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Hepatitis Crónica B : Evaluación del riesgo de eventos clínicos en pacientes con y sin tratamiento antiviral

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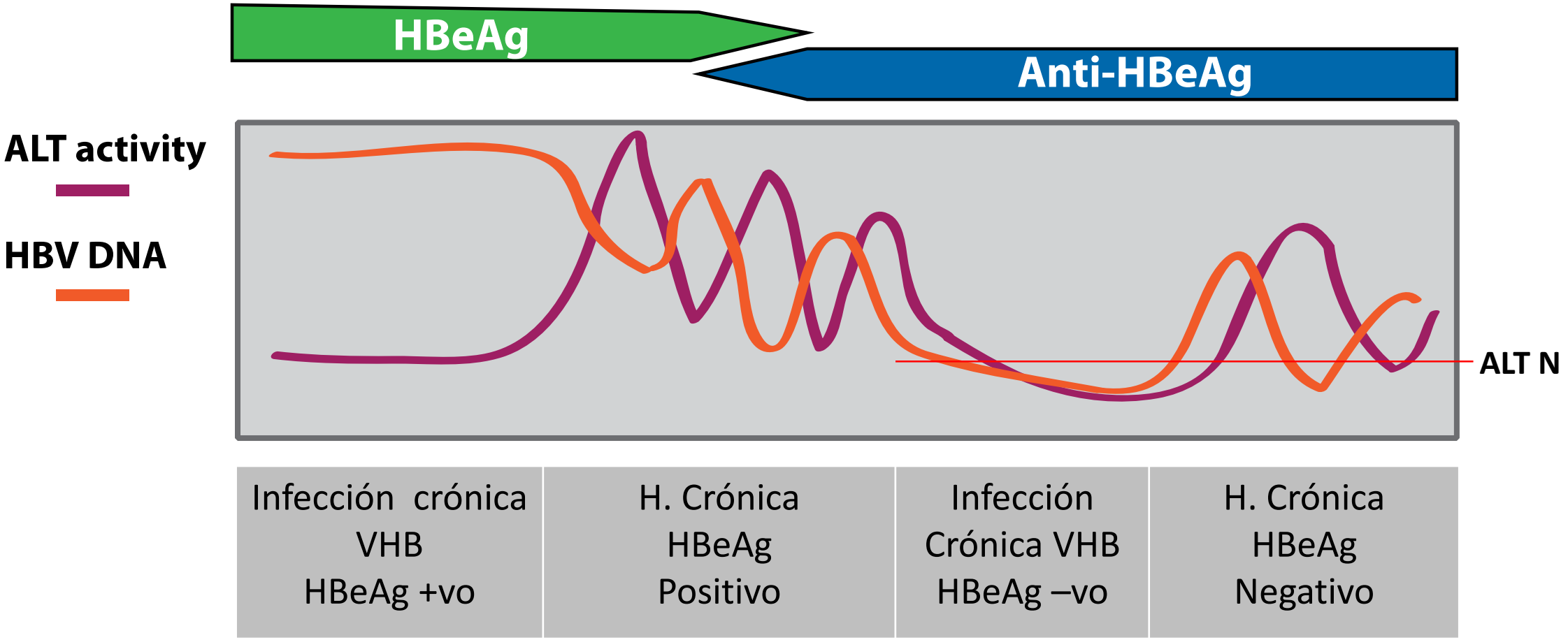
INVESTIGACIÓN PUERTA DE HIERRO

Fases infección por VHB



Indicación de Tratamiento

Hepatitis crónica HBeAg positivo y HBeAg negativo

- ADN VHB >2.000 UI/ml
- ALT >40 UI/l (si <40 UI/l y se cumplen los otros dos criterios)
- Actividad necroinflamatoria y/o fibrosis moderada valorada por biopsia o **elastometría**

- Si ADN VHB >20.000 UI/mL y ALT >2xVSN iniciar tratamiento sin considerar fibrosis.

  Es necesario descartar o confirmar cirrosis con elastometría para cribado CHC

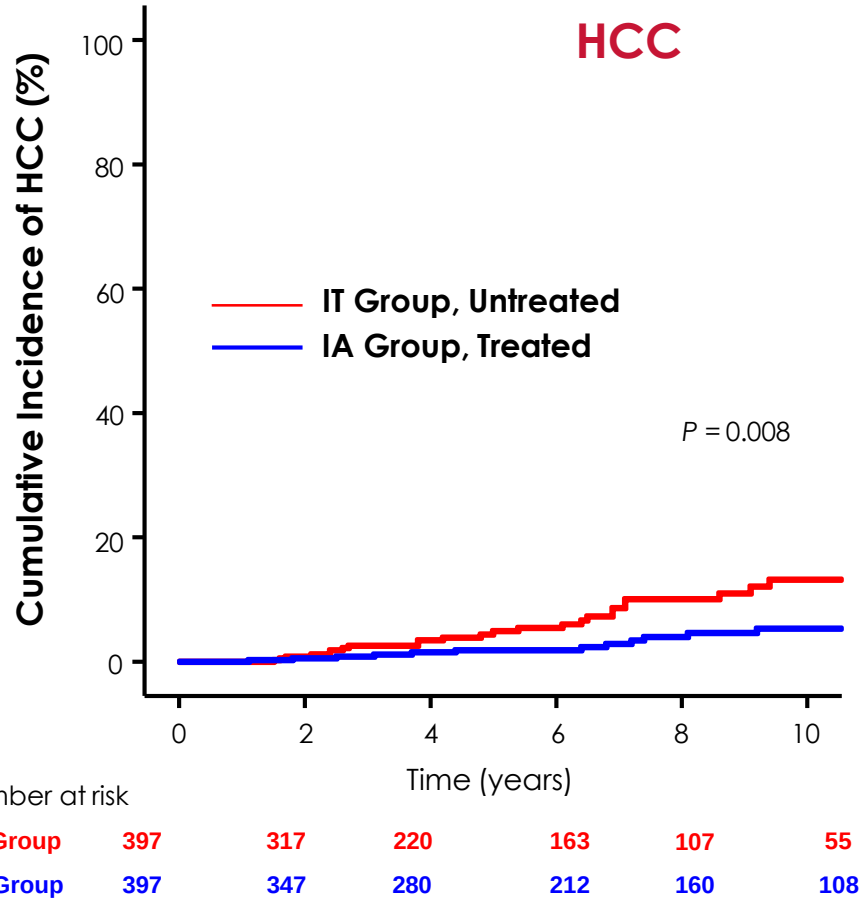
Infección crónica HBeAg positivo y HBeAg negativo

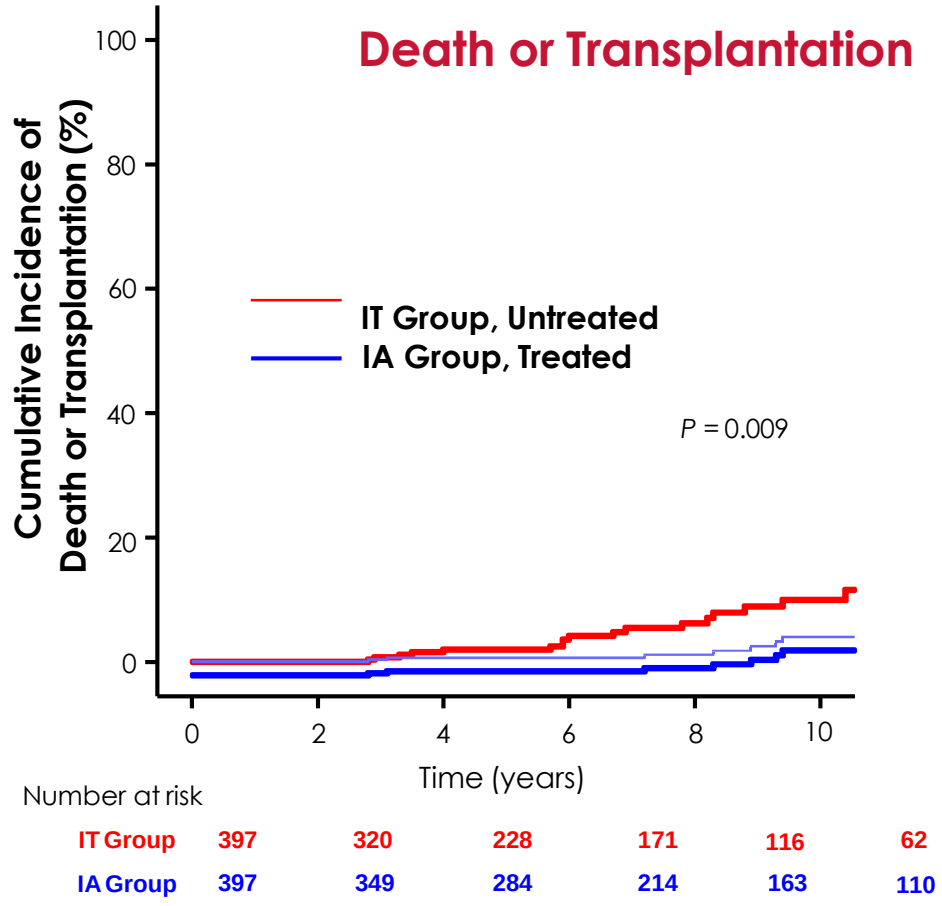
- **Historia familiar de CHC o cirrosis**
- Manifestaciones extrahepáticas

EASL Clinical Practice Guidelines. *J Hepatol,* 2017

HIGHER RISK OF HCC & DEATH IN UNTREATED IMMUNE-TOLERANT *vs.* TREATED IMMUNE-ACTIVE PHASE CHB

Propensity Score-Matched Cohorts

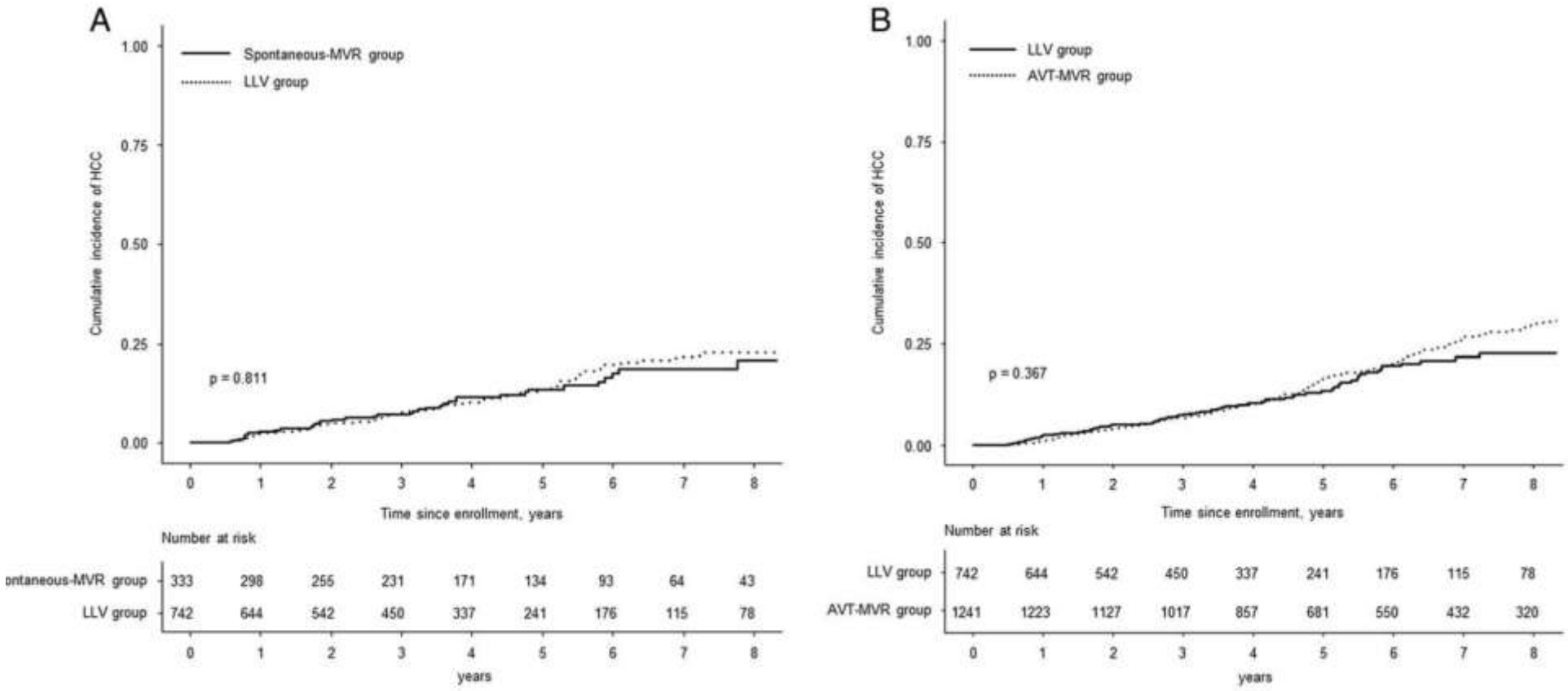




- 57% males, mean age 38±11 yrs, HBV DNA > 7 log , mean ALT 19 UI/L (16-25)
- ALT <19 U/L for females and <30 U/L for males (AASLD)

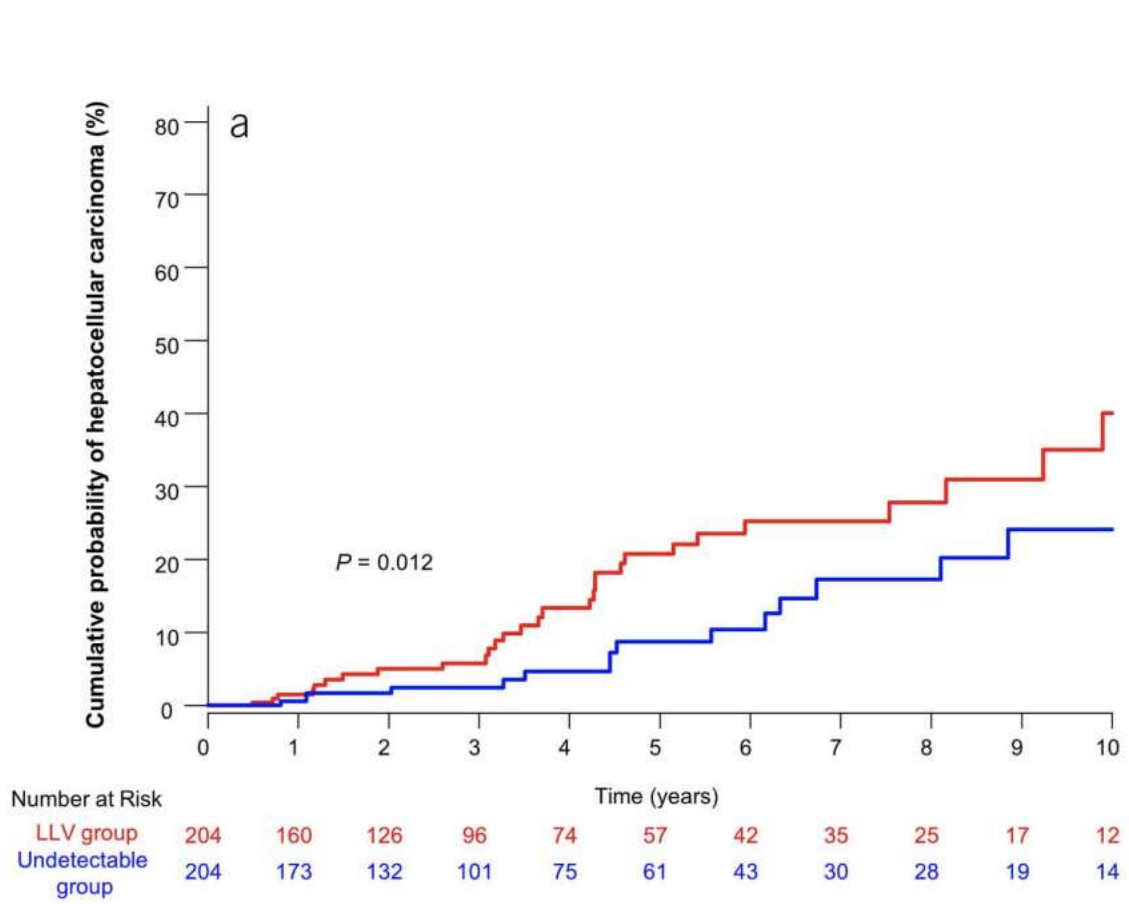
CHB: chronic hepatitis B; **HCC:** Hepatocellular Carcinoma; **HBV**: hepatitis B virus.
Kim GA, Lim YS, *et al.* Gut 2018;67:945–952.

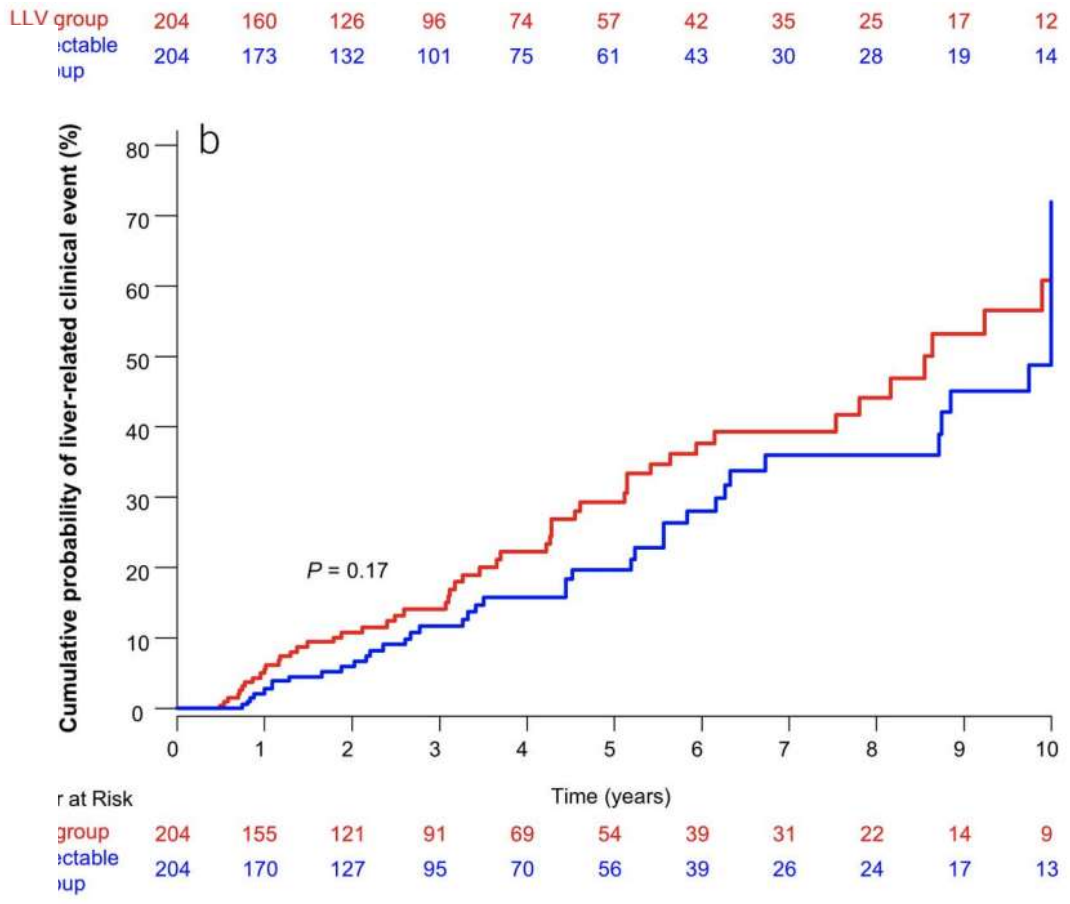
Low-level viremia in cirrhotic patients



Huang et al Hepatology 2022

Low viremia in VHB patients

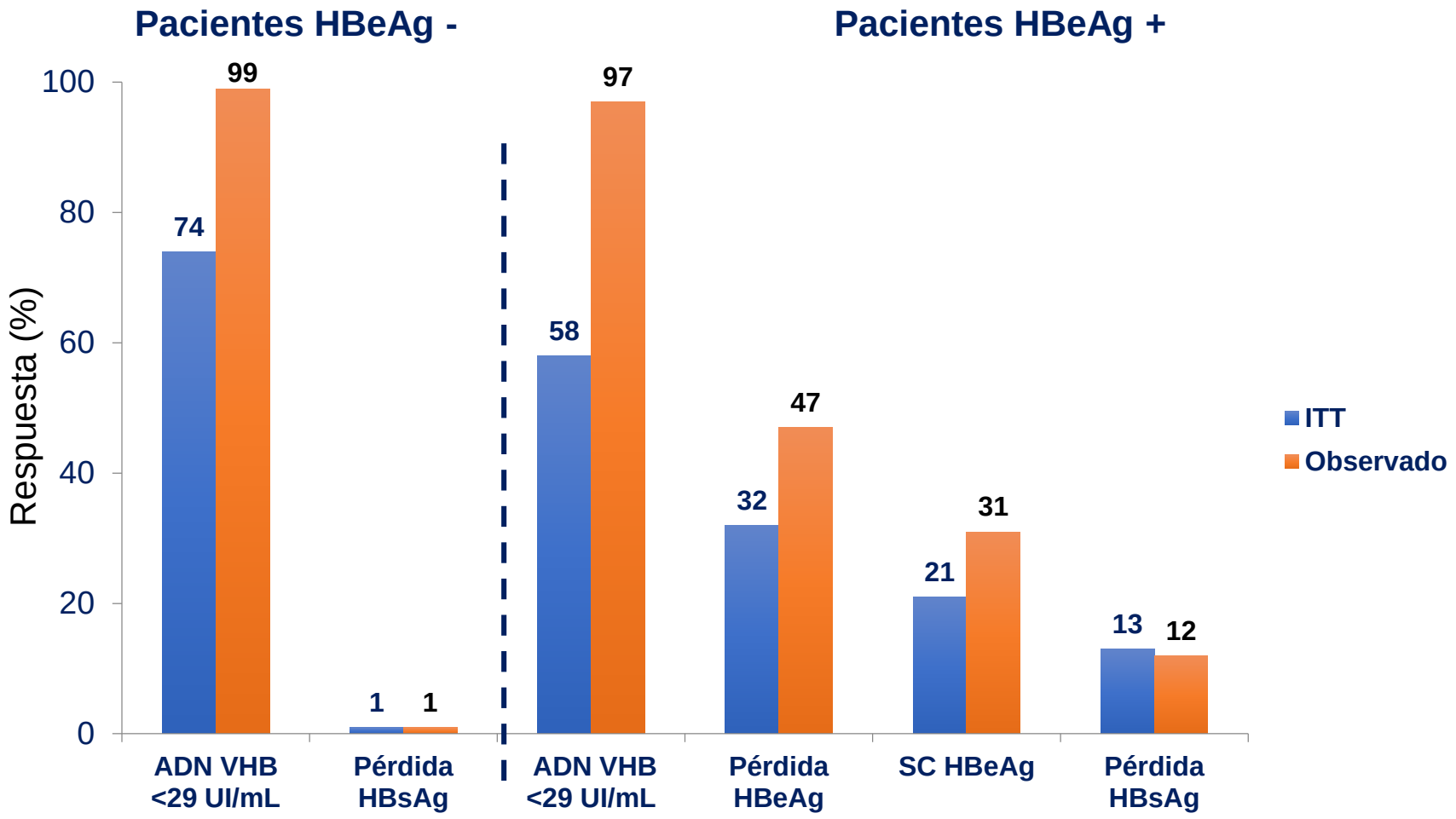




Zeung Am J Gastro 22

Eficacia de Tenofovir DF (TDF) en Hepatitis B

Seguimiento de **8 años** en dos ensayos randomizados



Marcellin P. *Hepatology,* 2014 (A)

Eficacia de Tenofovir DF (TDF) en Hepatitis B

Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection

	HBeAg status		
	HBeAg-negative[b]	HBeAg-positive[c]	All
HBV DNA <69 IU/mL, % (n/N)	100 (118/118)	97.5 (78/80)	99.0 (196/198)
HBV DNA <29 IU/mL, % (n/N)	100 (118/118)	97.5 (78/80)	99.0 (196/198)
ALT normalisation, % (n/N)	83.0 (88/106)	77.9 (60/77)	80.9 (148/183)
HBeAg loss, % (n/N)	–	52.2 (12/23)	52.2 (12/23)
HBeAg seroconversion, % (n/N)	–	27.3 (6/22)	27.3 (6/22)
HBsAg loss, % (n/N)	3.4 (4/117)	4.9 (4/81)	4.0 (8/198)

Marcellin P. *Liver Int, 2019*

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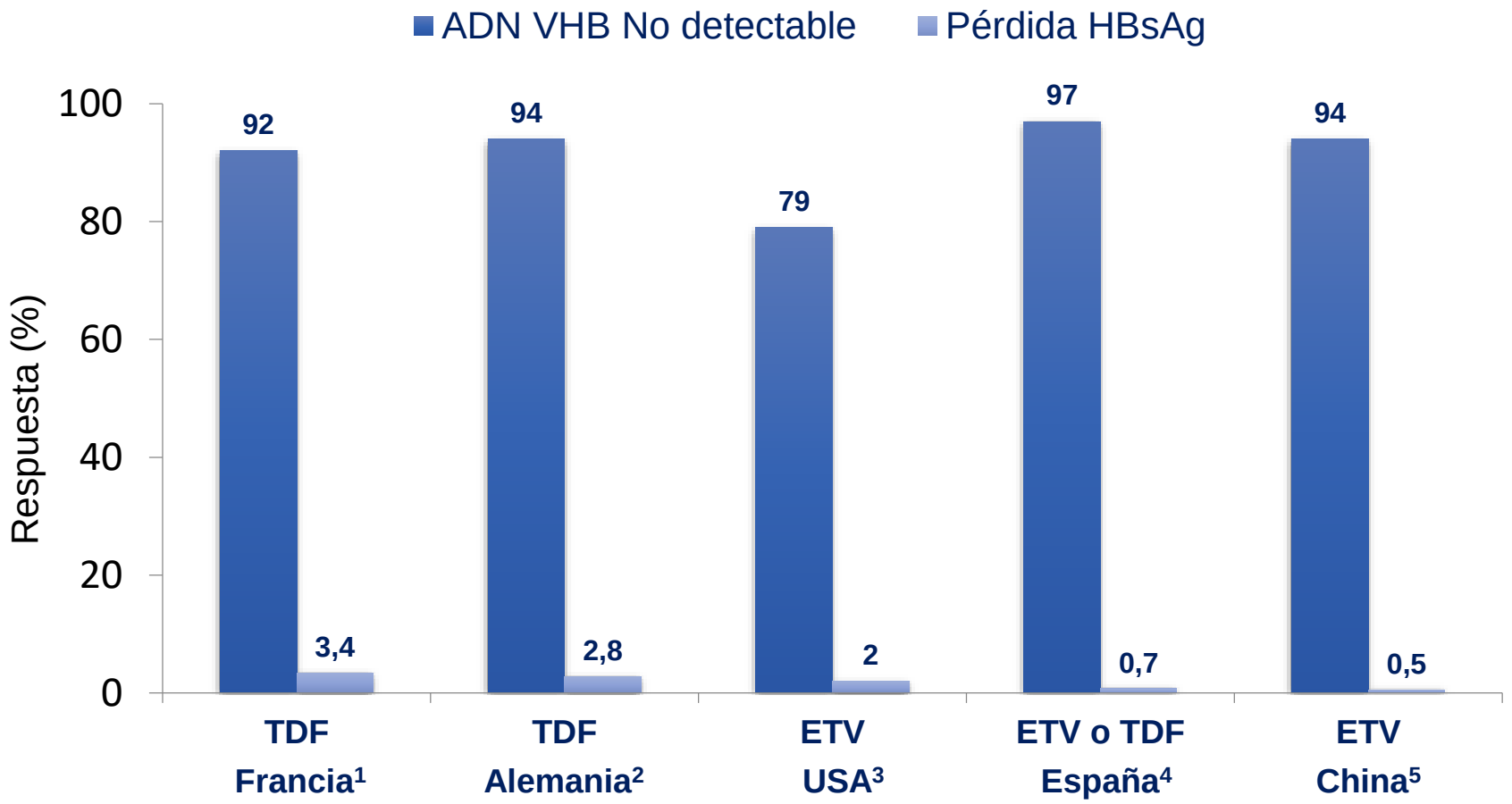
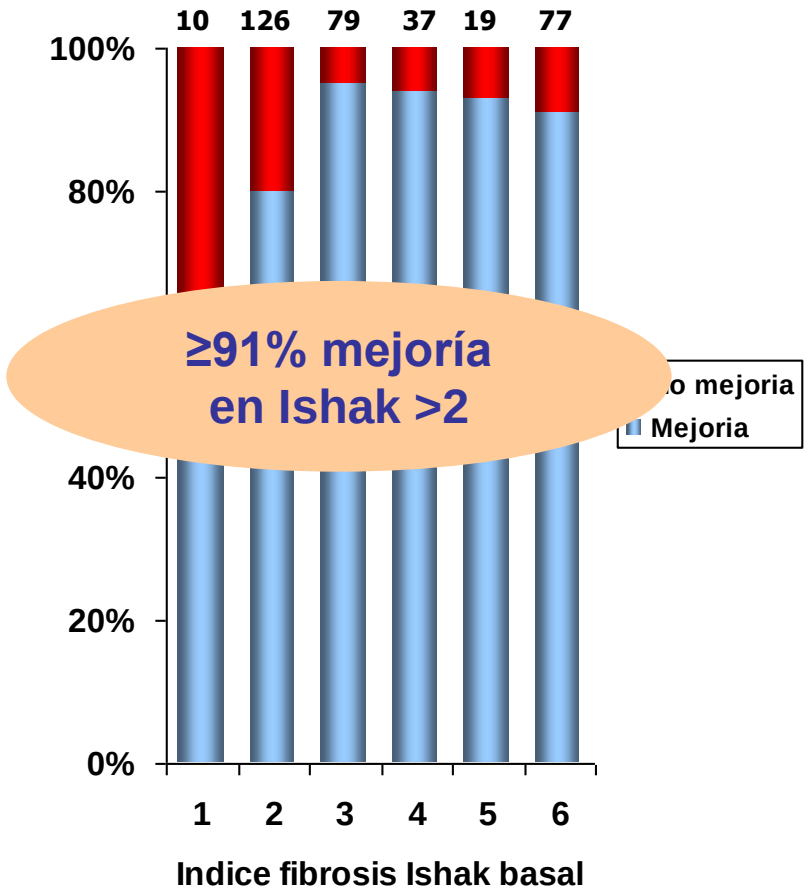
Eficacia de AN Vida Real a 3 años de Tratamiento HBeAg + y HBeAg -

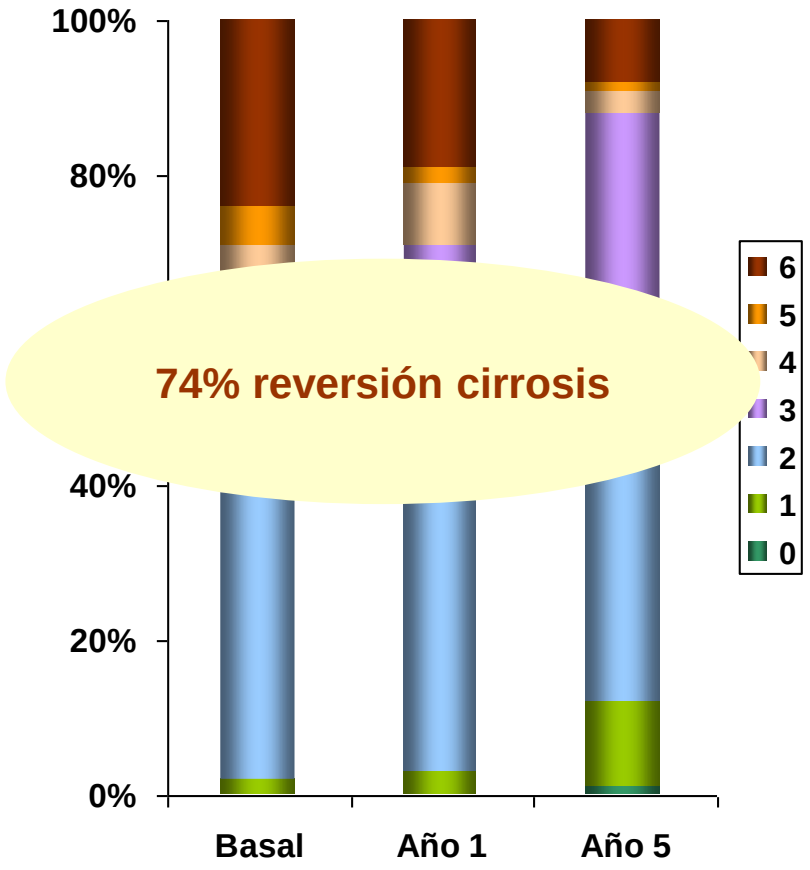


[1]Marcellin P. *Dig Dis Sci,* 2016. [2]Petersen J. *Dig Dis Sci,* 2016. [3]Ahn J. *Aliment Pharmacol Ther,* 2016
[4]Riveiro-Barciela M. *Dig Dis Sci,* 2017. [5]Seto KW. *J Gastroenterol Hepatol,* 2014

Respuesta Histológica con TDF 5 años

641 pacientes biopsia basal
348/641 (54%) biopsias pareadas
96/155 (62%) cirrosis biopsias pareadas



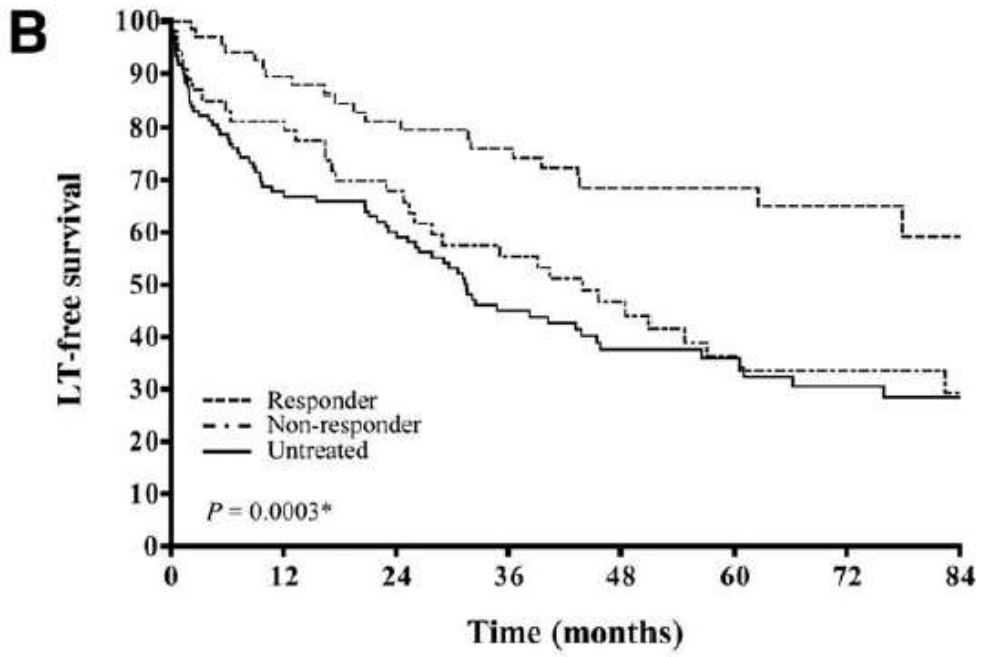


Marcellin P. *Lancet,* 2013

”

Supervivencia en Cirrosis Descompensada con AN

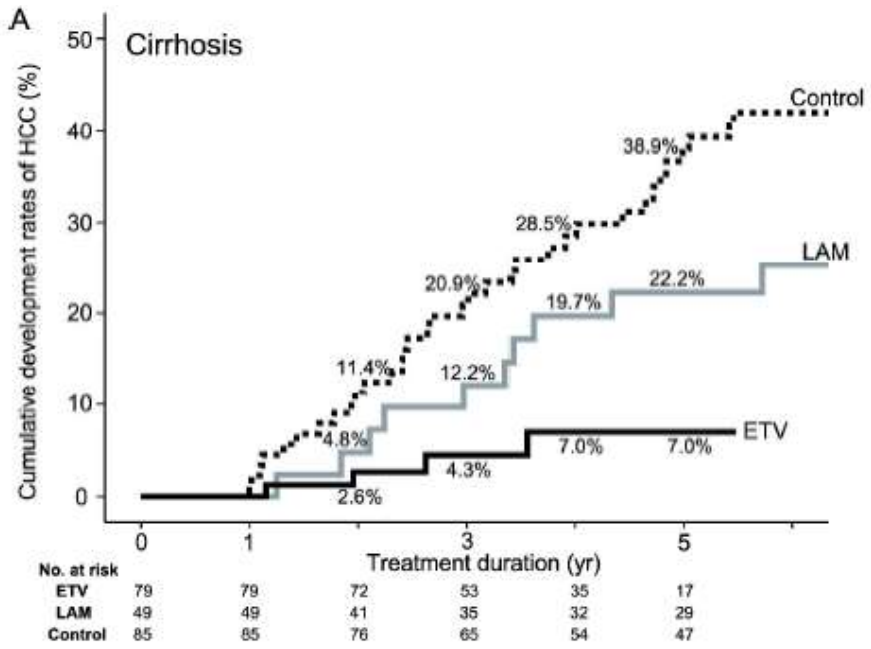
707 cirrosis con primera descompensación
284 no tratados (no criterios de reembolso)
423 tratados (LAM: 48% y ETV: 47%)
254 pareados (127 en cada grupo) por PS



Jang JW. *Hepatology,* 2015

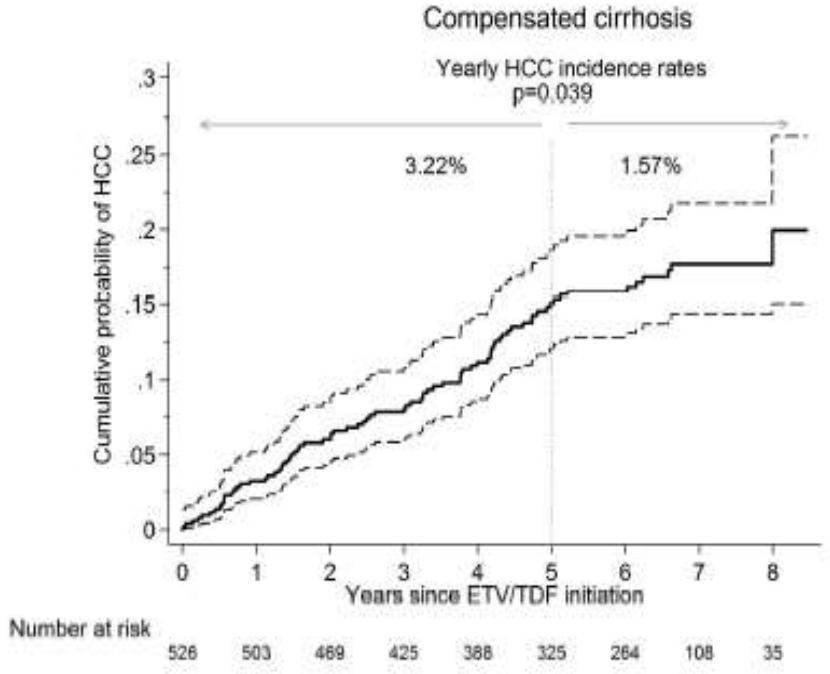
Reducción del Riesgo de CHC con AN

316 pacientes (**79 cirrosis**) tratados con ETV
182 pacientes (**85 cirrosis**) tratados con LAM
316 pacientes (**85 cirrosis**) no tratados
Todos los grupos pareados por PS



Hosaka T. *Hepatology,* 2013

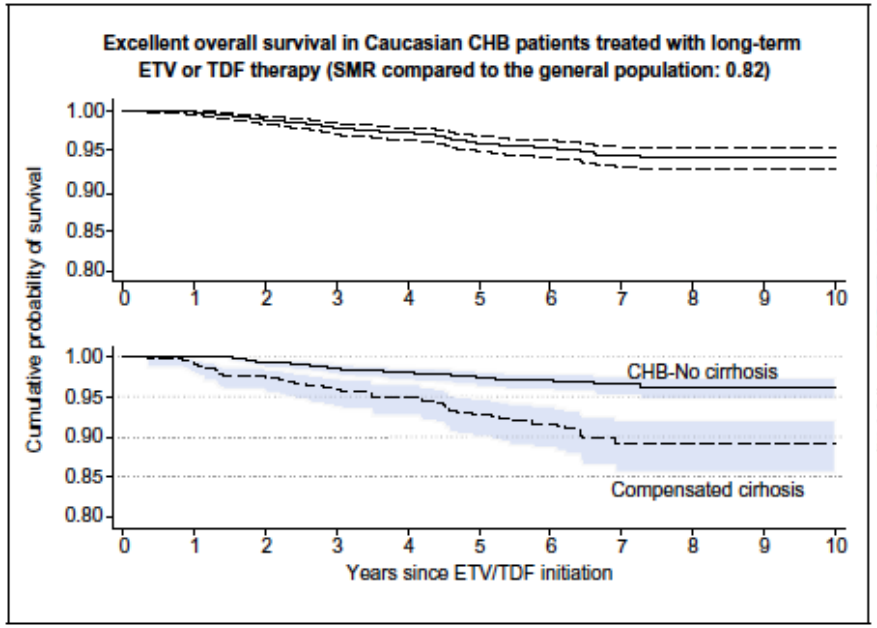
1951 pacientes tratados con ETV o TDF
1205 seguimiento durante 5-10 años



Papatheodoridis GV. *Hepatology,* 2017 (pp)

Supervivencia Similar a Población General en Tratamiento con AN

1.951 caucásicos (27% cirrosis compensada) sin CHC
10 centros europeos (2 de España)
Tratados con ETV o TDF durante ≥12 meses
Seguimiento mediano: 6 (1-14) años

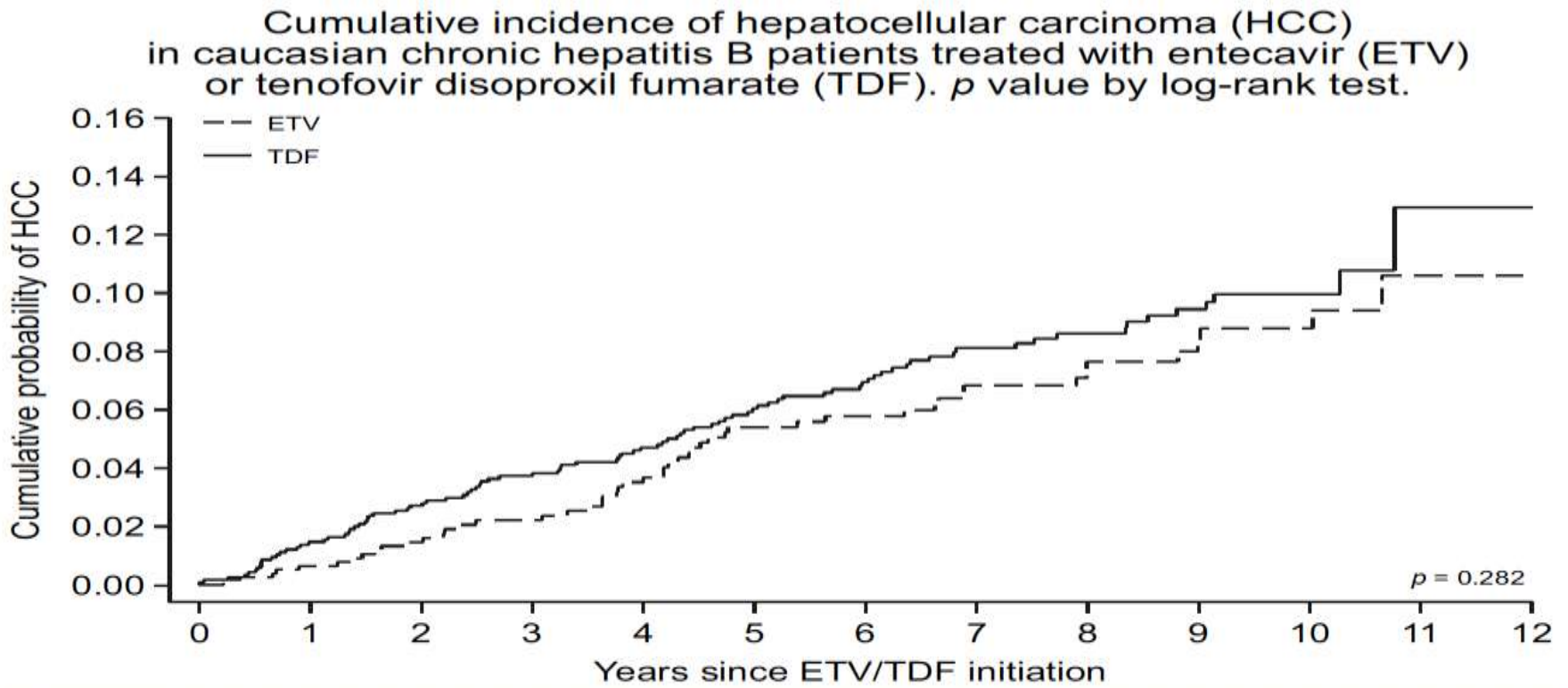


	SMR (95% CI)
All patients (N = 1,951)	0.82 (0.66–1.03)
Males (n = 1,379)	0.78 (0.62–1.01)
Females (n = 572)	1.00 (0.63–1.59)
CHB without cirrhosis (n = 1,379)	0.58 (0.41–0.82)
CHB with cirrhosis (n = 526)	1.22 (0.90–1.66)
Patients without HCC (n = 1,833)	0.58 (0.44–0.77)
Patients with HCC (n = 118)	3.09 (2.13–4.48)

CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; SMR, standardized mortality ratio; TDF, tenofovir disoproxil fumarate.

Papatheodoridis GV. *J Hepatol*, 2018

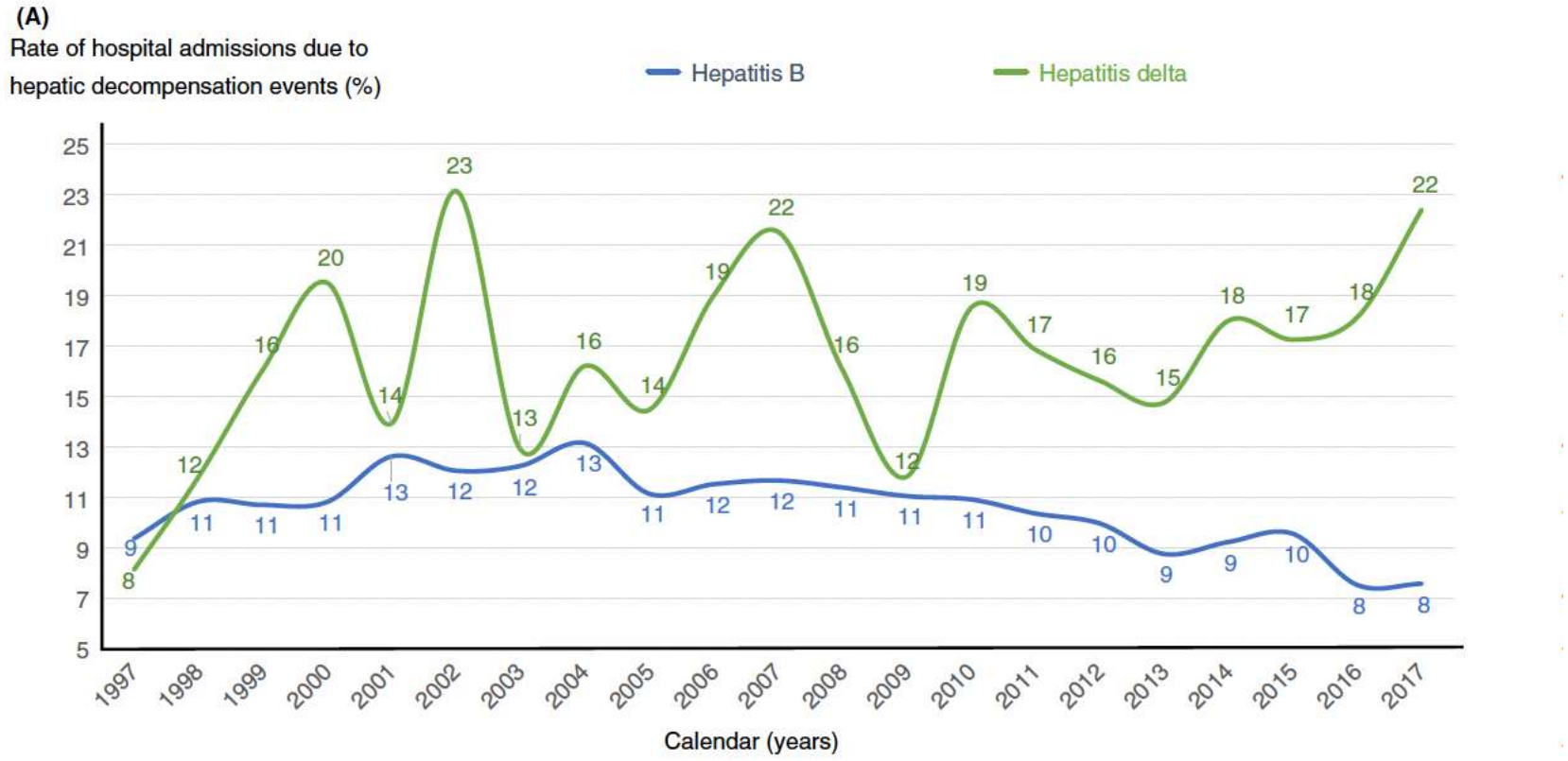
Efecto similar ETV vs TFV



N° at risk													
ETV	772	763	675	618	574	524	492	425	329	238	148	55	7
TDF	1,163	1,125	1,076	1,014	959	883	767	621	499	374	180	36	17

Papatheodoridis et al J Hepat 2020

Reducción de Hospitalizaciones en España por VHB



Ramos-Rincon APT 2022

Scores Predictivos de desarrollo de HCC

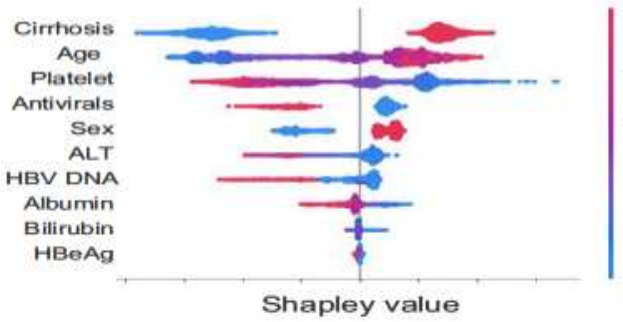
HCC risk score	Low/High-risk group cut-off	AUROC, c-statistic (95% CI)	Sensitivity, %	NPV, %
At baseline		5-year HCC prediction		
PAGE-B	10/18	0.80 (0.76, 0.83)	99.3%	99.8%
HCC-Rescue	65/85	0.81 (0.78, 0.84)	97.2%	99.5%
CAMD	8/14	0.79 (0.74, 0.83)	100%	100%
mPAGE-B	9/13	0.82 (0.78, 0.85)	97.8%	99.3%
AASL	6/20	0.81 (0.77, 0.84)	99.3%	99.7%
At baseline		10-year HCC prediction		
PAGE-B	10/18	0.78 (0.75, 0.81)	99.3%	99.8%
HCC-Rescue	65/85	0.81 (0.79, 0.84)	97.2%	99.5%
CAMD	8/14	0.80 (0.76, 0.83)	100%	100%
mPAGE-B	9/13	0.81 (0.78, 0.84)	97.8%	99.3%
AASL	6/20	0.80 (0.77, 0.83)	99.3%	99.7%

Papatheodoridis G et al J Hep Rep 2021

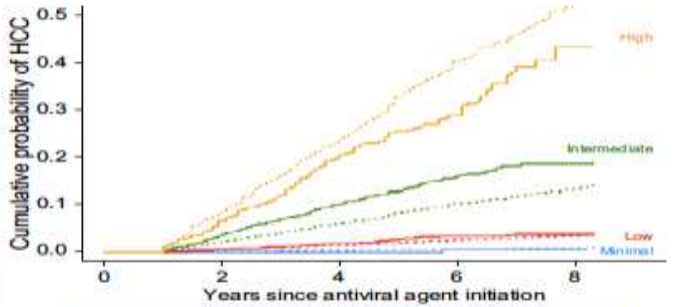
IA para la predicción de desarrollo de HCC

PLAN-B model for the prediction of HCC in patients with chronic hepatitis B

- Machine learning approaches (gradient-boosting machine algorithm)
- Entecavir or tenofovir-treated

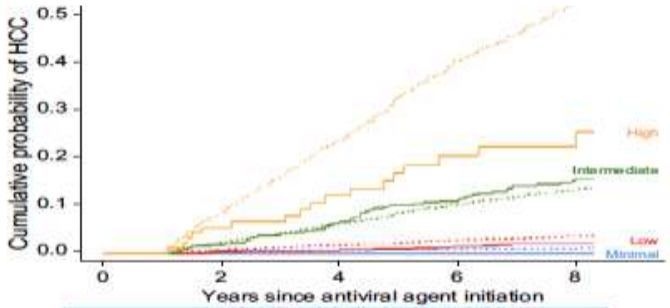


Derivation cohort
(Korea, n = 6,051)



Model	c-index	95% CI		p
		Lower	Upper	
PLAN-B	0.79	0.78	0.80	Ref.
PAGE-B	0.73	0.72	0.74	<0.001
mPAGE-B	0.75	0.74	0.76	0.004
REACH-B	0.63	0.61	0.64	<0.001
CU-HCC	0.72	0.71	0.73	<0.001

Korean validation cohort
(n = 5,817)



Model	c-index	95% CI		p
		Lower	Upper	
PLAN-B	0.81	0.79	0.83	Ref.
PAGE-B	0.75	0.73	0.77	<0.001
mPAGE-B	0.80	0.79	0.82	0.424
REACH-B	0.57	0.54	0.59	<0.001
CU-HCC	0.76	0.74	0.78	0.002

Caucasian validation cohort
(n = 1,640)

Kim et al J Hepatol 2021

Duración del tratamiento en Hepatitis B

- Objetivos óptimos: pendientes de consenso
  - HBeAg Perdida /seroconversion
  - Supresión HBV DNA
  - HBsAg Perdida /seroconversion
- Terapia indefinida
  - Especialmente en pacientes con cirrosis y fibrosis avanzada
- ¿ Se puede parar el tratamiento en algún paciente?

Eficacia de tratamiento en HBeAg+

Outcome, %	PegIFN	ETV	TDF	TAF
HBeAg seroconversion	**29-36** *(1 yr)**	**21** *(1 yr)* **21-22** *(3 yrs)*	**21** *(1 yr)* **21** *(3 yrs)*	**10** *(1 yr)* **18** *(2 yrs)*
HBsAg loss	**2-7** *(1 yr)**	**2** *(1 yr)* **4-5** *(3 yrs)*	**3** *(1 yr)* **8** *(3 yrs)*	**1** *(1 yr)* **1** *(2 yrs)*

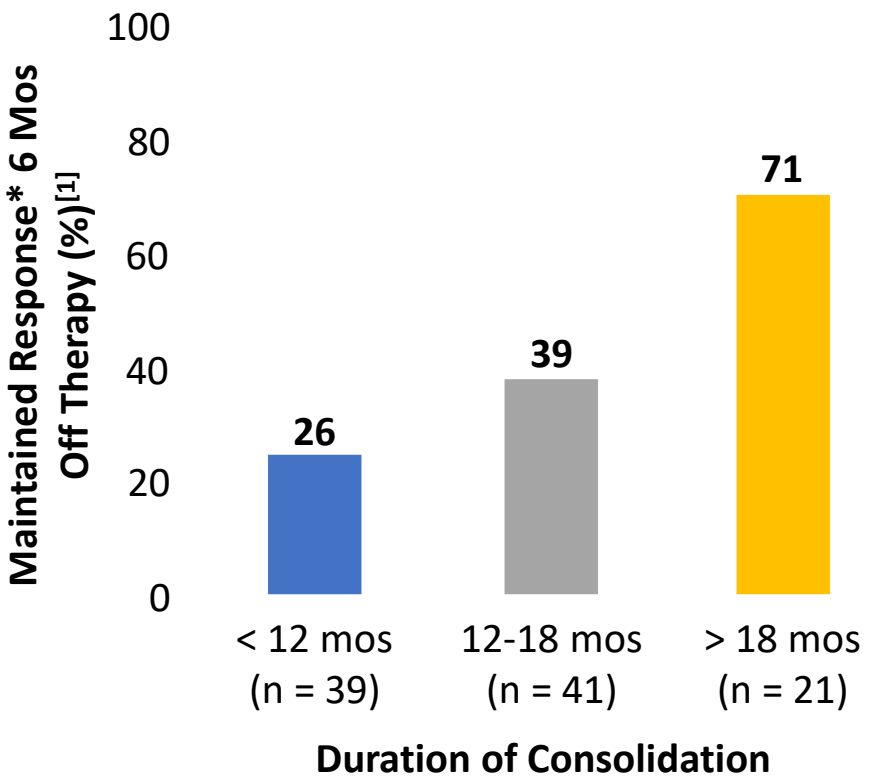
Terrault. Hepatology. 2018;67:1560. EASL. J Hepatol. 2017;67:370.

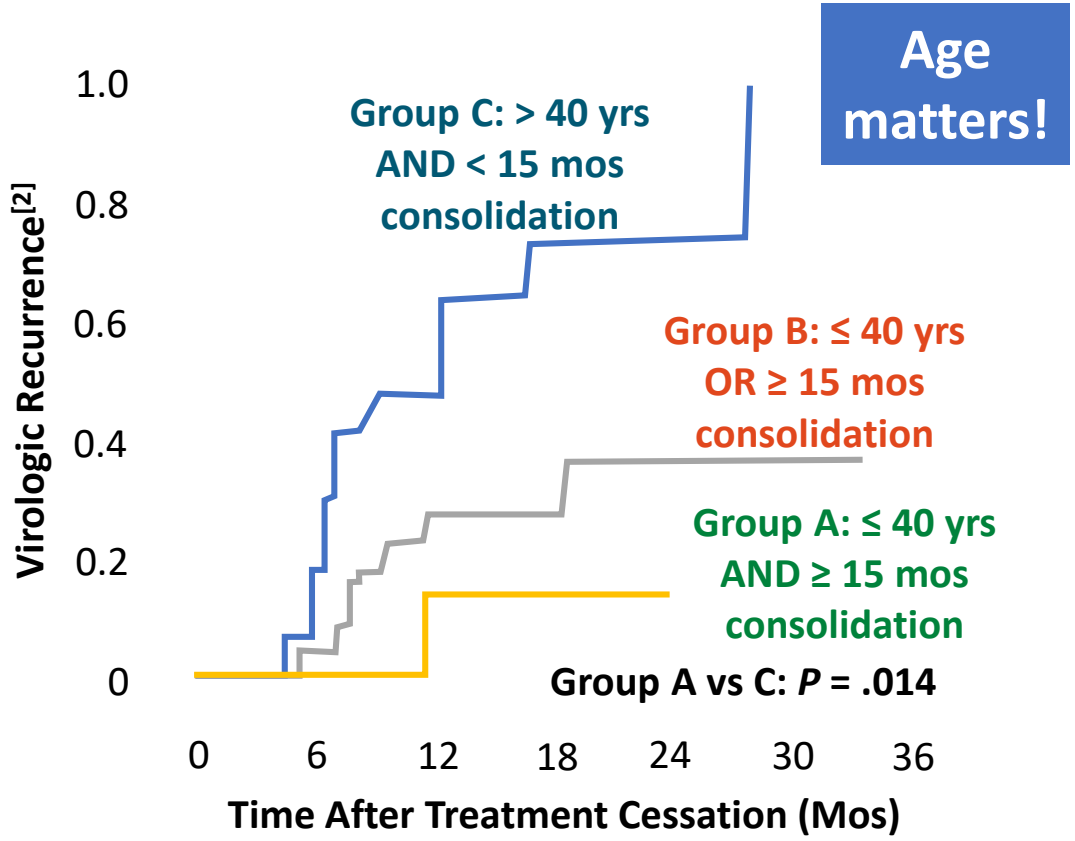
Treatment Duration for Patients With HBeAg-Positive CHB Who Seroconvert to Anti-HBe on NA Therapy

- AASLD guidance, if no cirrhosis[1]
  - **Can consider NA discontinuation** following a period of treatment consolidation with normal ALT, undetectable HBV DNA for at least 12 mos
  - Alternative approach to **treat until HBsAg loss**
- Across guidelines, length of consolidation therapy varies
  - AASLD[1] and EASL[2]: at least 12 mos
  - APASL[3]: at least 12 mos, preferably 3 yrs

1. Terrault. Hepatology. 2018;67:1560. 2. EASL. J Hepatol. 2017;67:370. 3. Sarin. Hepatol Int. 2016;10:1.

Fewer Relapses With Longer Duration of Consolidation After HBeAg Seroconversion





*HBeAg seroconversion and undetectable serum HBV DNA.

1. Dai. J Antimicrob Chemother. 2013;68:2332. 2. Song. World J Gastroenterol. 2012;18:6277.

HBeAg-Positive CHB: Summary

- In those with advanced fibrosis/cirrhosis, treat indefinitely unless a strong competing rationale for treatment discontinuation exists
- Otherwise, at time of seroconversion to anti-HBe
  - If ≤ 40 yrs of age, can consider stopping after ≥ 12 mos of consolidation therapy
  - If > 40 yrs of age, individualize decision to stop
    - Consolidation longer than 12 mos, treating to HBsAg loss may be preferred
- After stopping NA therapy
  - Need to monitor for recurrent viremia, ALT flares, seroreversion, and decompensation every 3 mos for at least 12 mos

Treatment Duration for Patients With HBeAg-Negative CHB

- AASLD guidance, if no cirrhosis[1]
  - **Treat indefinitely** (or until HBsAg loss), unless a compelling rationale for treatment discontinuation exists
- Across guidelines, more variability on when to consider stopping
  - EASL[2]: if no cirrhosis, at least 3 yrs of virologic suppression, and capacity for close monitoring after stop
  - APASL[3]: if no cirrhosis and at least 2 yrs of treatment with undetectable HBV DNA at 3 separate visits 6 mos apart, or if compensated cirrhosis with a careful monitoring plan

1. Terrault. Hepatology. 2018;67:1560. 2. EASL. J Hepatol. 2017;67:370. 3. Sarin. Hepatol Int. 2016;10:1.

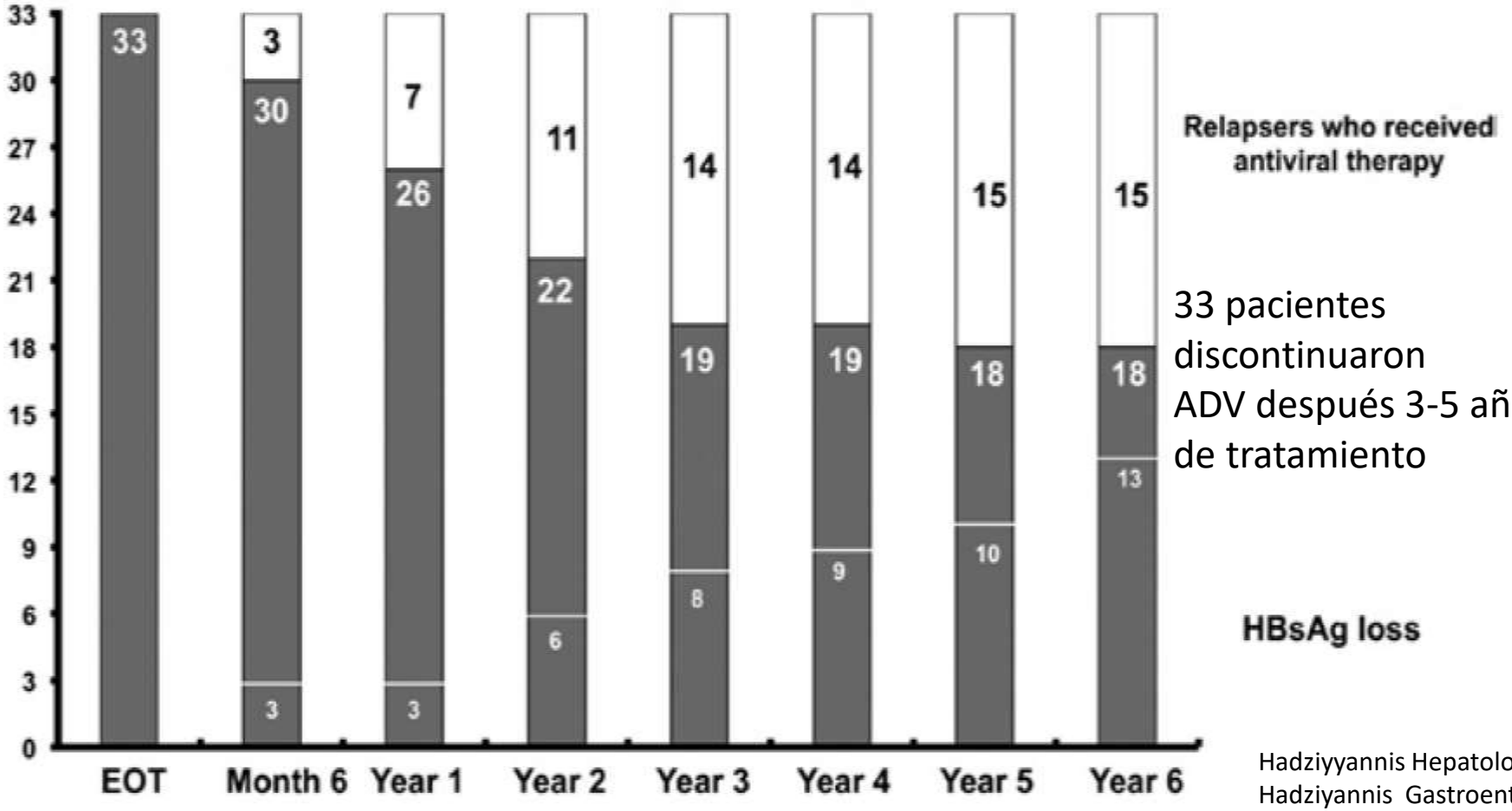
Eficacia del tratamiento en HBeAg neg

Outcome, %	PegIFN	ETV	TDF	TAF
HBV DNA suppression	**19** *(1 yr)**	**90-91** *(1-3 yrs)*	**93** *(1-3 yrs)*	**90-94** *(1-2 yrs)*
HBsAg loss	**4** *(1 yr)**	**0-1** *(1 yr)*	**0** *(1 yr)*	**0** *(1 yr)*

Terrault. Hepatology. 2018;67:1560. Terrault. Hepatology. 2016;63:261. EASL. J Hepatol. 2017;67:370.

Tratamiento finito de Hepatitis B

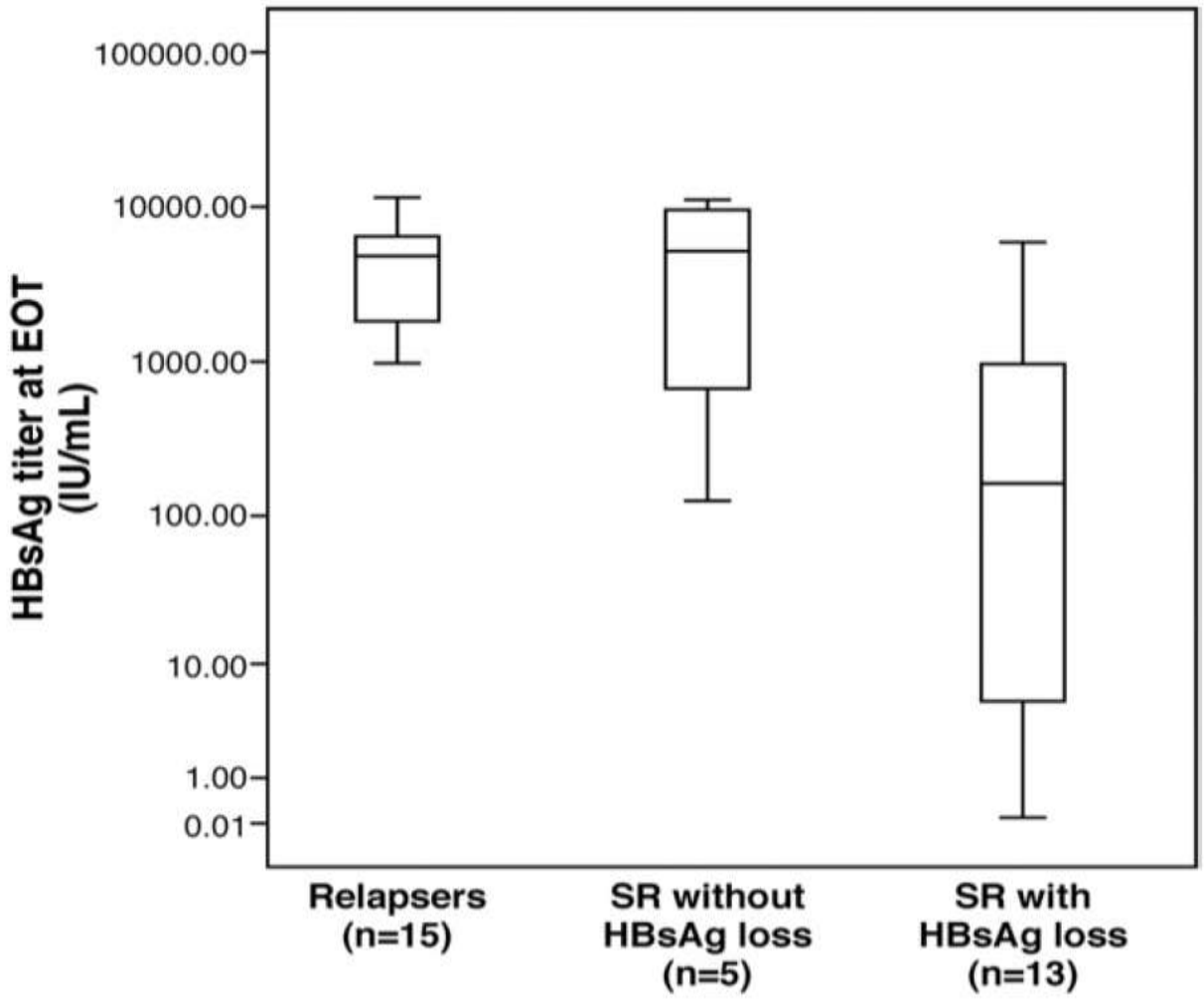
55 % continúan sin Tx
39% pierden el HBsAg



33 pacientes discontinuaron ADV después 3-5 años de tratamiento

Hadziyyannis Hepatology 2006
Hadziyannis Gastroenterology 2012

Tratamiento Finito Hepatitis B



Hadziyyannis Hepatology 2006
Hadziyannis Gastroenterology 2012

STOP: Stopping ETV or TDF in HBeAg-Negative CHB

- Prospective, randomized, controlled, open-label phase IV trial
  - 97% Asian

Wk 72

HBeAg-negative patients with CHB and virologic suppression,* ETV or TDF ≥ 12 mos, HBsAg+ ≥ 6 mos; no HCV or HIV coinfection, decompensated cirrhosis (N = 67)

Discontinue NA Therapy (n = 45)

Continue NA Therapy (n = 22)

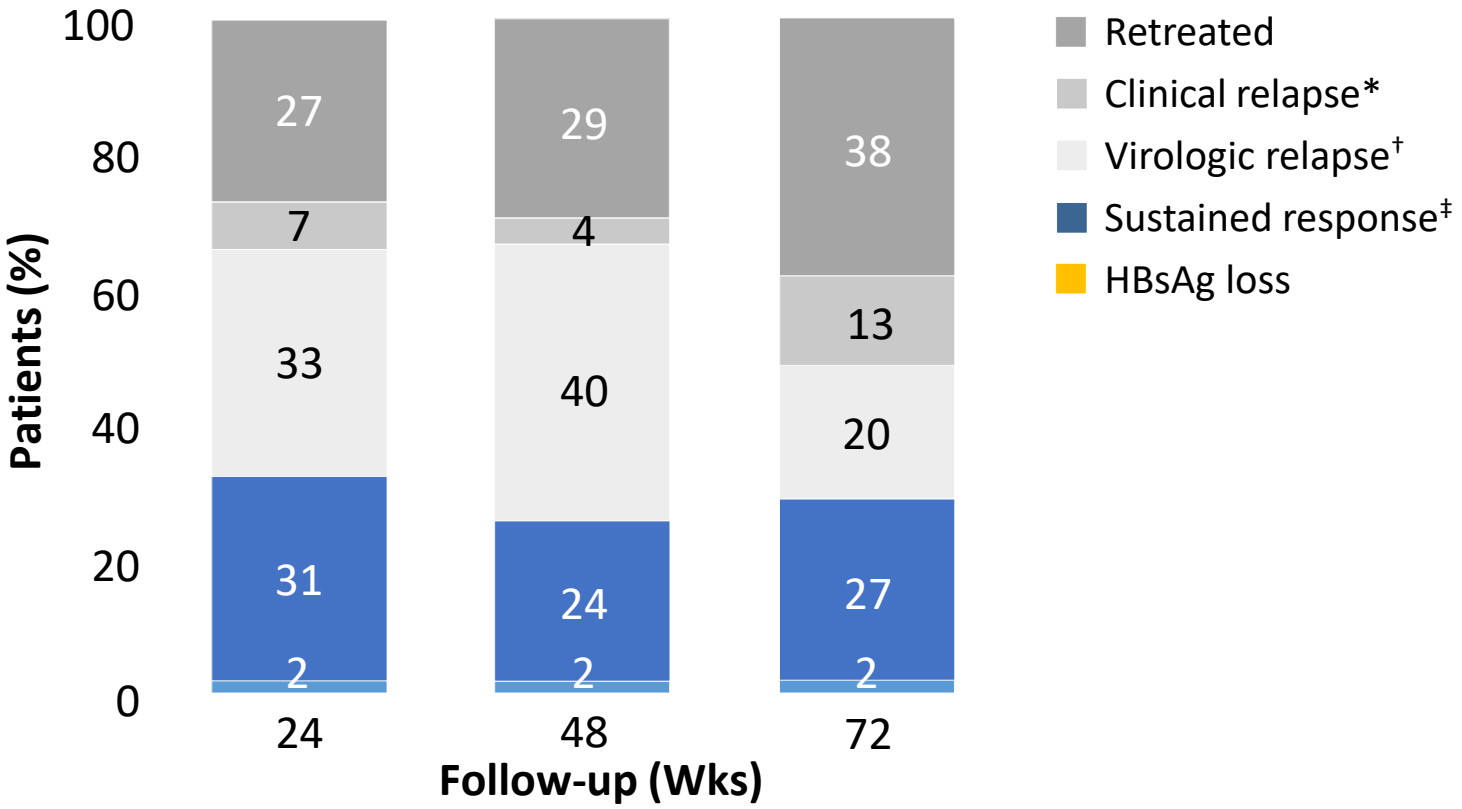
*If HBeAg+ at NA start, HBeAg seroconversion + undetectable HBV DNA ≥ 12 mos; if HBeAg-, undetectable HBV DNA ≥ 36 mos.

- Primary endpoint: HBV DNA < 2000 IU/mL at Wk 48

Patients retreated for HBeAg seroreversion, HBV DNA > 2000 IU/mL + (ALT > 5 x ULN at 2 consecutive visits or > 15 x ULN at any visit), or HBV DNA > 20,000 IU/mL at 2 consecutive visits; ALT ULN: 40 IU/mL.

Liem. AASLD 2018. Abstr 268.

STOP: Virologic Outcomes



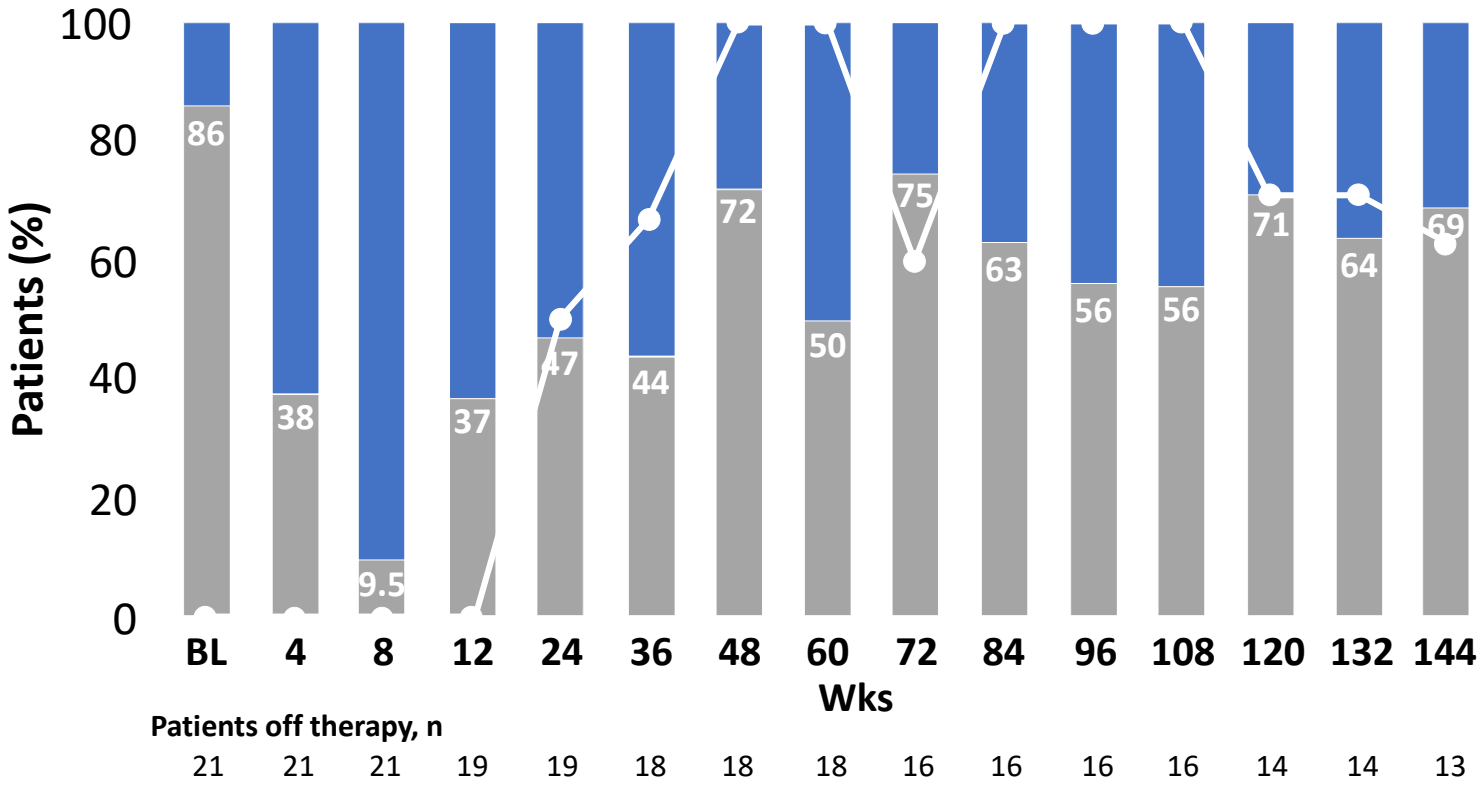
- Clinical relapse or retreatment in > 50%
- Only ~ 30% with sustained off-treatment response
- Very low rate of HBsAg loss, possibly related to predominance of Asians in study population

*HBV DNA > 2000 IU/mL + ALT > 1.5 x ULN. †Lone HBV DNA > 2000 IU/mL.
‡HBeAg negative + HBV DNA < 2000 IU/mL + ALT < 1.5 x ULN.

Liem. AASLD 2018. Abstr 268.

FINITE: Stopping Long-term TDF in HBeAg-Negative CHB

- Noncirrhotic patients with HBeAg-negative CHB who had received TDF for ≥ 4 yrs with HBV DNA suppression for ≥ 3.5 yrs and were randomized to stop TDF (n = 21)



Off therapy with HBV DNA > 2000 IU/mL and/or ALT ≥ ULN

Off therapy with HBV DNA < 2000 IU/mL and ALT ≤ ULN

Restarting therapy with HBV DNA < 2000 IU/mL and ALT ≤ ULN

19% (4/21) achieved HBsAg loss at Wk 144

62% (13/21) remained off therapy at Wk 144

Berg. J Hepatol. 2017;67:918.

Tratamiento HBeAg neg en Asia

- 691 pacientes HBeAg Negativo de Taiwan (mas de 6 meses con AN: ETV o TFV)
- 45% pacientes con cirrosis
- Tasa acumulada a los 6 años de perdida de HbsAg 13% :
  - Cirrosis 9%
  - No cirrosis 16%
- Tasa acumulada a los 4 años :
  - EOT HBsAg < 100 UI/ml : 30%
  - EOT HBsAg > 100 UI/ml : 0%

Series en pacientes HBsAg negativos

Source [Reference]		No.	Nuc	HBsAg loss
Hadziyannis	Greece [43]	33	ADV 4–5 yr	39%/5 yr
Siederdissen	Germany [45]	15	NUC > 3 yr	20%/4 yr
Berg	Europe [47]	21/21	TDF > 4 yr	19%/3 yr
Papatheodoridis	Greece [46]	57	ETV/TDF 5 yr	16%/1 yr
Chan	Hong Kong [42]	53	LAM 3 yr	23%/5 yr
Chi	Asian 80% [31]	59	NUC 5 yr	14%/3 yr
Jeng	Taiwan [32]	383 (CHB) 308 (LC)	ETV/TDF 3 yr	16%/6 yr 9%/6 yr
Chen	Taiwan [48]	234	ETV 3 yr	13%/5 yr

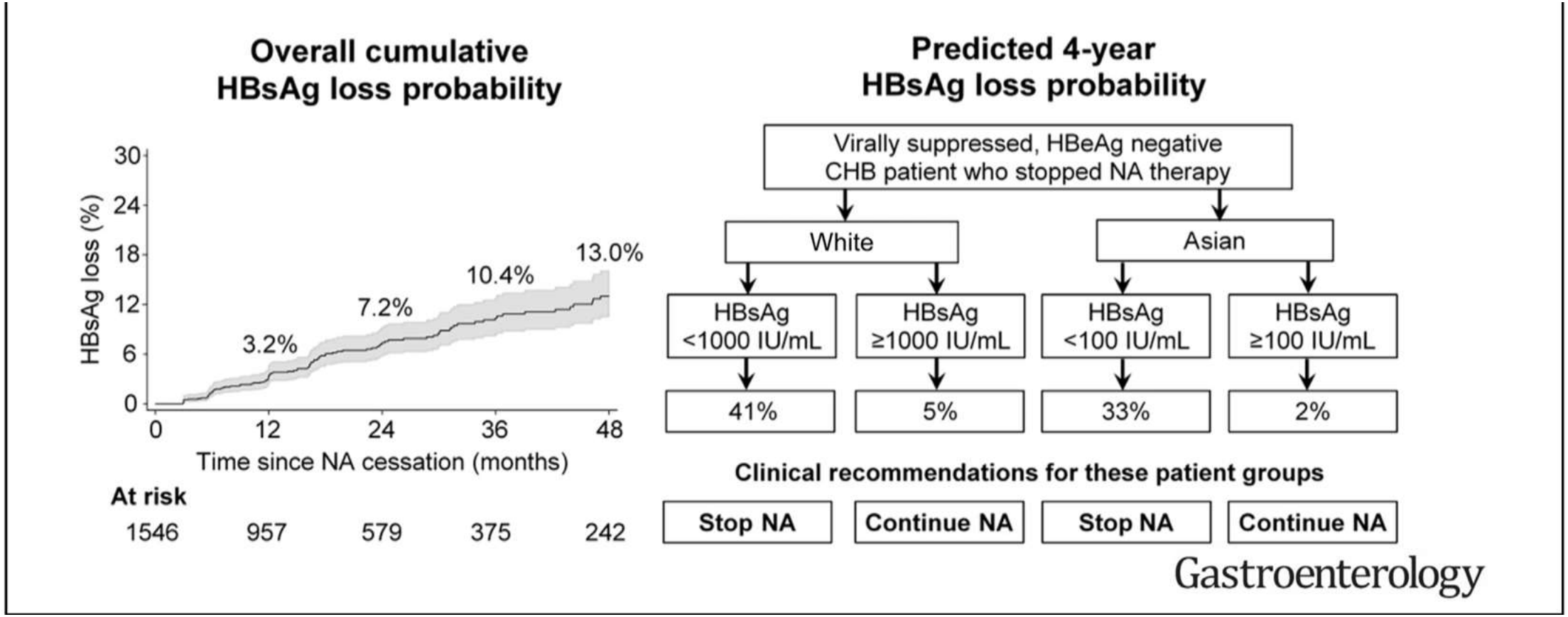
ETV entecavir, *Fu* follow-up, *TDF* tenofovir, *ADV* adefovir, *CHB* chronic hepatitis B, *ETV* entecavir, *LAM* lamividine, *LC* liver cirrhosis, *NUC* nucleos(t)ide analogs, *TDF* tenofovir, *yr* year

Retratados vs no retratados

Table 2 Higher HBsAg loss rate in patients with non-retreated off-NUC relapse

Source	HBsAg loss non-retreated vs retreated	Reference
Hadziyannis	5 yr: 12/18 (66.7%) vs 1/15 (6.7%); $p = 0.027$	[43]
Chi	3 yr: 9/33 (27.3%) vs 0/26 (0%)*	[31]
Berg	3 yr: 4/13 (31%) vs 0/8 (0%)*	[49]
Jeng	6 yr: 19%/150 vs 1%/269 (HR: 8.4; $p < 0.01$)	[32]
Chen	5 yr: 18%/27 vs 0%/111 (HR: 18.6; $p < 0.001$)	[48]

Tratamiento Finito con AN



Hirode et al Gastro 2022

Base racional

- Control inmunológico y aclaramiento viral depende de Linfocitos T CD8
- En pacientes con infección crónica por VHB :
  - Respuesta ineficaz: Linfocitos exhaustos por sobre-exposición al antigeno
- Supresion crónica del HBV-DNA consigue una revitalización del sistema inmune

↓

Suspension del AN : Rebote súbito del DNA y re –exposición al Antigeno

↓

Control inmune de la infección por VHB

PROS AND CONS OF STOPPING THERAPY

Pros	Cons
HBsAg loss increase survival	HBV DNA rebound
State of inactive carrier	ALT flares
Long term therapy off in 50%	
Reduced Costs	

Needs
Careful selection of patients
Active retreatment plan based on HBV DNA increase

HBsAg: hepatitis B surface antigen; **HBV**: hepatitis B virus.

EASL Clinical Practice Guidelines. J Hepatol 2017; 67: 370

Lecciones aprendidas

- Recidiva es casi universal
- Dimension clínica de esta recidiva es muy variable
- Descompensación es muy infrecuente y solo ocurre en pacientes con cirrosis
- Es necesario definir mejor las poblaciones que se pueden beneficiar
- Son necesarios nuevos marcadores de respuesta a la suspensión
  - Cuantificación del HBsAg (Basalmente y durante el tratamiento)
  - Hepatitis B core related antigen
  - Fragmentos HBsAg

Lecciones aprendidas

- Es necesario definir la necesidad de retratamiento
  - Actividad inflamatoria persistente mas de 3 meses
  - Picos de ALT > 5 veces : No demasiado pronto/ No demasiado tarde
  - Utilizacion de la cuantificación del HBsAg para definir tipo de rebrote
  - Elevacion de la bilirrubina necesita tratamiento inmediato
- Monitorizacion estrecha
  - ALT cada mes (3 meses) y despues trimestral
  - HBV-RNA cada 3 meses
  - Intensificar seguimiento si existe un pico de ALT