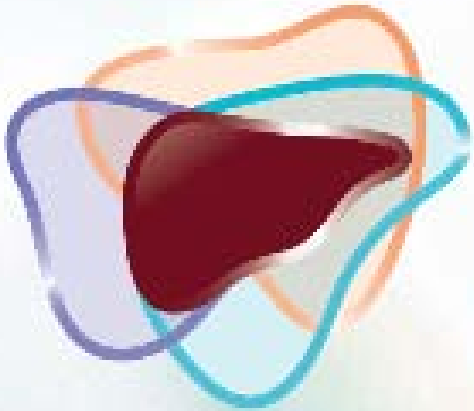
Should we stop long term nucleoside analogue therapy in CHB?

Teerha Piratvisuth M.D.

NKC Institute of Gastroenterology and Hepatology

Prince of Songkla University, Thailand



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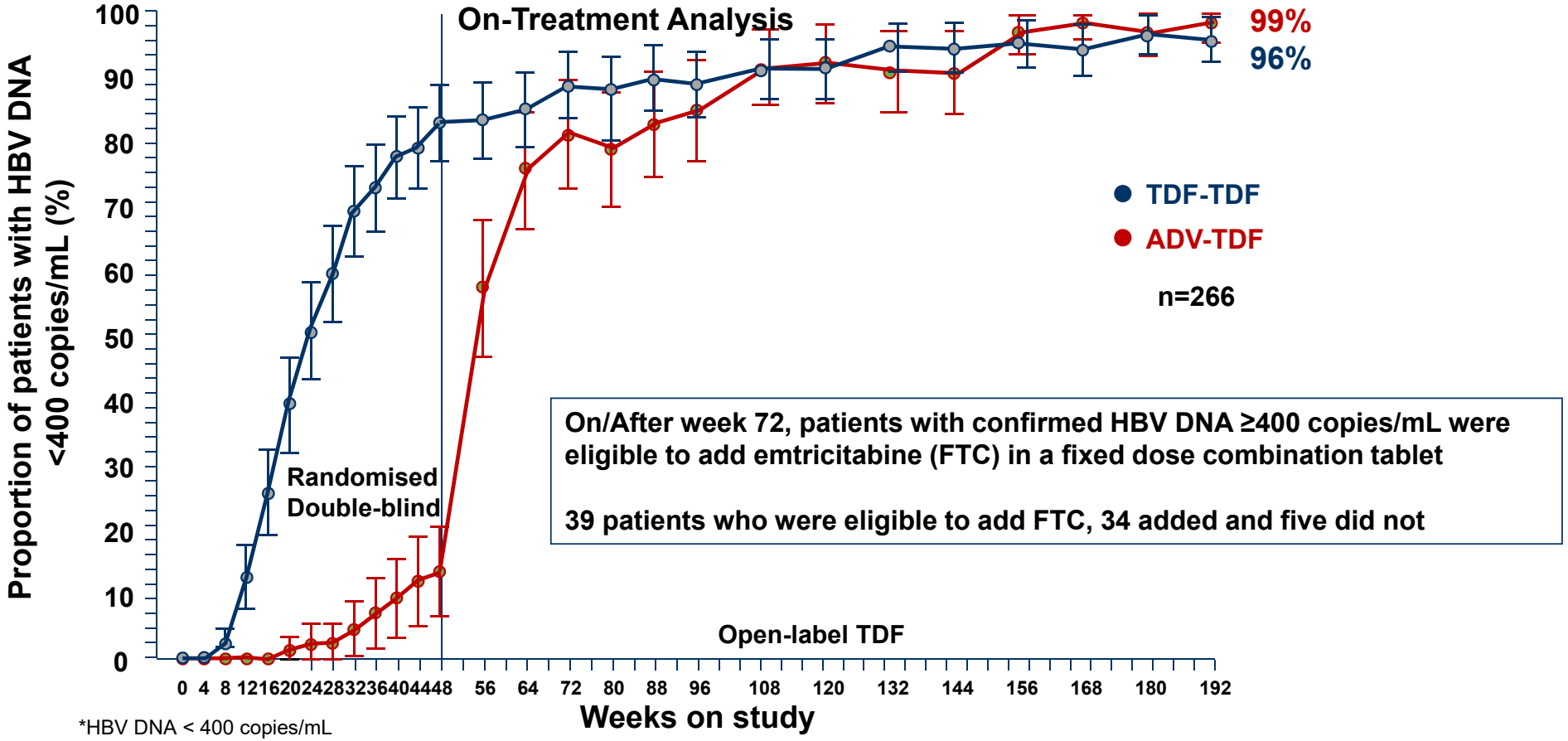
TDF 4-year clinical trial HBV DNA suppression* data: HBeAg(+)ve patients

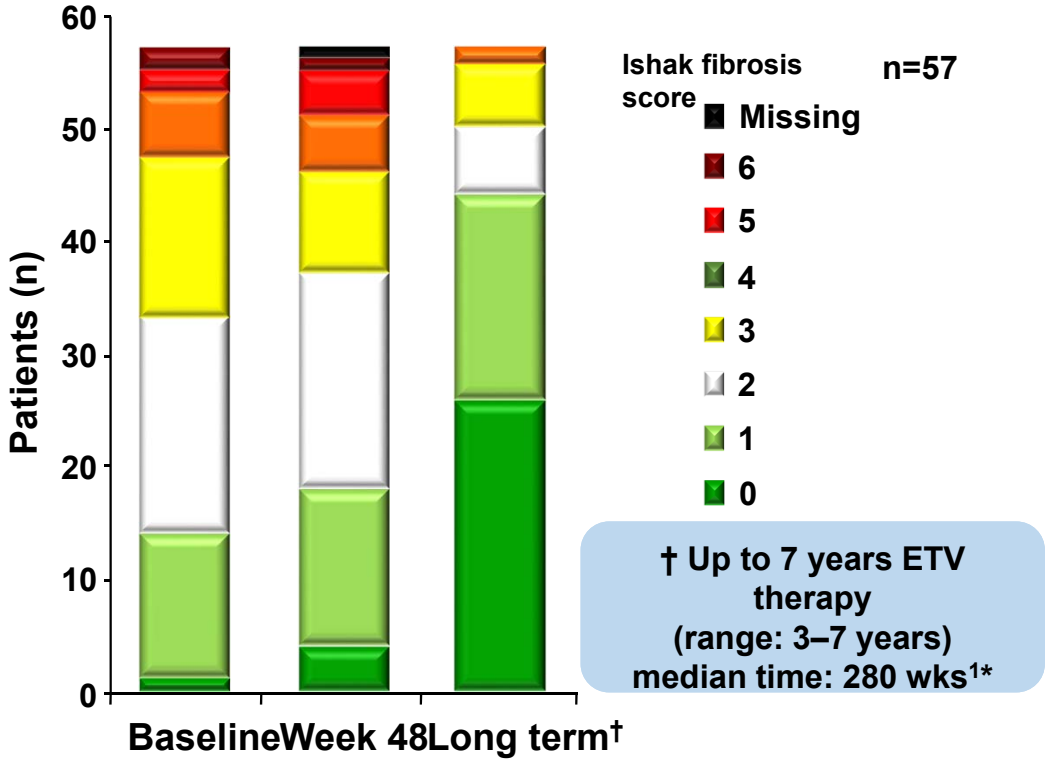


*HBV DNA < 400 copies/mL

Illustration includes 19 patients who added FTC and had HBV DNA <400 copies/mL at week 192

Adapted from Heathcote E et al. 61st AASLD 2010. Poster 477. Available at http://www.natap.org/2010/AASLD/AASLD_28.htm [Accessed Aug.2011]

Improvement in liver fibrosis score with long-term NA therapy

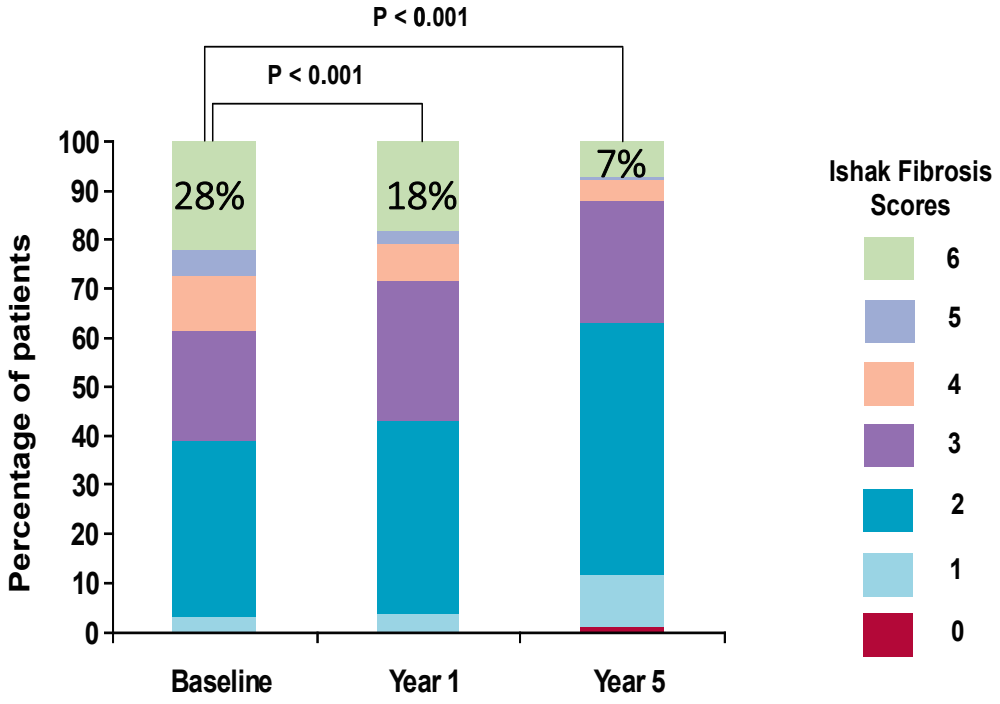


† Up to 7 years ETV therapy (range: 3–7 years) median time: 280 wks[1]*

*All patients had maintained HBV DNA suppression with undetectable HBV DNA

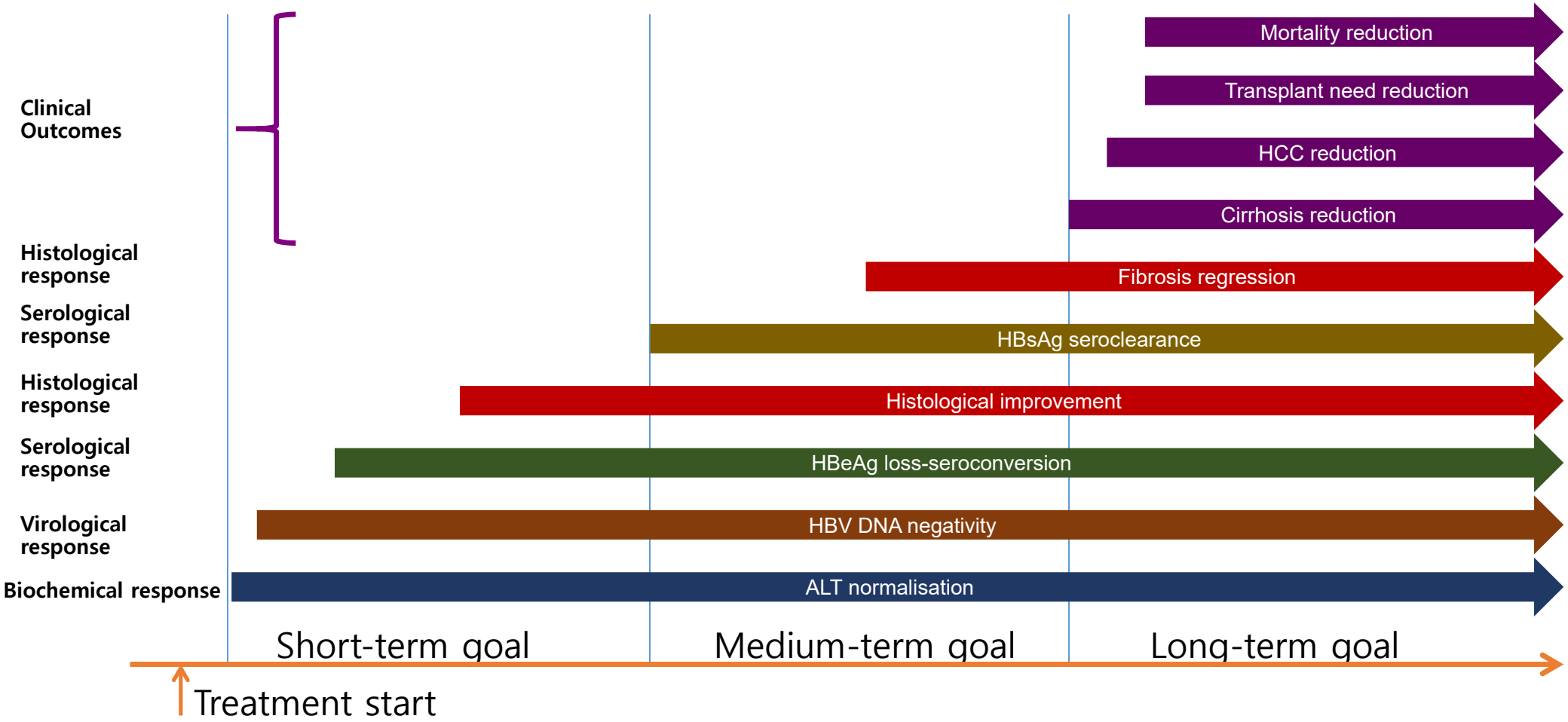
Chang T-T, et al. *Hepatology* 2010;52:886–93. 2. Baraclude® (entecavir) SmPC May 2011.

- Patients in Long-term Tenofovir
  - 348 had liver biopsies at baseline, 1 and 5 years



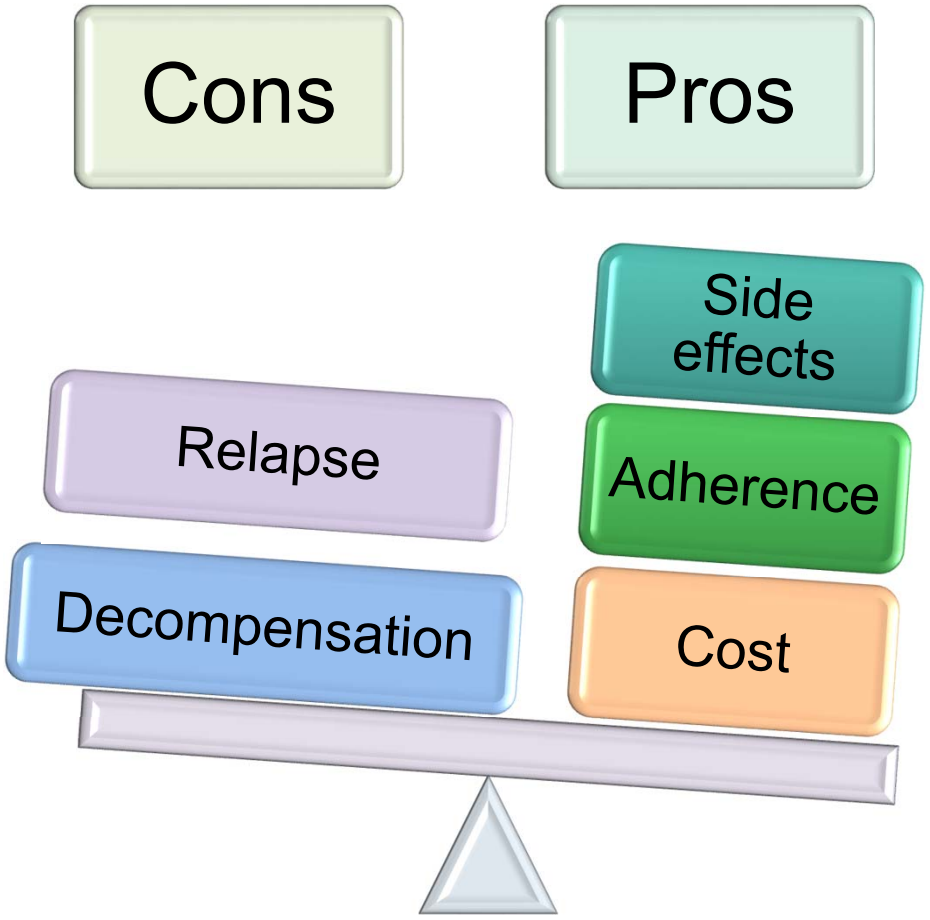
Marcellin P, et al. The Lancet 2013; 381(9865): 468-475.

Long-term NA therapy have multiple benefits

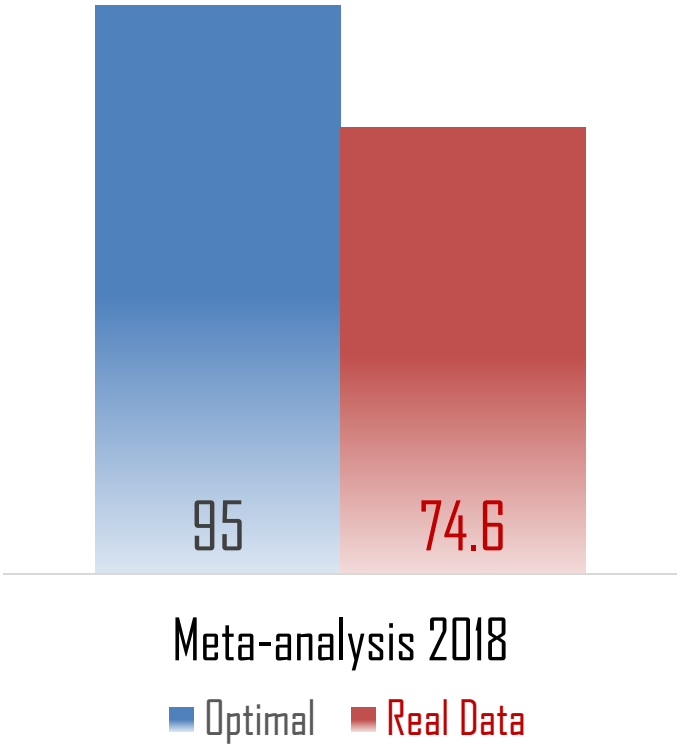


Su TH, et al. Expert Rev Gastroenterol Hepatol 2014; doi:10.1586/17474124.2015.960398.

Why do we want to stop NAs?

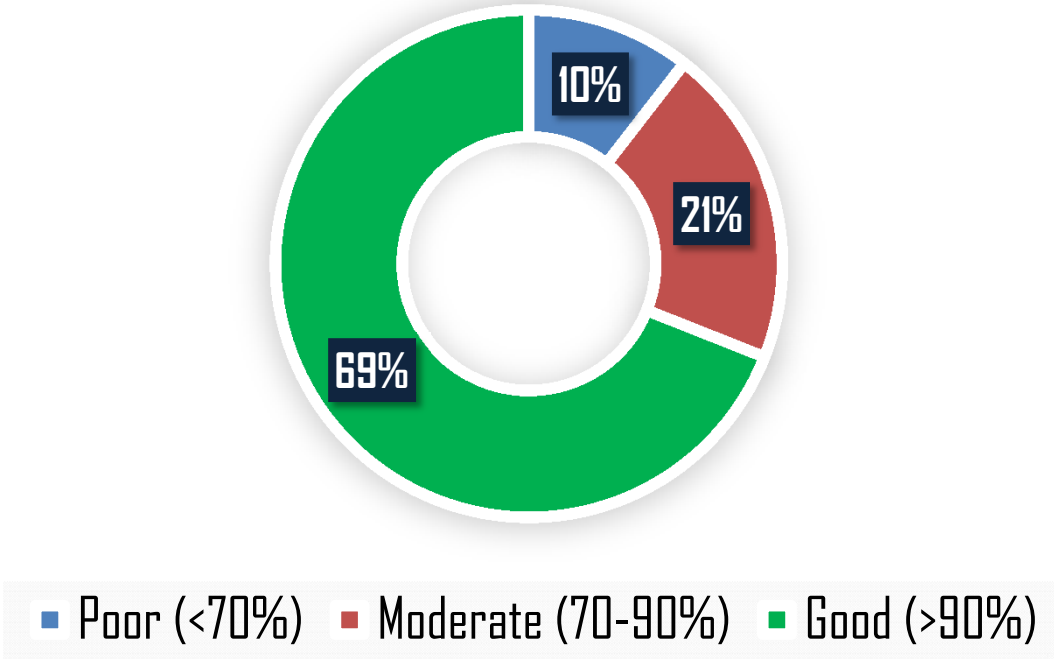


Adherence is Real Problems!



23,823 patients, 30 studies,
Median F/U time 16 mo

Ford N. Hepatol Commun. 2018;2:1160-1167.



894 treatment-naïve CHB patients received ETV
Korea, Median F/U time 5.2 years

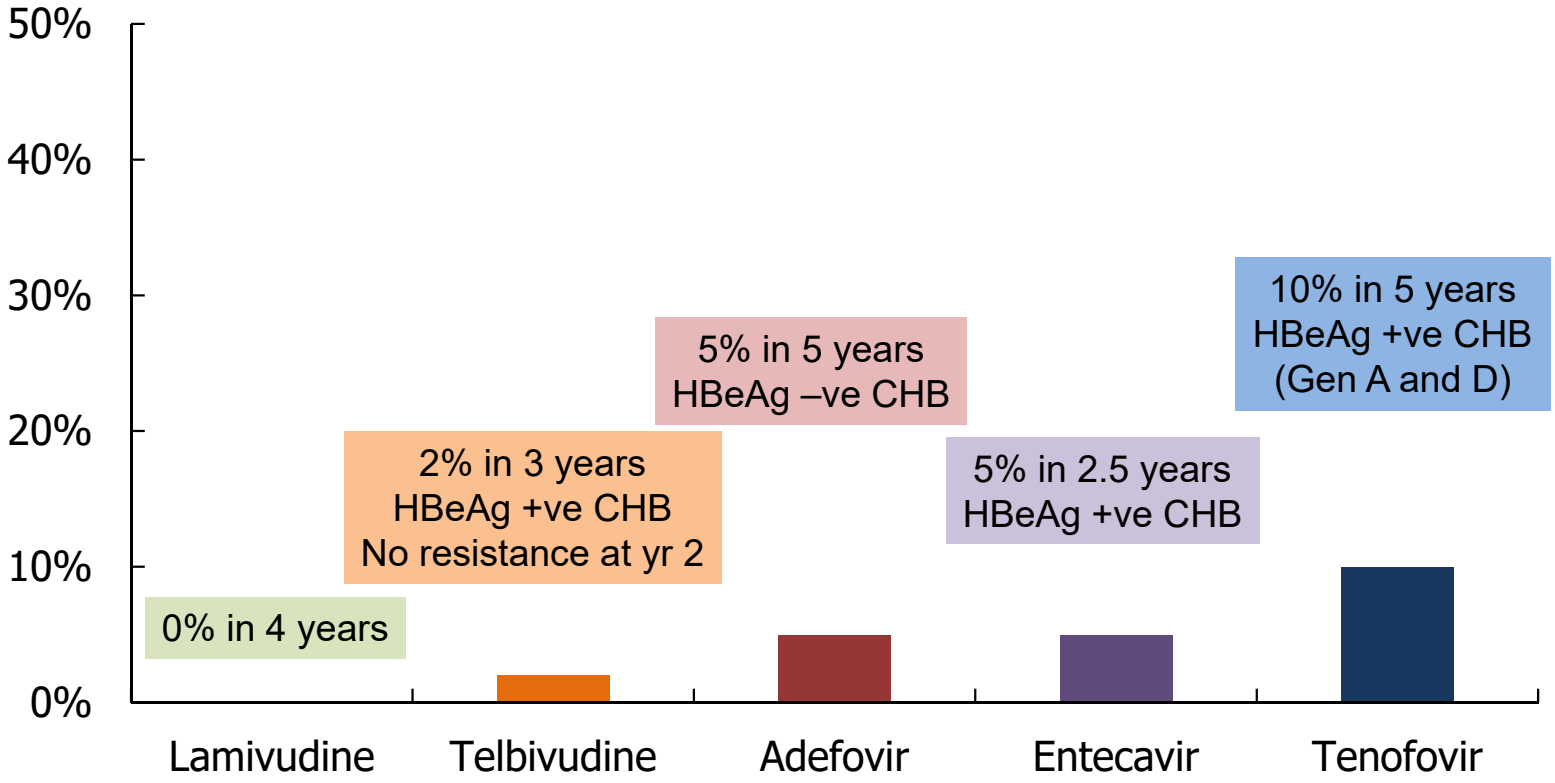
Shin JW. Am J Gastroenterol. 2018 Jul;113(7):998-1008.

NA treatment cessation recommendations in the current hepatitis B virus guidelines

Society	HBeAg(+)	HBeAg(-)	Cirrhosis
EASL (2017)	HBsAg clearance (safest) HBeAg seroconversion and HBV DNA undetectability with 6-12 mo of consolidation therapy	HBsAg clearance Selected patients with ≥ 3 yr virological suppression	Not recommended
AASLD (2016)	HBsAg clearance HBeAg seroconversion with at least 12 mo of persistently normal ALT levels and undetectable serum HBV DNA levels	HBsAg clearance	Not recommended
APASL (2016)	HBeAg seroconversion with undetectable HBV DNA and persistently normal ALT levels with 1-3 yr of consolidation therapy	HBsAg clearance After treatment for at least 2 yr with undetectable HBV DNA documented on 3 separate occasions, 6 mo apart	Could be considered in compensated cirrhosis with careful monitoring

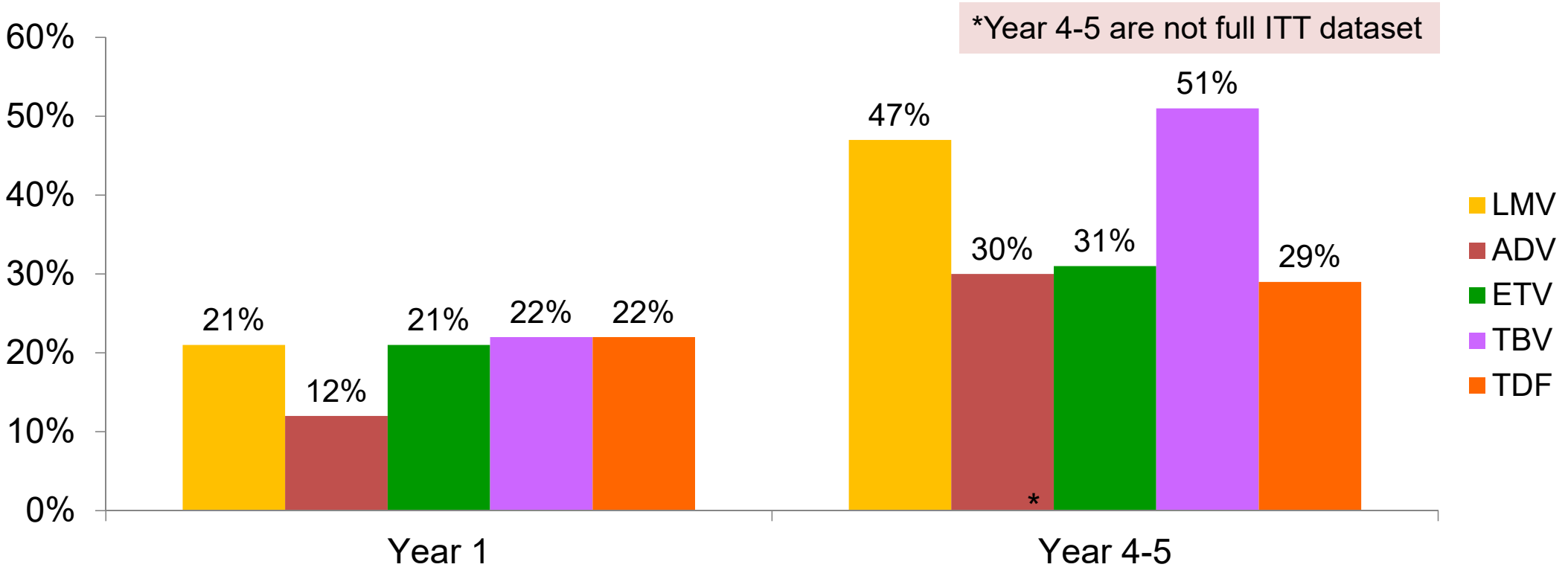
Terrault N, et al Hepatology 2016;63:261-83; EASL. J Hepatol 2017;67:370-98; Sarin S, et al. Hepatol Int 2016;10:1-98.

HBsAg clearance is the ideal treatment endpoint for NA, but it is difficult to achieve



Chang et al., JGH 2004; Hsu et al., APASL 2009;
Hadziyannis et al., Gastroenterol 2006;
Han et al., AASLD 2008, Marcellin et al., Lancet 2013

On-treatment HBeAg seroconversion by different antiviral drugs is low

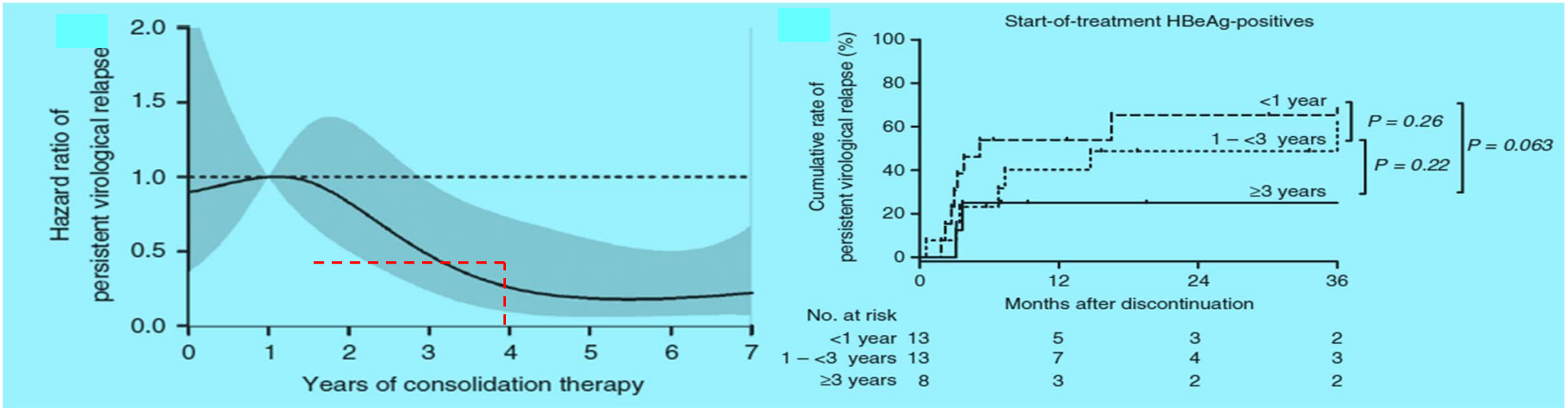


More than 60% of the NAs-treated patients need treatment more than 9 years

Chang et al., J Gastroenterol Hepatol 2004, Marcellin et al, Hepatology 2008
Han et al, AASLD 2008, Wang et al, AASLD 2009, Heathcote AASLD 2010

Extension of consolidation to >3 years can reduce risk of virological relapse in HBeAg+ve

- 35 HBeAg positive patients on NA x 2.5 (1.5-5.5) years with consolidation after HBeAg seroconversion for 1.1 (0.7-3.0) years
- Cumulative rate of virological relapse (HBV DNA >2000 IU/ml) = 63% in 1 year and 74% at 3 years

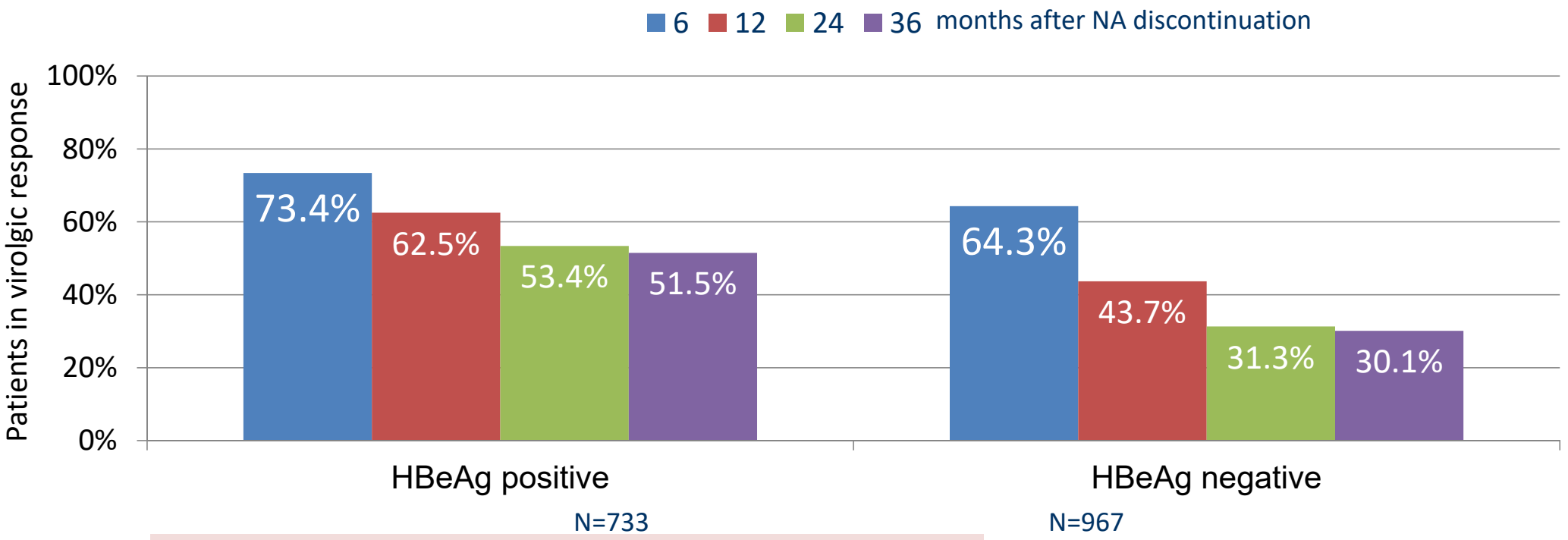


Chi H, et al. Aliment Pharmacol Ther 2015;41:867-76.

Consequence after NA cessation

Significant proportion of patients have relapse after discontinuation of NAs

- Pooled analysis of 25 studies among patients stopped NA
- HBeAg seroconversion in HBeAg positive and HBV DNA undetectable in HBeAg negative pts on NA

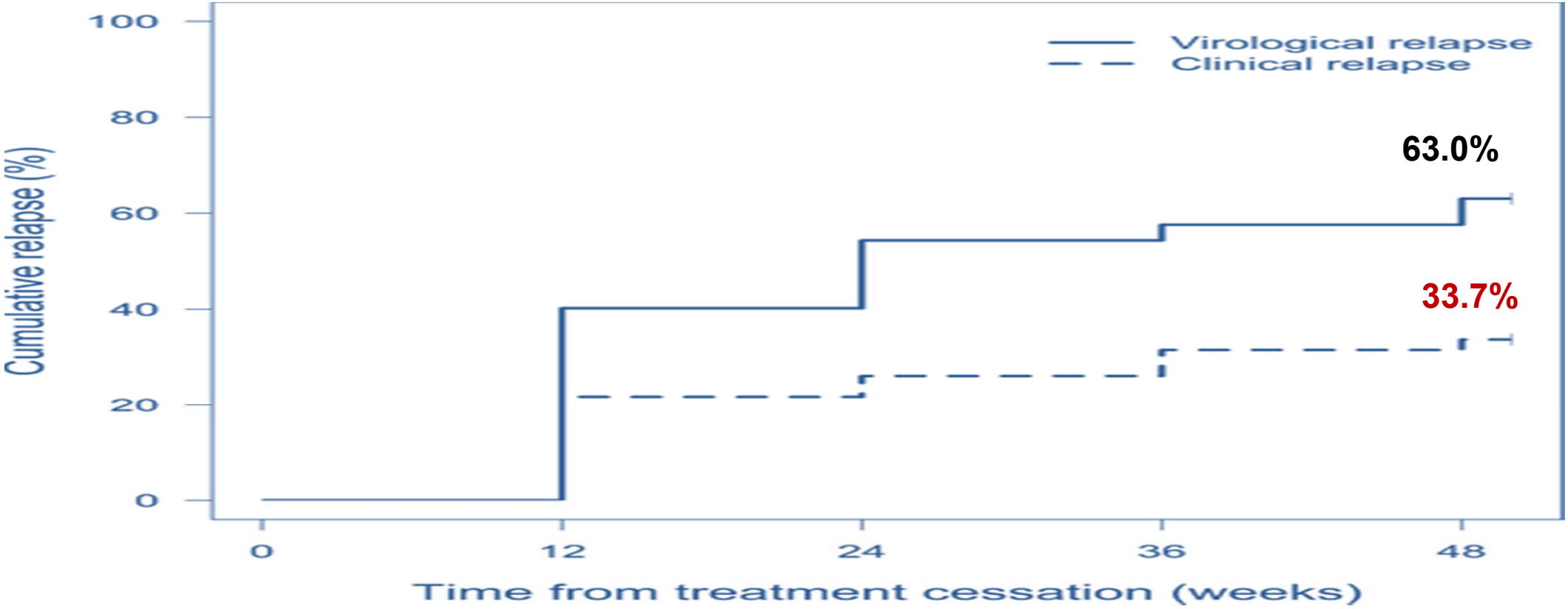


Post-treatment Virologic response = HBV DNA <20,000 IU/ml

Papatheodoridis G, et al. Hepatology 2016;63:1481-92

Relapse after NA discontinuation in Thai patients

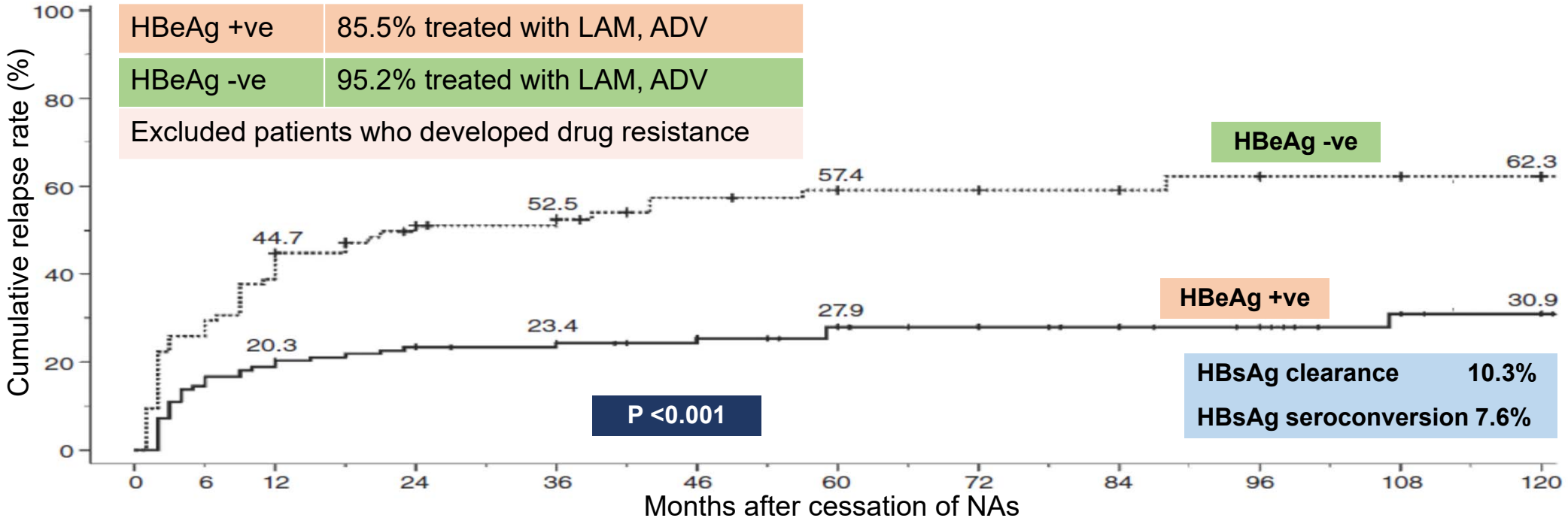
- **Single center at PSU, Thailand, non cirrhotic, both HBeAg+/-, APASL stopping criteria**



Kaewdech A. Piratvoisuth T. etal Liver Int. 2020

Cumulative relapse rates during10 years after NA cessation in patients with chronic hepatitis B

HBeAg +ve	85.5% treated with LAM, ADV
HBeAg -ve	95.2% treated with LAM, ADV
Excluded patients who developed drug resistance	



Virologic relapse defined as HBV DNA > 2,000 IU/ml.

Number of patients at risk of relapse

HBeAg (+)	138	118	112	100	86	70	56	46	40	20	23	21
HBeAg (-)	85	63	52	38	35	26	23	19	17	12	9	8

Liu F., et al. J Dig Dis. 2018 Sep;19(9):561-571.

Systemic review: Cessation of long-term NA therapy in HBeAg-negative CH-B

22 studies with a total of 1,732 patients

A 1-year virological relapse	<70%
An 1-year clinical relapse	<50% <30% if Baseline HBV DNA < $2x10^5$ IU/ml Consideration therapy > 18 months
Required retreatment	26-48%
Severe ALT flare	Rare
Hepatic decompensation	1 patient in 165 patients with cirrhosis

Virological relapse: HBV DNA > 2,000 IU/ml
Clinical relapse: HBV DNA > 2,000 IU/ml + ALT elevation

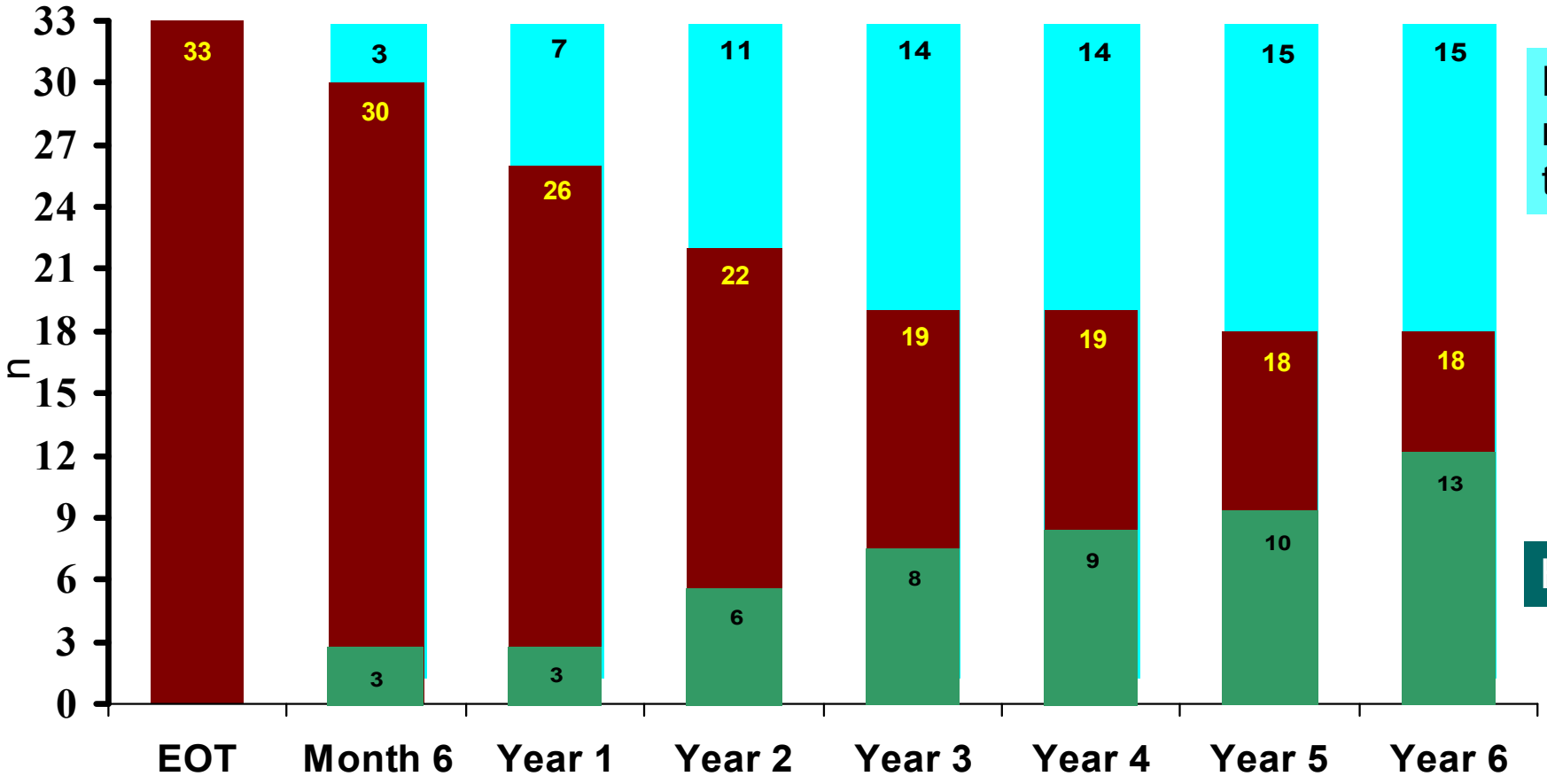
Chang ML., et al. Aliment Pharmacol Ther. 2015; 42.

Decompensation & Death after NA cessation

Study	Population	Median FU	Decompensation	Death	S-loss
Jeng 2018	**691** Taiwan 44.6% cirrhosis	~ 3 y	Annual incidence: **2.95% cirrhosis** **0% non-cirrhosis**	Annual incidence: **1% cirrhosis** **0% non-cirrhosis**	6%
Kuo 2019	**507** Taiwan 0% cirrhosis	~ 2 y ETV ~1+ y TDF	**1.58%** **non-cirrhosis**	**0%** **non-cirrhosis**	8% (e-neg)
Ma 2019	**535** Taiwan 0% cirrhosis	~ 1 y	**1.3%** **non-cirrhosis**	**0.19%** **non-cirrhosis**	1% (e-neg)

Hepatology. 2018 Aug;68(2):425-434. Aliment Pharmacol Ther. 2019 Jan;49(2):218-228. PLoS One. 2019 Oct 4;14(10):e0222221.

Sustained Responses and Loss of HBsAg in HBeAg-Negative Patients With Chronic Hepatitis B Who Stop Long-Term (4-5 years) Treatment With Adefovir

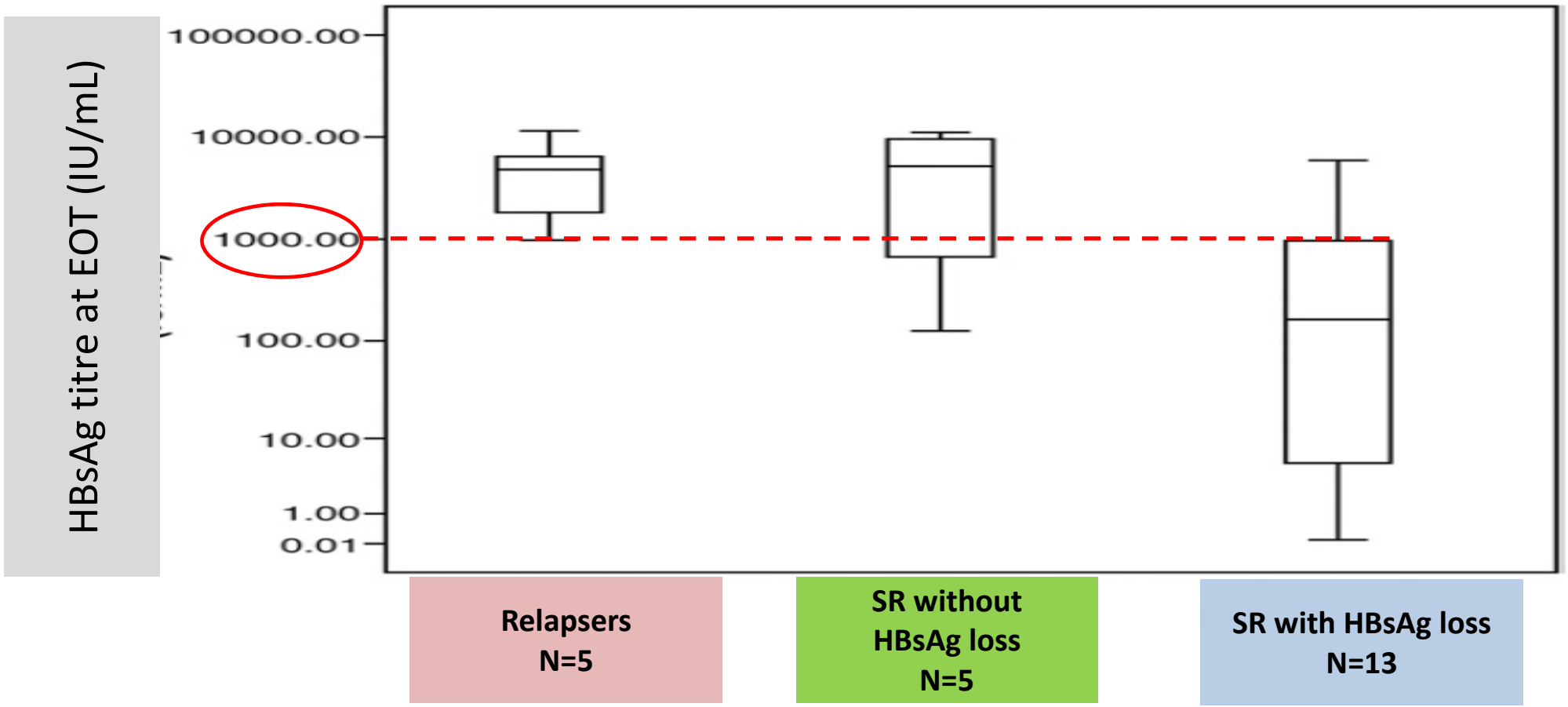


Relapsers who received antiviral therapy 45%

HBsAg loss 39%

Hadziyannis SJ., et al. Gastroenterology 2012;143:629–636.

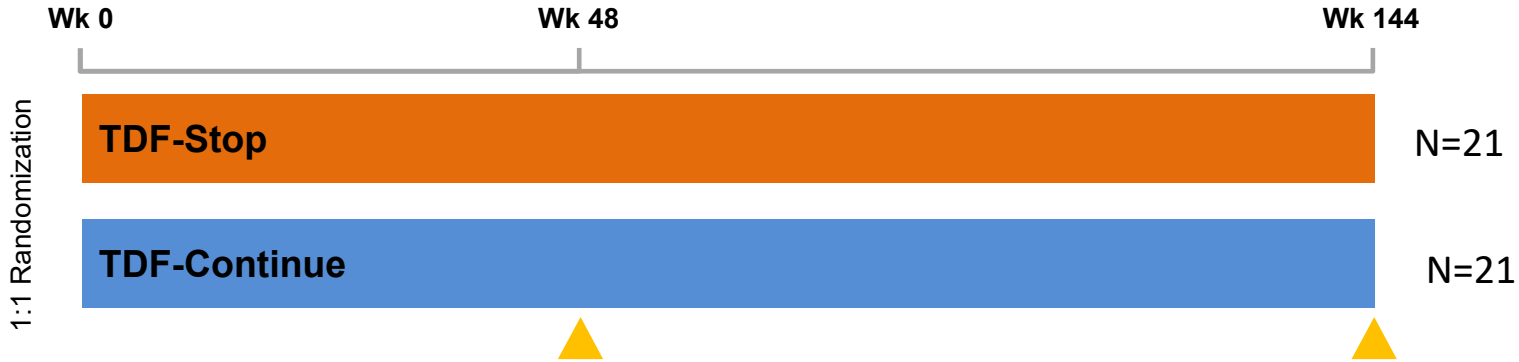
4-5 years ADV for naïve HBeAg (-) patients : EOT HBsAg titres and long-term sustained response patterns



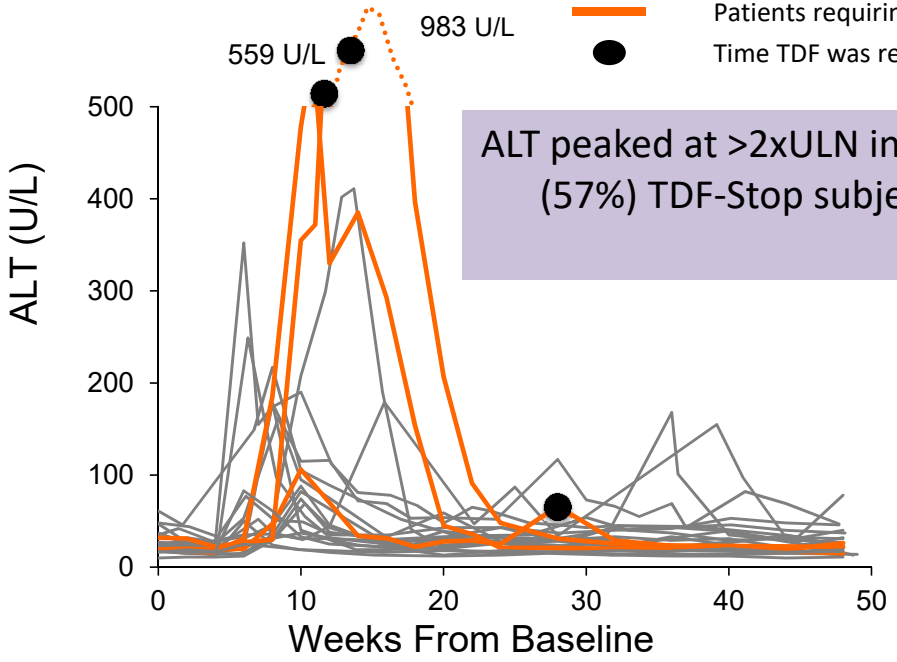
Hadziyannis S et al. Gastroenterology 2012;143:629-36

Multi-center study in Europe

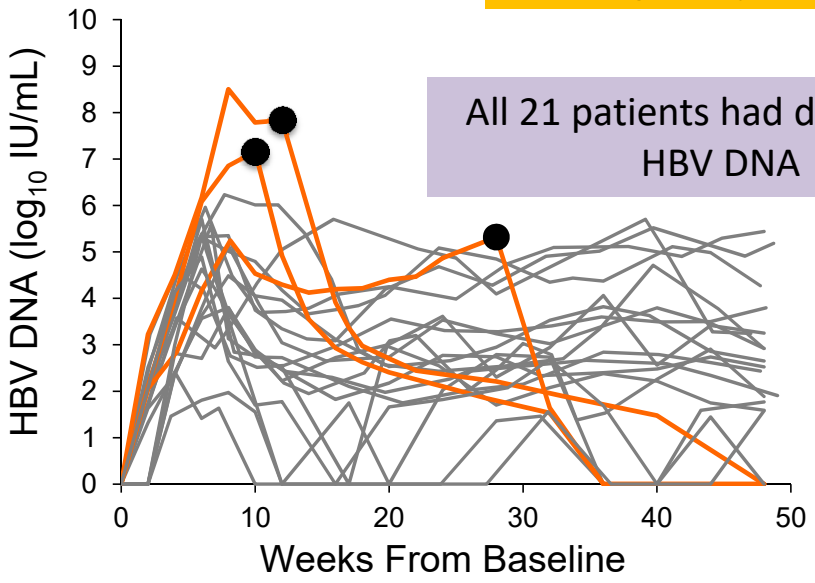
CHB patients
- **HBeAg-negative**
- **≥4 years TDF therapy**
- **HBV DNA UD >3.5 yrs**
- **No cirrhosis**



Primary endpoint:
HBsAg loss by Week 144



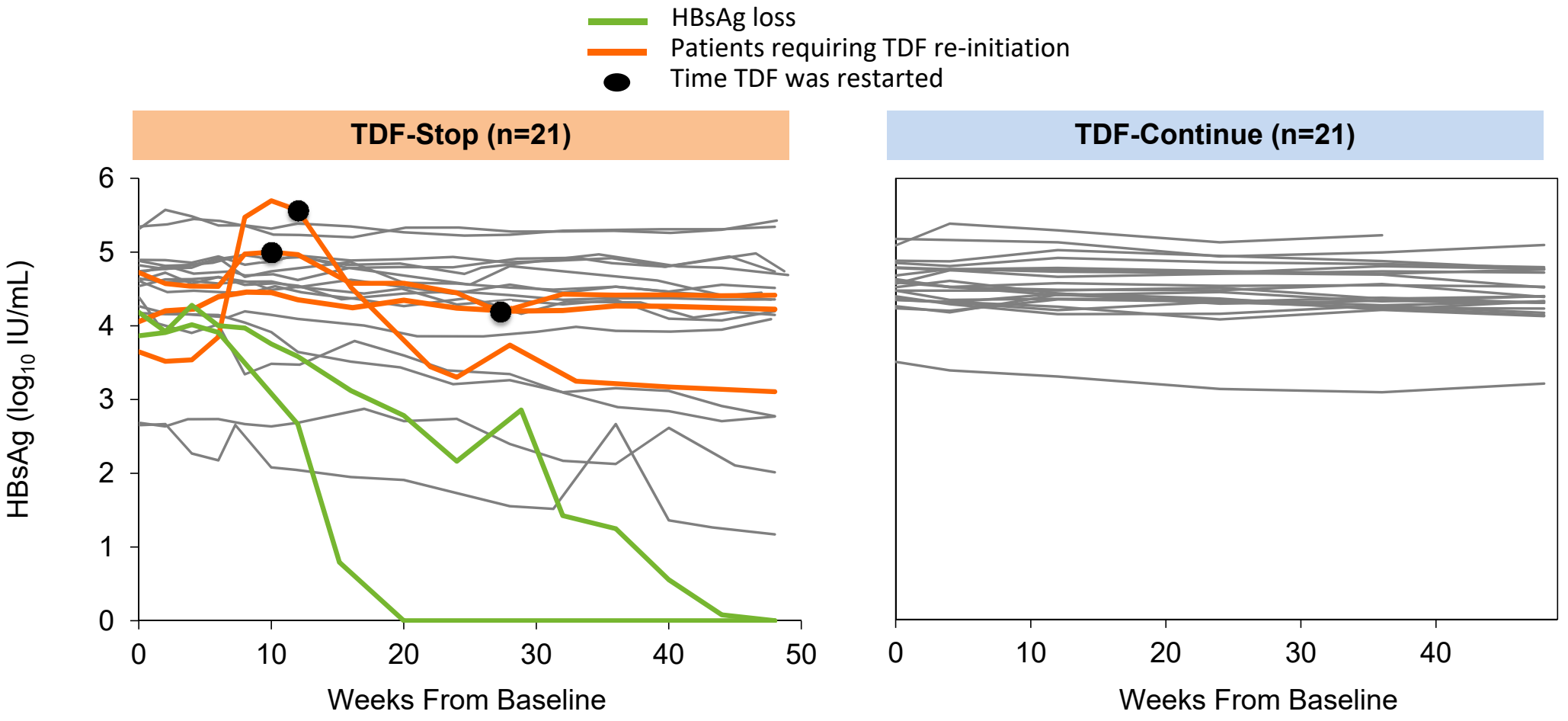
ALT peaked at >2xULN in 12/21 (57%) TDF-Stop subjects



All 21 patients had detectable HBV DNA

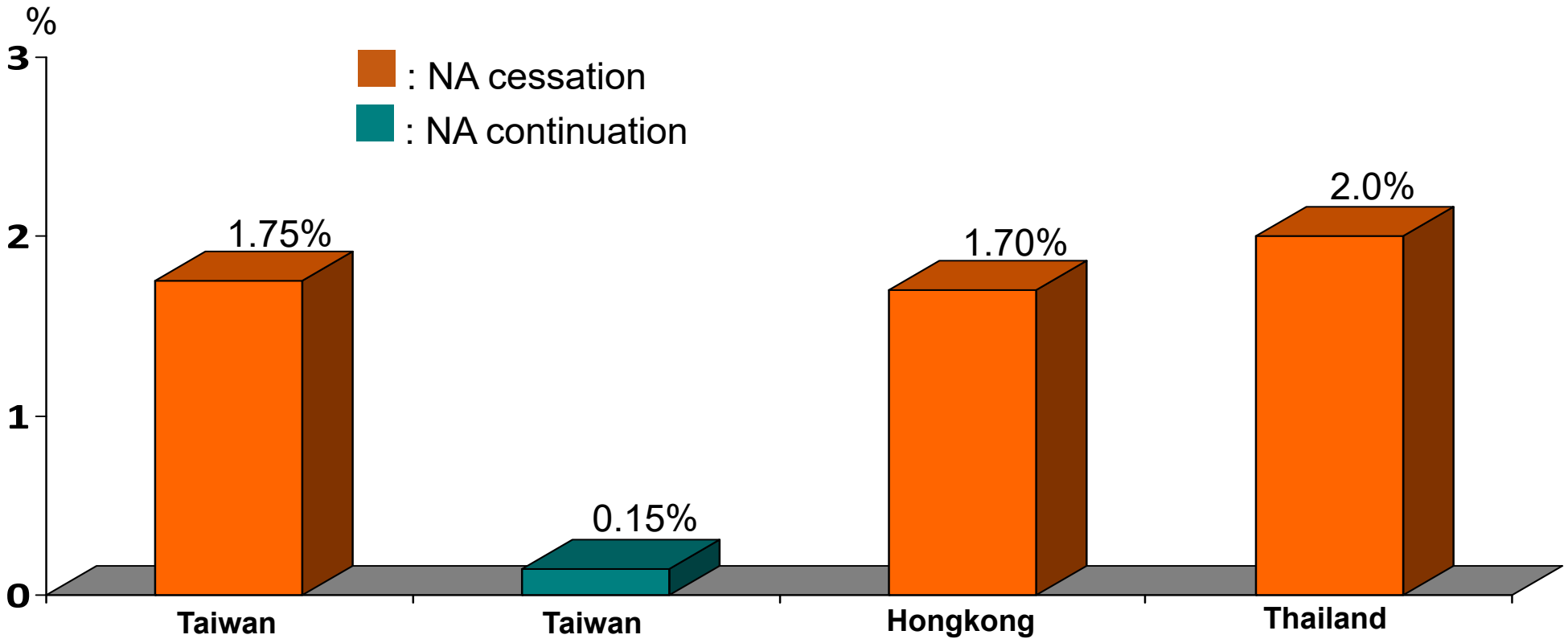
Berg T, et al. EASL 2015

Profound HBsAg decline in TDF stop group



Berg T, et al. EASL 2015

Annual incidence of HBsAg clearance is higher in NA discontinuation



Jen WJ. et al. Hepatologey 2018; 68

Wong GH. et al. Liver Int. 2020; 40

Kaewdech A. Piratvisuth T. et al. Liver Int 2020.

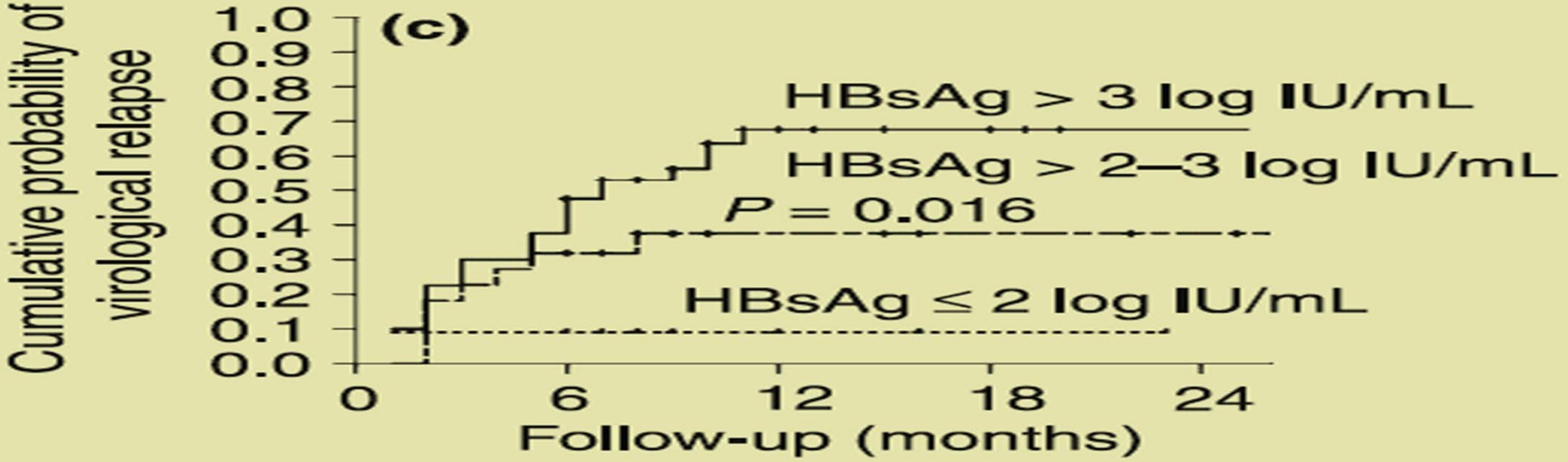
Factors and biomarkers for predicting sustained response after NA discontinuation in CH-B treatment

Factor	NA discontinuation
Sex	Female predicts sustained response
Age	Older is correlated to higher relapse
NA treatment duration	Extended therapy is with lower relapse rate
ALT	ALT is controversial
HBV DNA	Lower baseline HBV DNA, lower relapse rate
qHBsAg	Low qHBsAg predicting sustained response

Chen CH. et al. J Hepatol. 2014;61:515–522.; Papatheodoridis G. et al. Hepatology. 2016;63:1481–1492; Liu F. et al. J Gastroenterol Hepatol. 2011;26:456–460.; HA M. et al. Arch Virol. 2012;157:285–290.; Nagaoka S. et al. Hepatol Res. 2016;46:E89–E99.; Jeng WJ. et al. Hepatology. 2013;58:1888–1896.; Cao J. et al. J Infect Dis. 2017; 215:581-589.

qHBsAg level is associated with relapse rate after NUC treatment discontinuation

84 CHB patients (49% HBeAg positive, 69 pts treatment naïve) were treated with anti-viral agents (lamivudine, adefovir, entecavir)and stopped the treatment according to the recommendations of the APASL*

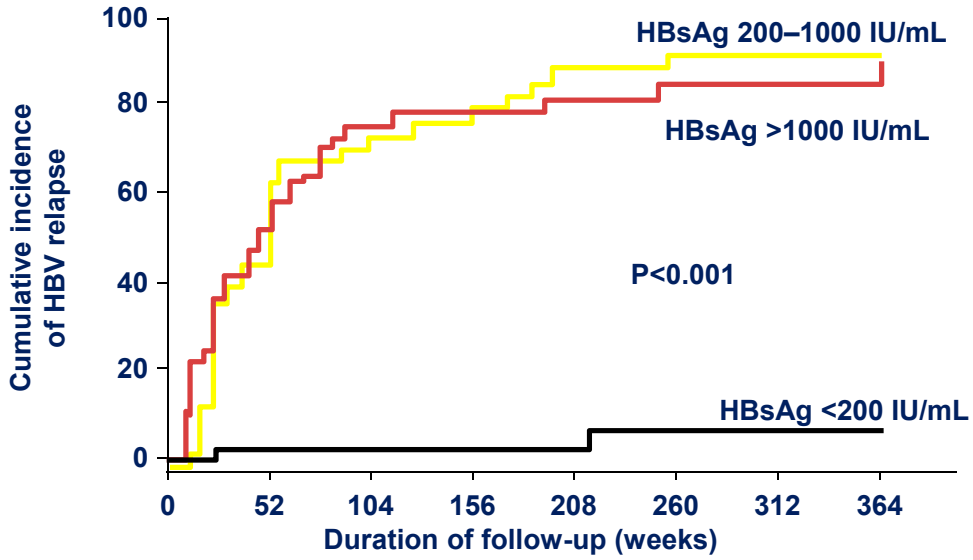


*anti-viral agent was stopped in HBeAg-positive patients when HBeAg seroconversion with undetectable HBV DNA was documented on two separate occasions at least 6 months apart. In HBeAg-negative patients, treatment discontinuation would be considered if undetectable HBV DNA has been documented on three separate occasions 6 months apart.

Liang Y. et al. Aliment Pharmacol Ther. 2011; 34: 344-52.

qHBsAg predicts HBsAg loss and HBV relapse after LAM discontinuation in HBeAg-ve

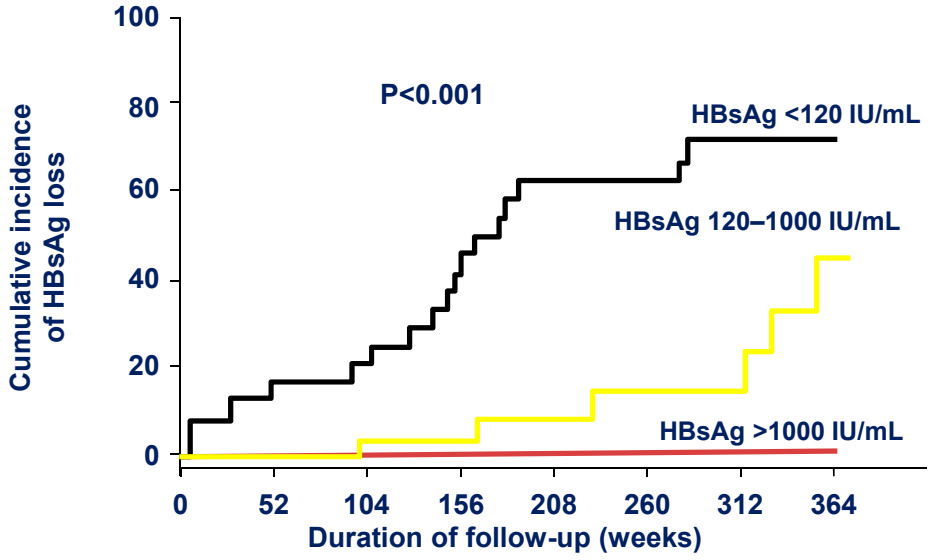
Virological relapse*



No. at risk HBsAg (IU/mL)

>1000	39	19	10	8	7	5	2	1
200–1000	36	19	9	7	4	3	3	1
<200	30	29	28	25	20	16	10	9

HBsAg loss



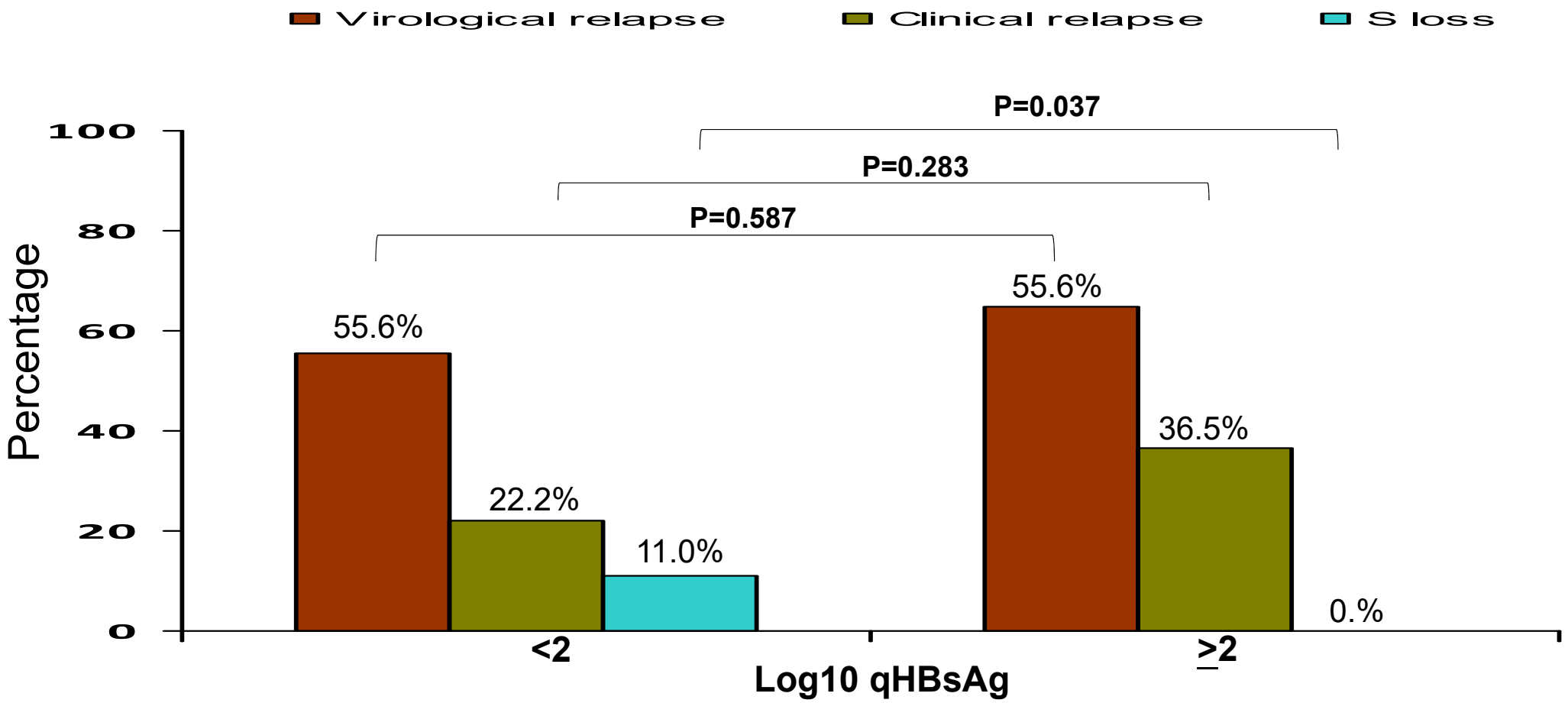
No. at risk HBsAg (IU/mL)

<120	24	20	19	14	9	8	4	4
120–1000	42	31	24	20	16	10	8	4
>1000	39	35	26	21	17	14	8	2

Chen CH, et al. J Hepatol 2014; doi.org/10.1016/j.jhep.2014.04.029 (epub ahead of print)

*defined as serum HBV DNA >2,000 IU/mL in 2 measurements at least 3 months apart

qHBsAg at EOT did not predict sustained response, but it's associated with HBsAg loss



Kaewdech A. Piratvisuth T. et al. Liver Int 2020.

EOT HBsAg Levels for prediction of HBsAg loss after NA cession

Author	Year	EOT HBsAg (IU/mL)	N	HBsAg loss (HBeAg –ve)
Chen	2014	<120 120-1,000 >1,000	24 42 39	79.2% 14.3% 0
Jeng	2017	<100 100-499 ≥500	114 274 303	21.1% 4.4% 2.3%
Yao	2017	≤50 51-100 101-150 151-200	45 23 22 29	55.6% 65.2% 31.8% 20.7%

Liu J, Li T, Zhang L, Xu A. Hepatology. 2019;70:1045–1055

Biomarkers for predicting safety NA-treatment discontinuations in patients with CHB

Virological parameters

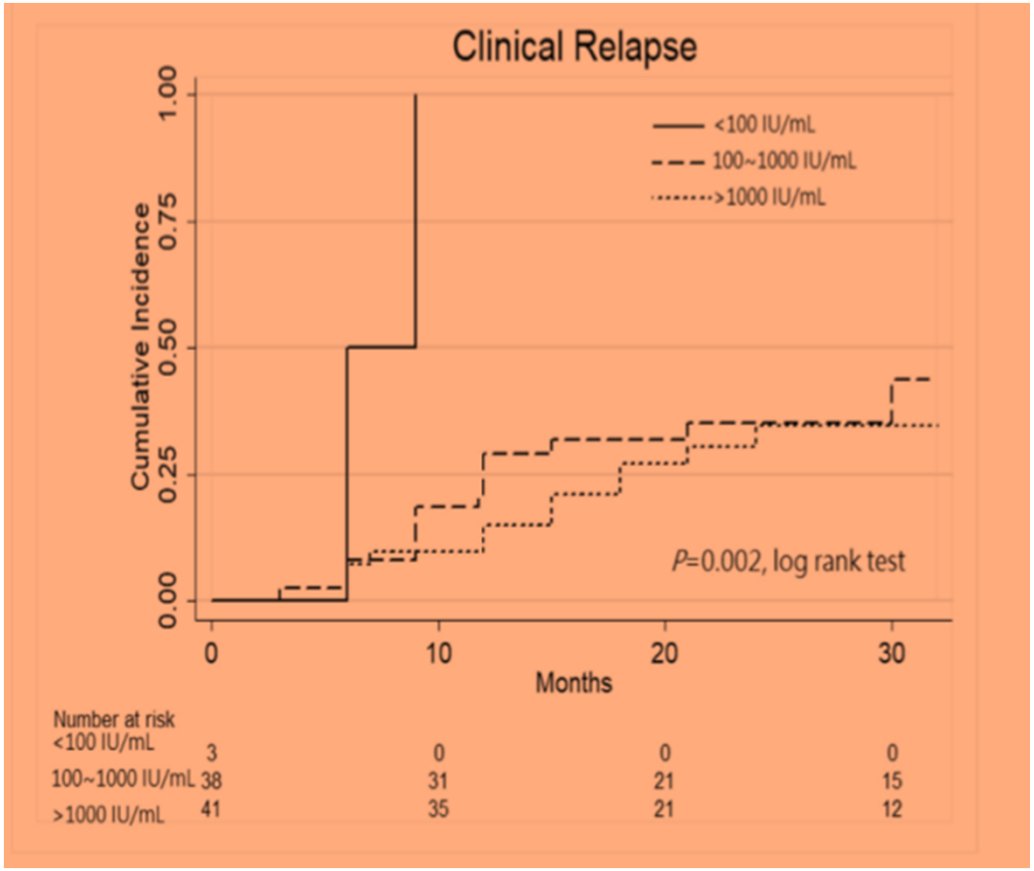
- AntiHBc
- HBV RNA
- HBcrAg

Immunological parameters

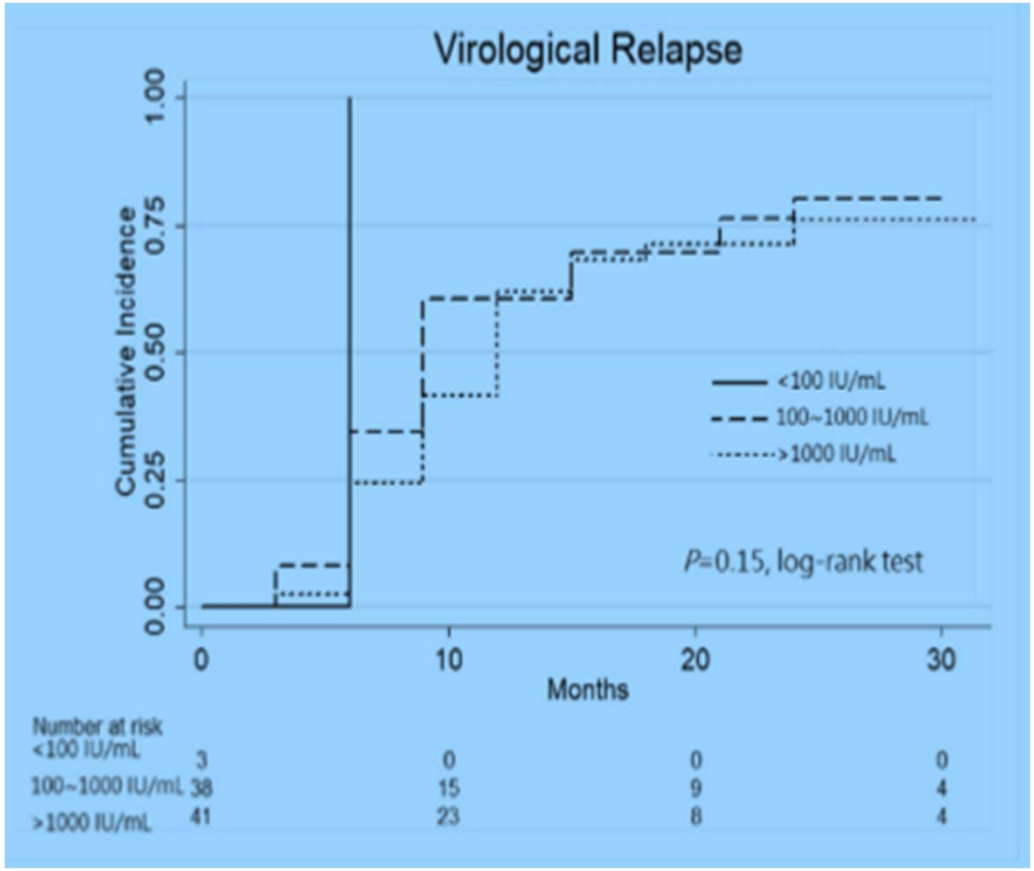
- HBV specific CD8 T cell
- PD-1 expression
- NK cell expression
- Cytokine profiles
- IP-10, IL-10

Moreno-Cubero E., et al. World J Gastroenterol 2018; 24(17): 1825-1838

Clinical relapse according to anti-HBc levels after NA discontinuation

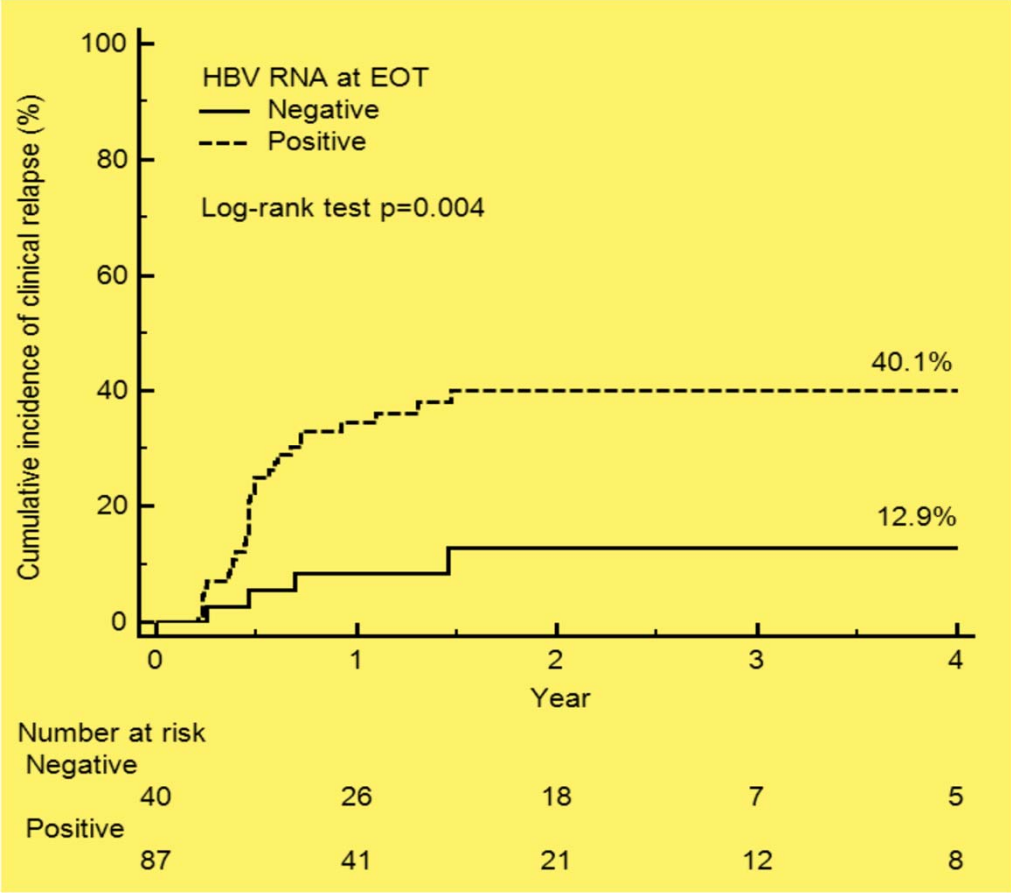


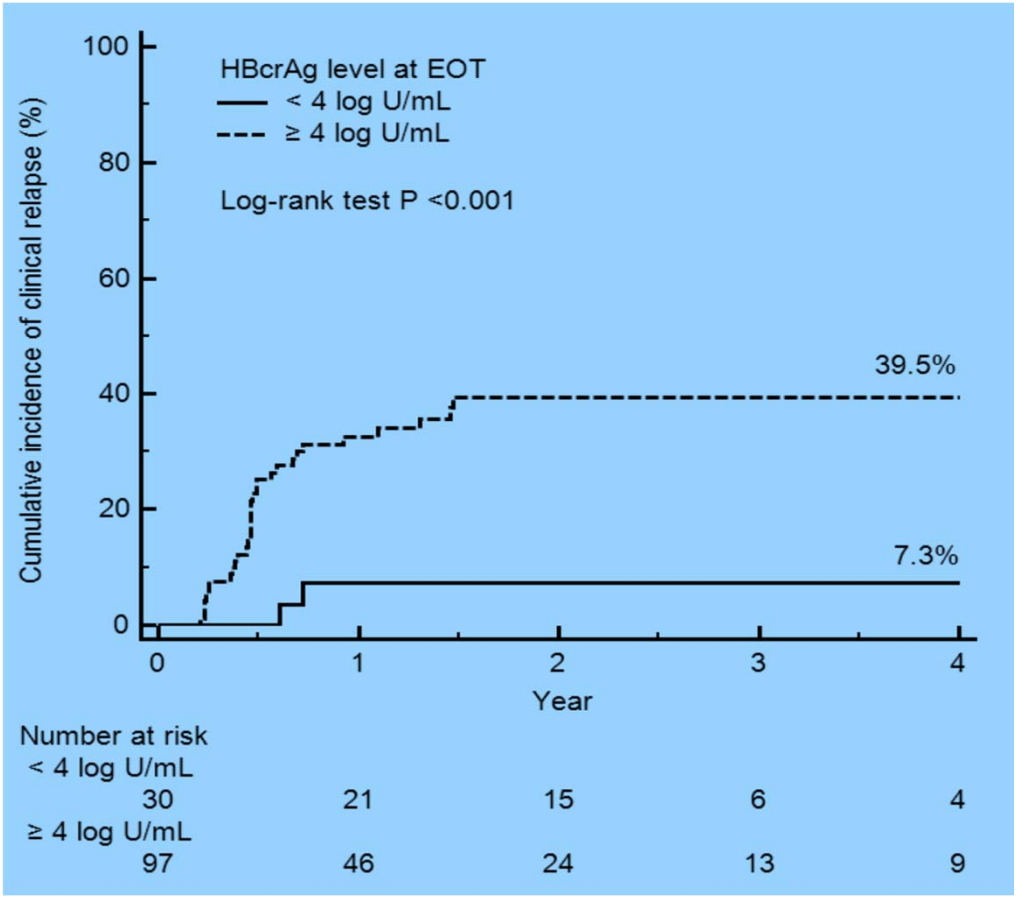
Virological relapse according to anti-HBc levels



Tseng CH. Et al., J Formos Med Assoc 2018 Oct;117(10)_915-921

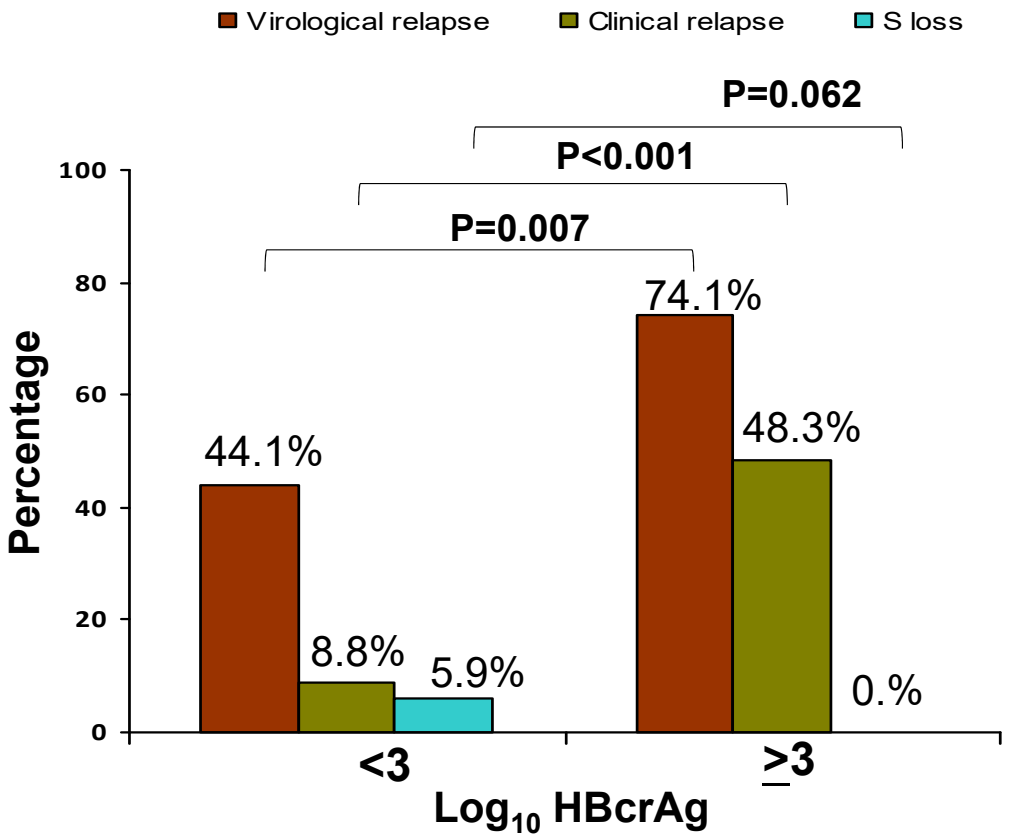
Cumulative incidences of clinical relapse after NA discontinuation stratified by HBV RNA and HBcrAg

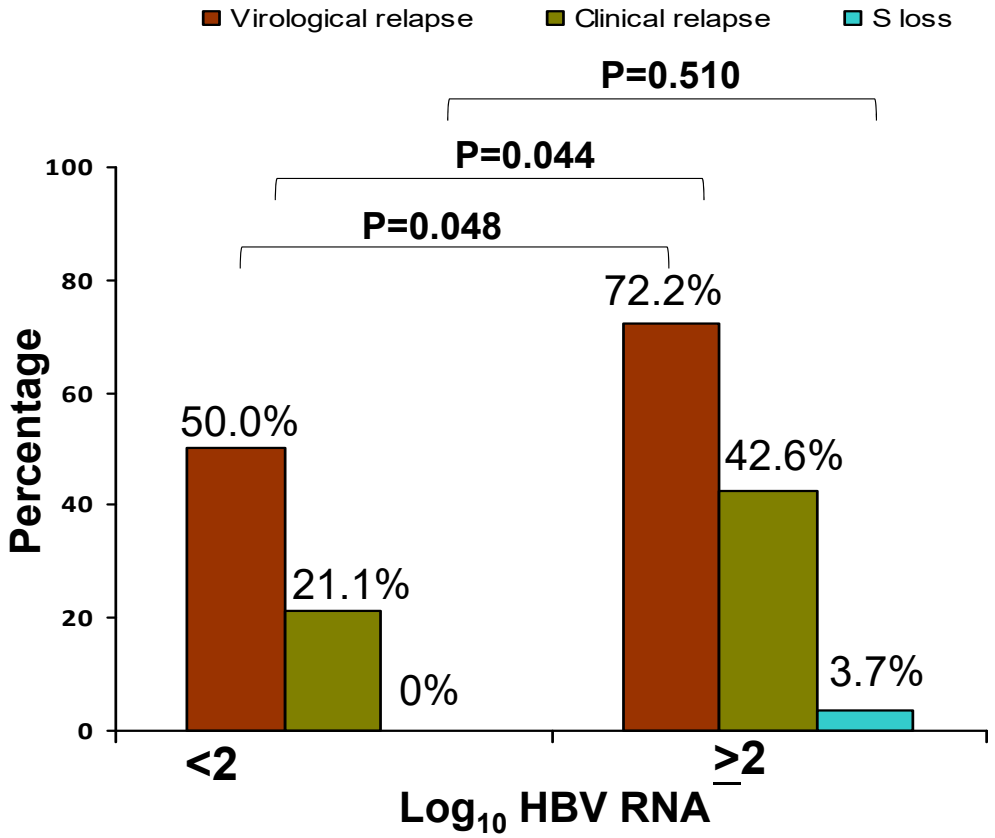




Fan R. et al. J Infectious 2020.

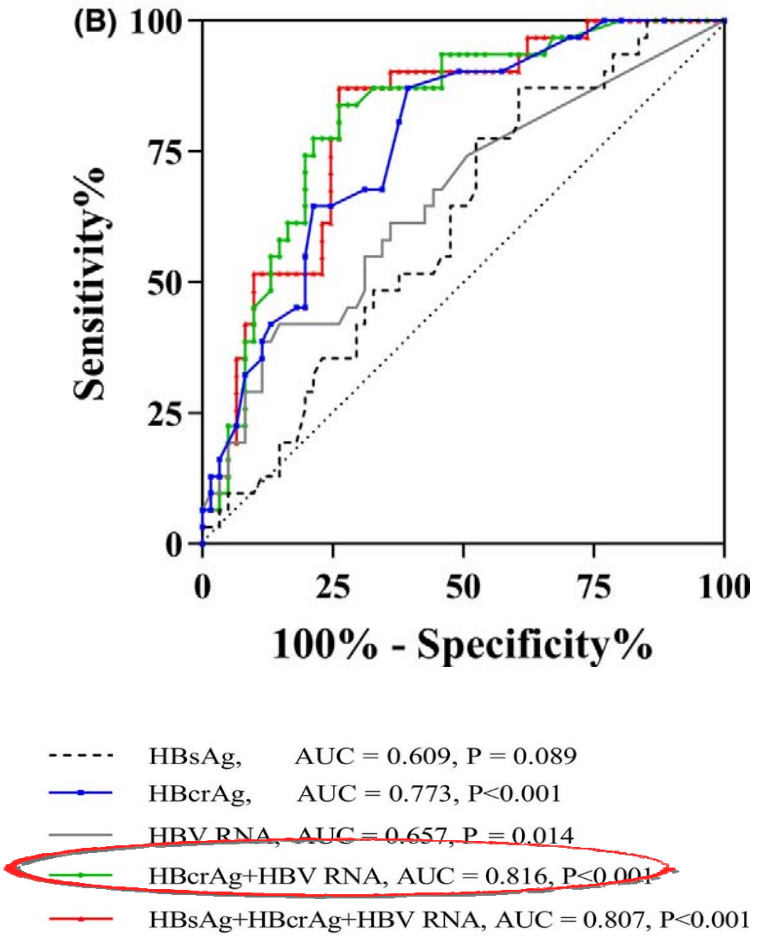
HBcrAg and HBV RNA for prediction of relapse after NA cessation in CHB





Kaewdech A. Piratvisuth T. et al. Liver Int 2020.

Combined HBcrAg + HBV RNA for prediction of Clinical Relapse



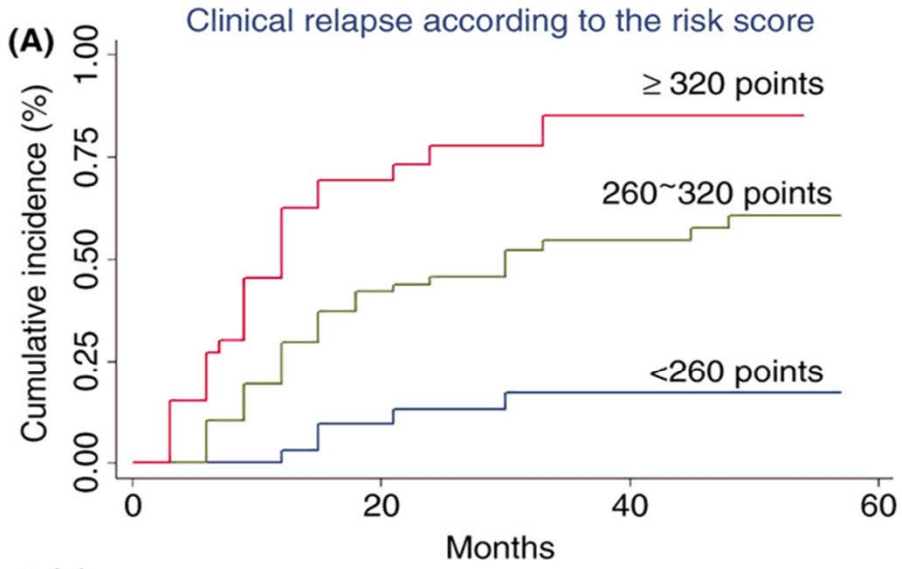
Biomarkers and cutoff values	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Log_{10} **HBcrAg** (3.0 U/mL) and log_{10} **HBV RNA** (2.0 copies/mL)	100.0	23.0	39.7	100.0
Log_{10} **HBcrAg** (3.0 U/mL), log_{10} **HBV RNA** (2.0 copies/mL) and log_{10} **qHBsAg** (2.0 IU/mL)	100.0	6.6	35.2	100.0

Kaewdech A. Piratvisuth T etal Liver Int. 2020 .

SCALE-B To Predict Clinical Relapse

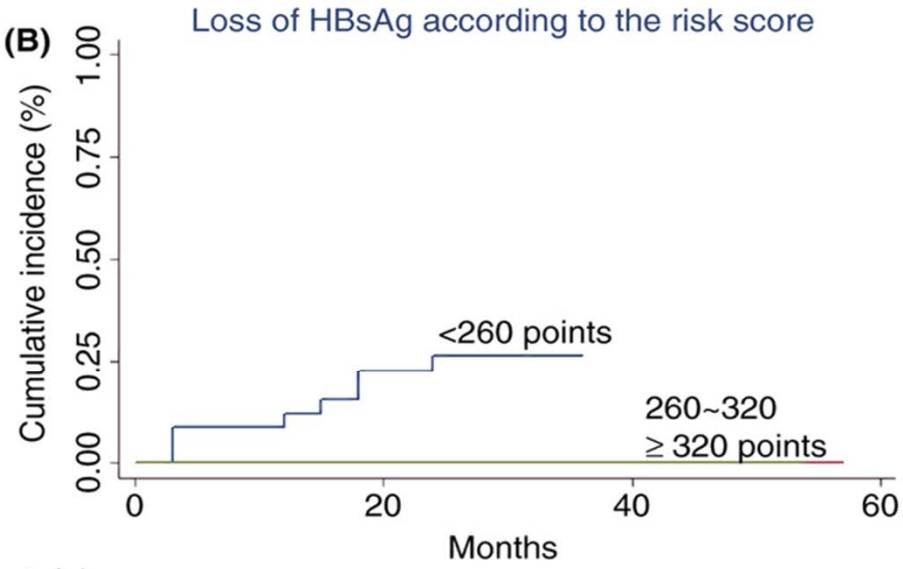
S urface antigen
C ore-related antigen
A ge
AL T
tE nofovir
for HB V

35*HBsAg (log IU/mL) + 20*HBcrAg (log U/mL) + 2*age (year) + ALT (U/L) + 40 for tenofovir use



Number at risk

<260 points	34	26	15	3
260~320 points	68	34	15	2
≥ 320 points	33	8	1	0



Number at risk

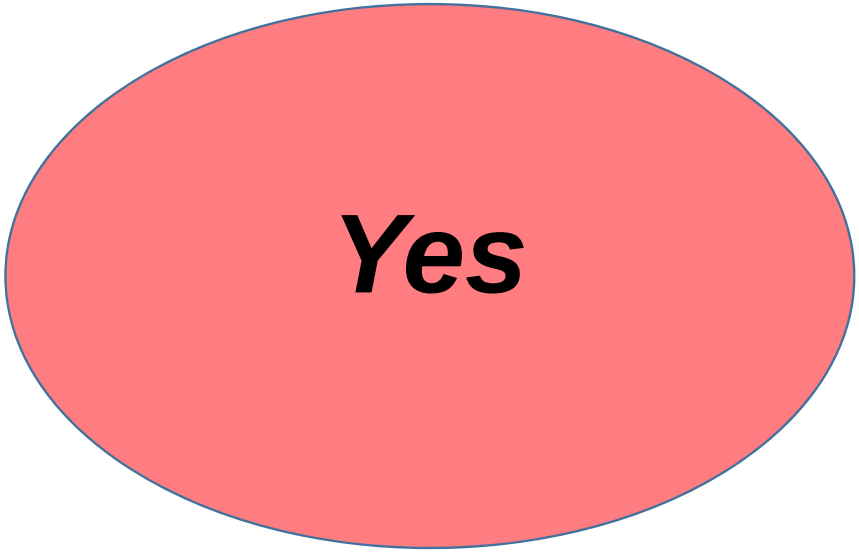
<260 points	34	22	0	0
260~320 points	68	36	7	1
≥ 320 points	33	11	2	0

Hsu Y-C, et al. Aliment. Pharmacol. Ther. 2019;49:107–115

Conclusion

- Although long term NA therapy for chronic hepatitis B can suppress HBV DNA and improve serological and clinical outcomes, but it also leads to poor compliance, increased cost and long term side effects
- NA cessation results in virological and clinical relapse, but severe hepatitis flare leading to decompensation and death is rare
- NA cessation could improve sustained HBV response including HBsAg clearance

Should we stop long term nucleoside analogue therapy?



The recommended strategy for cessation of NA therapy in CHB

Consider cessation of NA therapy

NA therapy > 2 years without genotypic resistance, with consolidation therapy > 1-2 years, compensated liver

Safe cessation by using biomarkers for prediction of sustained response

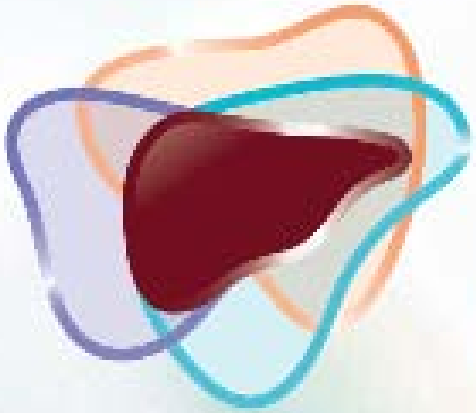
Virological and Immunological markers

Off-therapy follow-up

1. monitor monthly in the first 3 months, every 3-6 months afterward for 1-2 years, and every 6 months afterward. HBV DNA every 3 months for 1-2 years and then when indicated.
2. Weekly or biweekly follow-up of ALT, bilirubin and prothrombin time in relapses with rising ALT or ALT > 5X ULN.

NA re-treatment

1. Impending or overt hepatic decompensation
2. Persistent ALT elevation or repeated clinical relapses or high risk for disease progression
3. Under risk of HBV reactivation (eg. Immunosuppression or chemotherapy)



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COLLABORATION AND CURE

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Thank you