96	ARM A	ARM B	p value
HBV DNA ≤20 IU/mL	24/79 (31%)	79/79 (100%)	<0.001
ALT flare	28/79 (35%)	0	–
NA re-installed	11/79 (14%)	N/A	–
No NA indication†	54/79 (68%)	N/A	–

- No patient in ARM A had a severe SAE possibly related to NA discontinuation

CONCLUSION

- The STOP-NUC study demonstrates the potential of discontinuation of long-term NA treatment for inducing durable immune control and functional cure in patients with HBeAg-negative CHB

EASL™ The Home of Hepatology

Summary

Long-term Nucleos(t)ide therapy leads to viral suppression but not HBsAg clearance.

Main reasons are the persistence of cccDNA and the host deficient immune response thatprevent HBV cure

Long time safety of Nucs can be improved with the use of TAF in population with comorbidities

HCC is reduce with Nucs but still is a concern

New Drugs such as antivirals and Immunomodulators are under investigation with the aim to achieve HBsAg loss

The role of Nucs discontinuation in noncirrhotics HBeAg negative patients is still unclear