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Controversies in CHB Treatment

Henry LY Chan, MD, FRCP (Edin, Lond), FAASLD
Director, Center for Liver Health
Associate Dean (External Affairs), Faculty of Medicine
The Chinese University of Hong Kong

Achieved by current first-line antiviral therapy (ETV/TDF/TAF)

- Once daily oral medicine with almost no side effect
- Potent viral suppression with minimal/no risk of drug resistance
- Histologic improvement and regression of liver cirrhosis
- Reduction in risk of HCC
- Improved patient survival

Controversies remains…

1. Immune tolerant patients – treat or observe?
2. Inactive carriers – do they exist?
3. Stopping NA before HBsAg loss – is it feasible?
4. Functional cure – is it needed?

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Immune tolerant patient

Treat or Observe?

Arguments towards treating patients in immune tolerant phase

1. High HBV DNA = high HCC risk

2. Missed patients with silent immune clearance with liver injury?

3. Current treatments are safe and effective

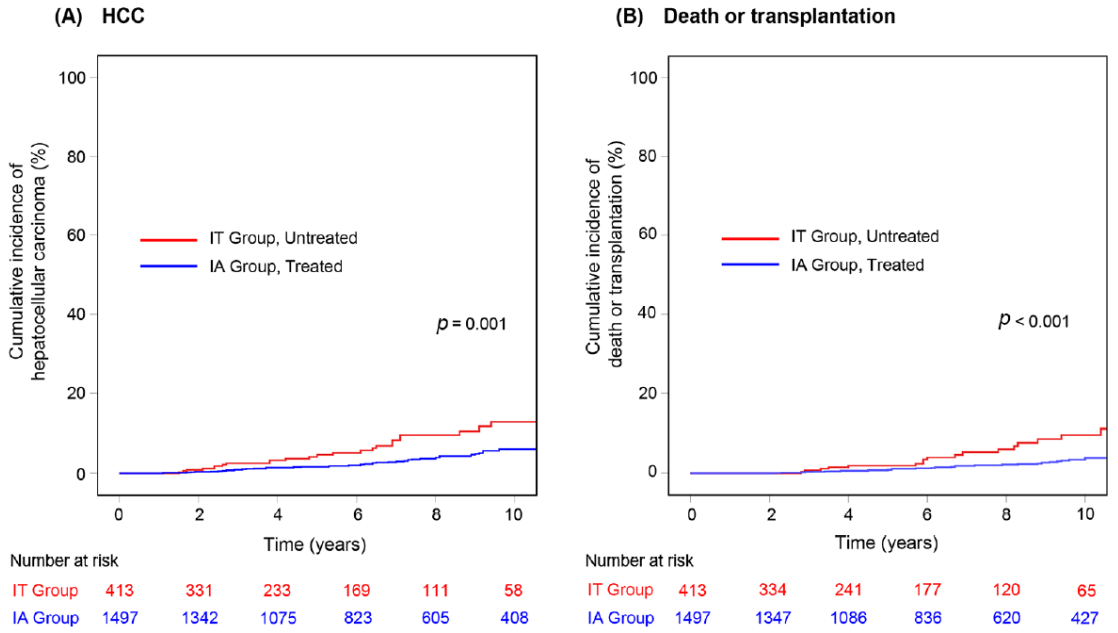
REVEAL-HBV cohort

- 3653 Taiwanese patients followed for 11.4 years
- Increased risk of HCC with HBV DNA level >2000 IU/ml
- Age <30 = 0%, 30-39 = 33%
- HBeAg positive = 15%
- ALT normal (<45 U/L) = 94%
- Liver cirrhosis = 2%

- Most patients were older HBeAg-negative inactive CHB but NOT immune tolerant patients

Chen CJ et al. *JAMA*. 2006;295:65-73

Immune tolerant patients have more HCC and higher mortality?



413 immune tolerant (IT) patients with no treatment vs 1497 immune active (IA) patients on NA based on virology and biochemistry (no fibrosis assessment)

? Immune clearance patients misclassified in IT group

- Mean age 38 years old
- 26% had HBV DNA 4-7 log IU/ml
- Higher HBV DNA associated with lower risk of HCC (aHR 0.63) and death/transplantation (aHR 0.73)

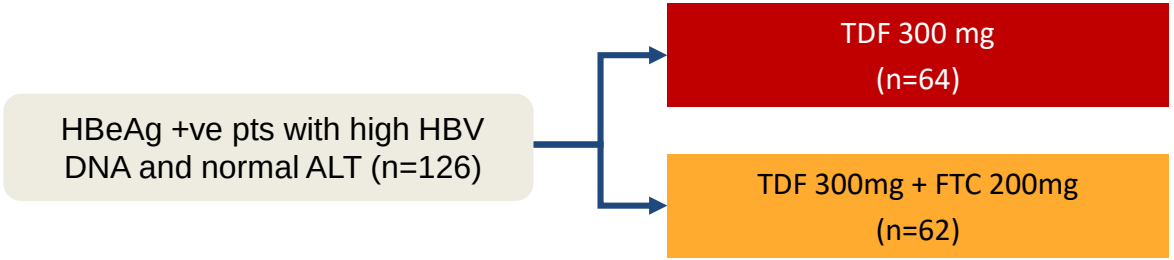
Kim GA, et al. Gut 2018;67:945-52.

Liver fibrosis assessment for advanced fibrosis in HBeAg positive patients to consider antiviral therapy

AASLD 2018	APASL 2016	EASL 2017
Age >40 HBV DNA >20,000 ALT > ULN but <2x ULN	**Age > 35** ALT 1-2x ULN FH of HCC/cirrhosis	**Age > 30** ALT normal FH of HCC/cirrhosis

Terrault N, et al. Hepatology 2018;67:1561-99; Sarin S, et al. Hepatol Int 2016;10:1-98; EASL. J Hepatol 2017;67:370-98

Ineffective antiviral treatment for immune tolerant patients



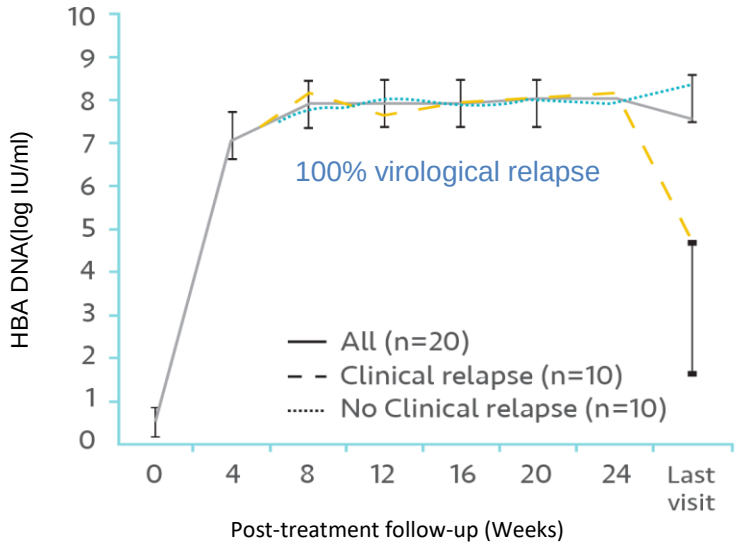
Response = HBV DNA < 69 IU/ml at week 192

	TDF n=64	TDF/FTC n=62	p-value
Primary endpoint			
HBV DNA <69 IU/mL	55%	76%	0.016
Secondary endpoints			
HBeAg seroconversion	5%	0%	0.244
HBsAg loss	0%	0%	

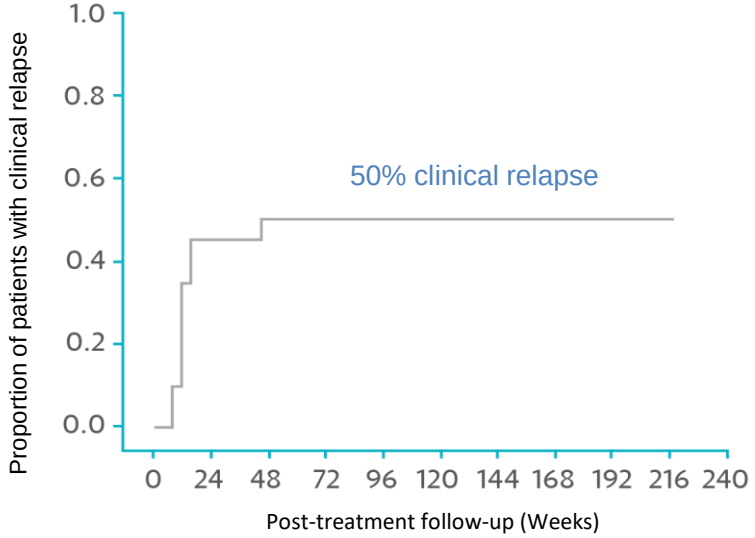
Chan HL, et al. Gastroenterology 2014;146:1240-8

High rate of relapse after cessation of TDF in immune-tolerant CHB patients

Virological relapse
HBV DNA >2,000 IU/ml



Clinical relapse
HBV DNA >2,000 IU/ml
ALT > 2x ULN



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Wong VW, … Chan HL. J Clin Gatroenterol 2018;52:347-52.

Inactive carriers

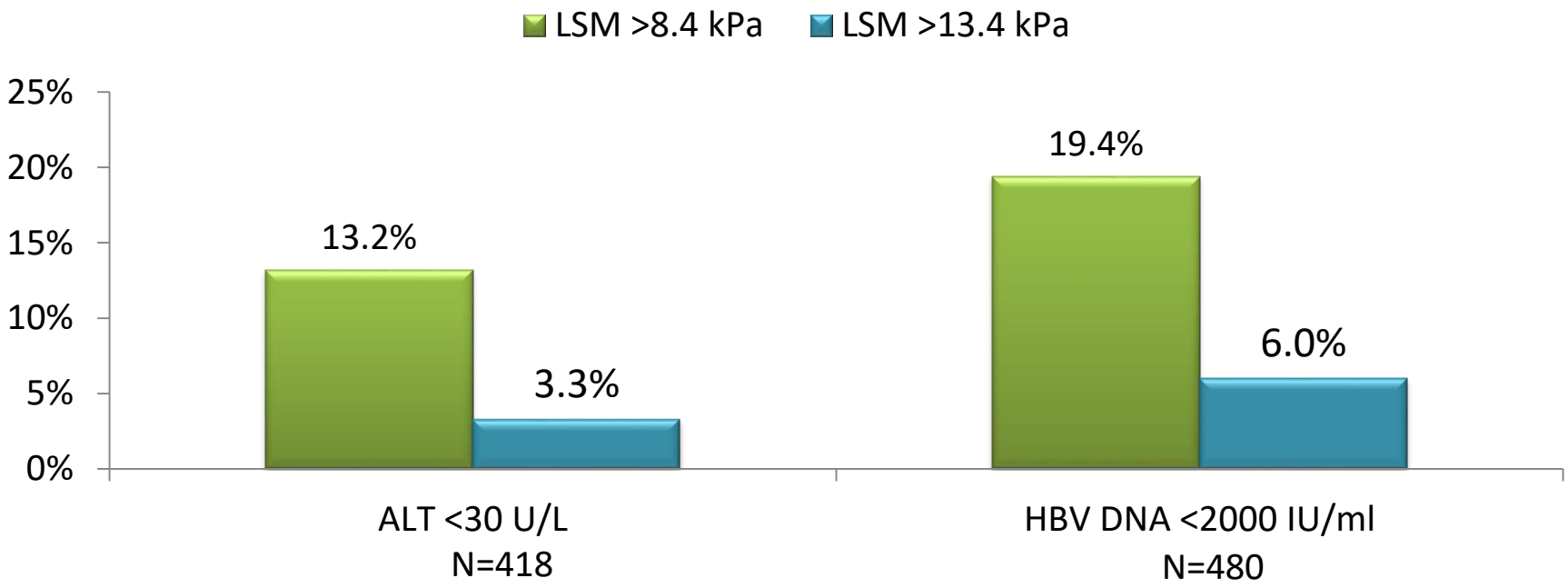
Do they exist?

Definition of inactive carriers – the Guidelines

EASL 2012	AASLD 2009	APASL 2016
HBeAg negative, anti-HBe positive, low HBV DNA (<2000-20000 IU/ml), normal ALT for at least 1 year	HBeAg negative, HBV DNA <2000 IU/ml, normal ALT for at least 1 year tested 3 monthly	HBeAg negative, anti-HBe positive, HBV DNA <2000 IU/ml, persistently normal ALT, no evidence of liver injury

Lok ASF and McMahon BJ. Hepatology 2009; Sarin S, et al. Hepatol Int 2016;10:1-98; EASL. J Hepatol 2012;57:167-85

Significant proportion of HBeAg-negative patients with low ALT and HBV DNA have significant liver fibrosis on Fibroscan



Wong GL, … Chan HL. Am J Gastroenterol 2008;103:3071-81

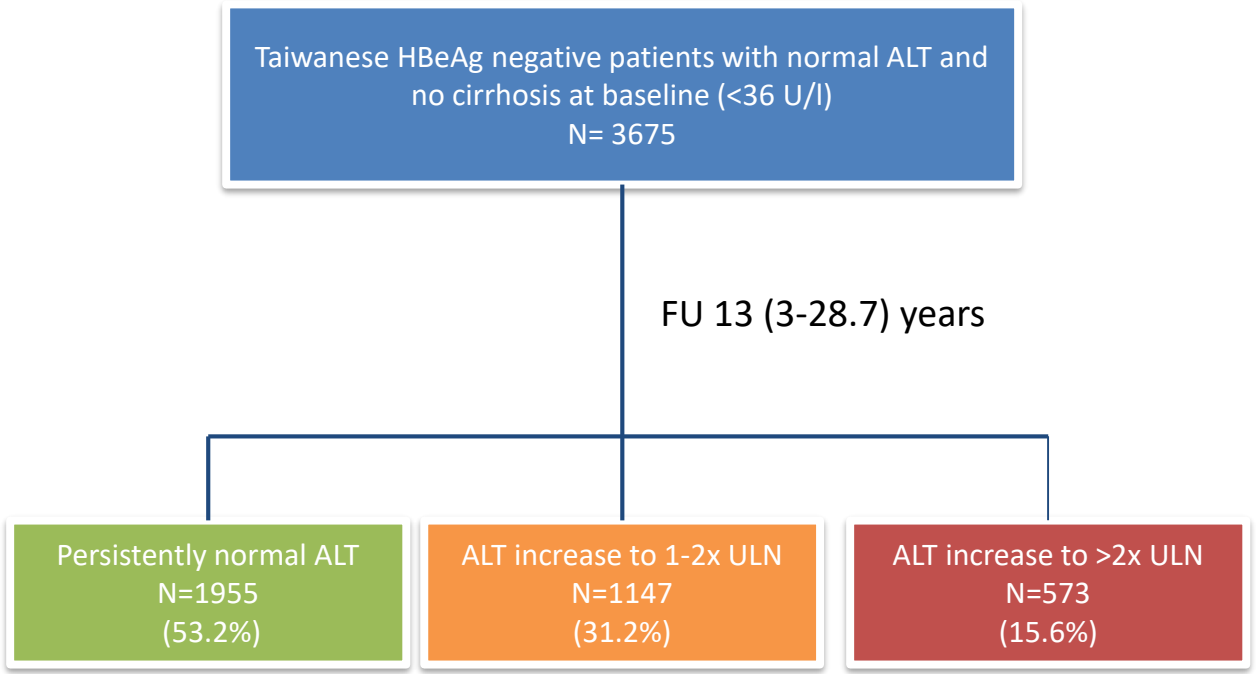
Transient elastography has better prediction for advanced liver fibrosis and cirrhosis than serum biomarkers in chronic hepatitis B (B1)

Normal ALT

≤5.0 kPa No fibrosis	>5.0 - 6.0 kPa Insignificant fibrosis	>6.0 kPa – 9.0 kPa Gray zone	>9.0 – 12.0 kPa Advanced fibrosis	>12.0 kPa Cirrhosis
Reassurance	Observe	Liver biopsy	Consider treatment	Consider treatment

EASL. J Hepatol 2015;63:237-64
Chan HLY, et al. J Viral Hepat 2009;16:36-44

Significant proportion of HBeAg-negative patient with normal ALT develops ALT elevation on FU



Tai DI, et al. Hepatology 2009;49:1859-67

Value of HBV DNA and HBsAg quant testing

The combination of HBsAg and HBV DNA levels can identify inactive carriers

Prediction of:	Inactive infection
HBsAg levels HBV DNA levels	<1000 IU/mL plus <2000 IU/mL

Confirmed in independent studies

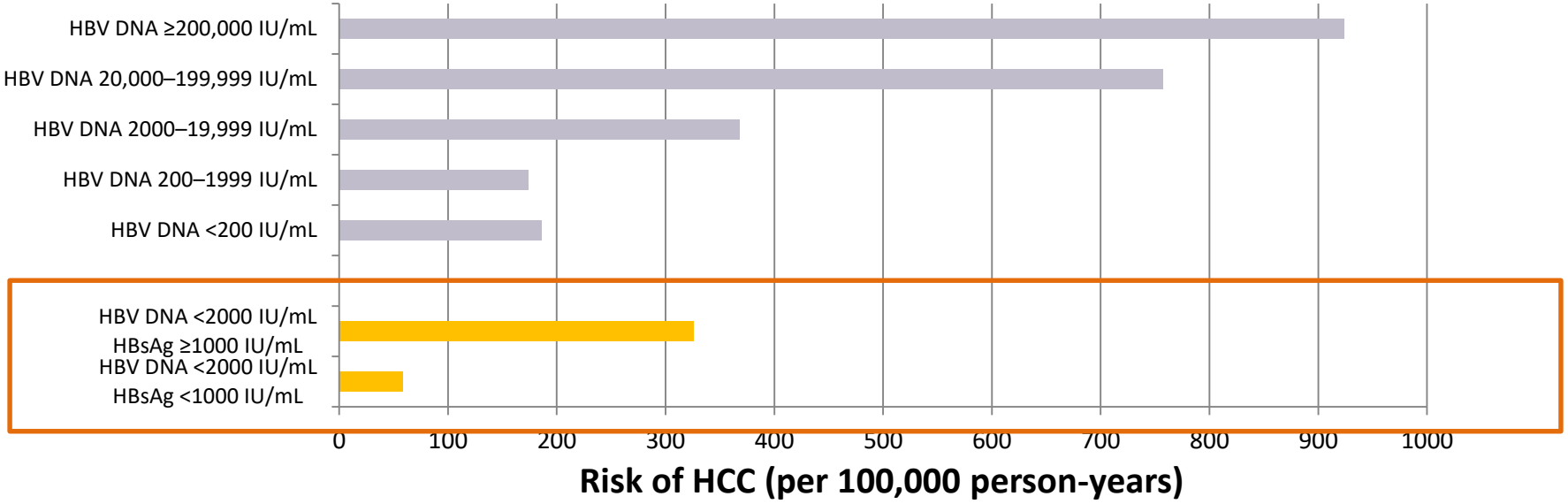
Brunetto 2010	Manesis 2010	Martinot-Peignoux 2011
209 patients genotype D	242 patients	165 patients genotypes A-E
PPV 87.9%	**PPV 89.7%**	**PPV 90%**

Brunetto et al. Gastroenterology 2010; Manesis et al. AASLD 2010; Martinot-Peignoux APASL 2011

HBsAg <1000 IU/ml and HBV DNA <2000 IU/ml : Very low risk of HCC

ERADICATE-B Study

2,688 Taiwanese chronic hepatitis B patients followed for a mean of 14.7 years



Tseng et al. Gastroenterology 2012; Chan HL. Gastroenterology 2012

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Stopping NA before HBsAg loss

Is it feasible?

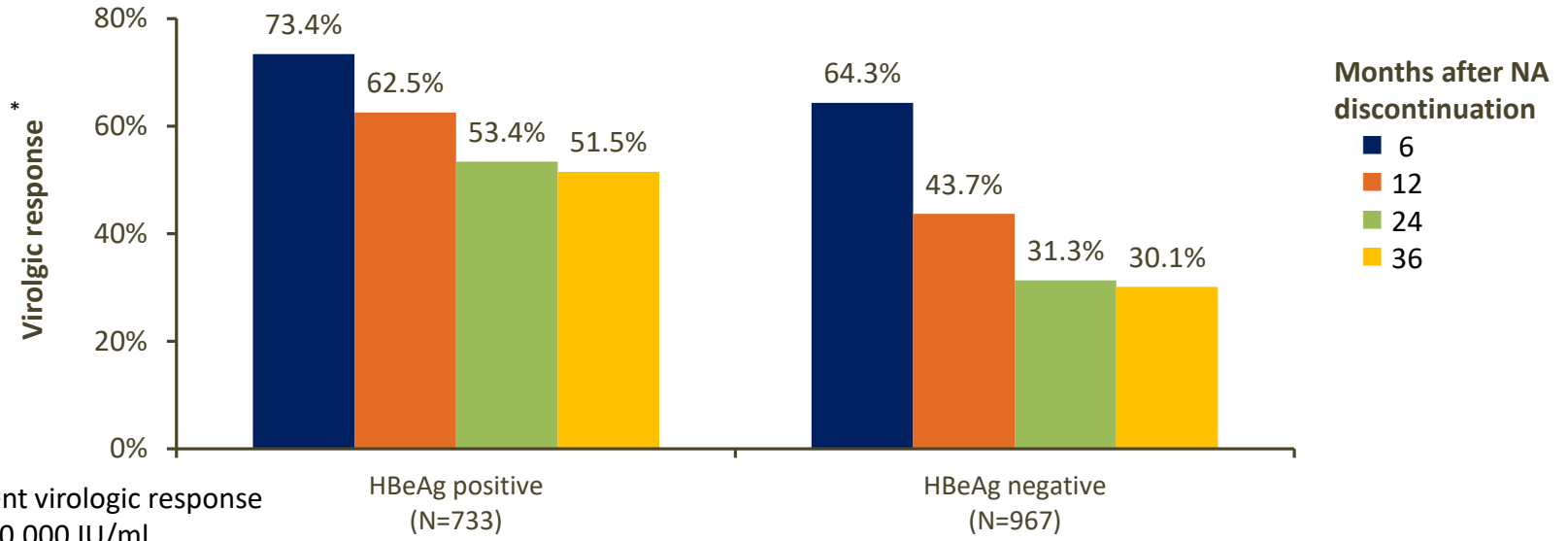
Stopping rules with NUCs for HBV therapy

CHB Treatment Guidelines	AASLD[1] (April 2018)	EASL[2] (April 2017)	APASL[3] (January 2016)
HBeAg +ve	HBeAg seroconversion + undetectable DNA + normal ALT for ≥12 months	HBeAg seroconversion with 12 months of consolidation	HBeAg seroconversion + undetectable DNA + normal ALT for ≥12 months, preferably 3 years
HBeAg -ve	Indefinite treatment (HBsAg loss)	HBsAg clearance **OR** HBV DNA undetectable for ≥3 years	HBsAg clearance for 12 months **OR** Treatment for at least 2 years + DNA undetectable 3 times 6 months apart

1. Terrault N, *et al. Hepatology* 2018;67:1561-99; 2. EASL. *J Hepatol* 2017;67:370-98; 3. Sarin S, *et al. Hepatol Int* 2016;10:1-98.

Significant proportion of patients have relapse after discontinuation of NA

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



*Post-treatment virologic response = HBV DNA <20,000 IU/ml.

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

End of treatment HBsAg cutoff at 100 IU/ml best predicts relapse – a systematic review

- 11 studies including 1716 patients
- Minimum NA treatment for 24 months and post-NA FU of 12 months
- Discontinued NA after HBeAg seroconversion (HBeAg positive) and undetectable HBV DNA

At ≥12 months off therapy	HBsAg <100 IU/ml	HBsAg >100 IU/ml
Virological relapse	9.1% - 19.6%	31.4% - 86.8%
Clinical relapse	15.4% - 29.4%	48.1% - 63.6%
HBsAg loss	21.1% - 58.8%	3.3% - 7.4%

Virological relapse = HBV DNA >2000 IU/ml from UD; Clinical relapse = virological relapse + ALT >2x ULN

Liu J, et al. Hepatology 2019;70:1045-55.

Multi-centre study in Europe: FINITE study

e-

CHB patients
- HBeAg-negative
- ≥4 years TDF therapy
- HBV DNA UD >3.5 years

Wk 0 — Wk 48 — Wk 144

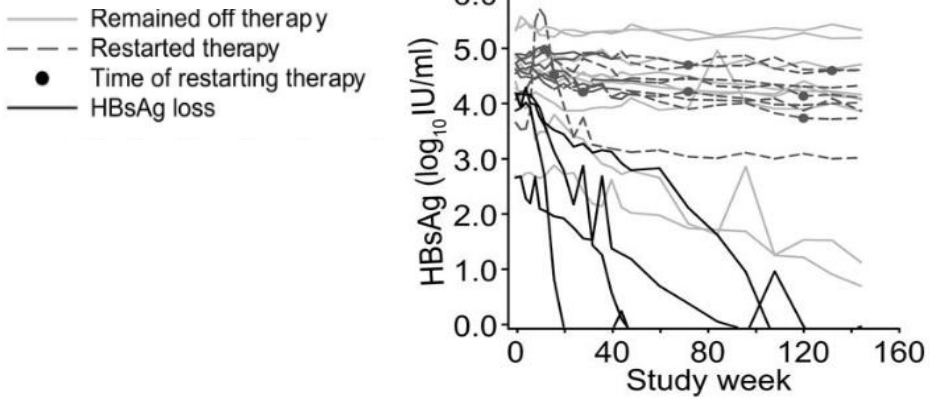
TDF-Stop — N=21

1:1 Randomisation

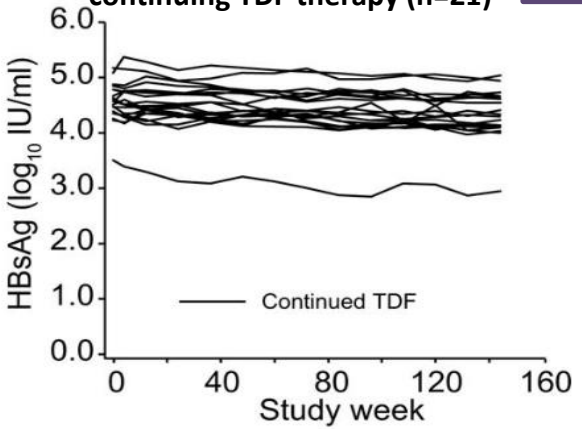
TDF-Continue — N=21

Primary endpoint: HBsAg loss by Week 144

HBsAg kinetics in patients stopping TDF therapy (n=21)



HBsAg kinetics in patients continuing TDF therapy (n=21)



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Berg T, *et al. J Hepatol* 2017;67:918–24.

HBsAg loss between European and Asian patients after stopping NA

e-

- HBsAg loss from HBeAg-negative patients in Europe
  - Greece [Daring-B]: **29%** in 2 years (n=60)
  - Germany [FINITE]: **19%** in 2 years (n=21); [Stop-NUC]: **10%** in 2 years (n=79)
  - Spain: **30%** in 2-3 years (n=27)

- Systematic review with 1,085 predominant East Asian patients at least 1 year post-stopping NA
  - Random effect pooled estimate of HBsAg loss = **2%**

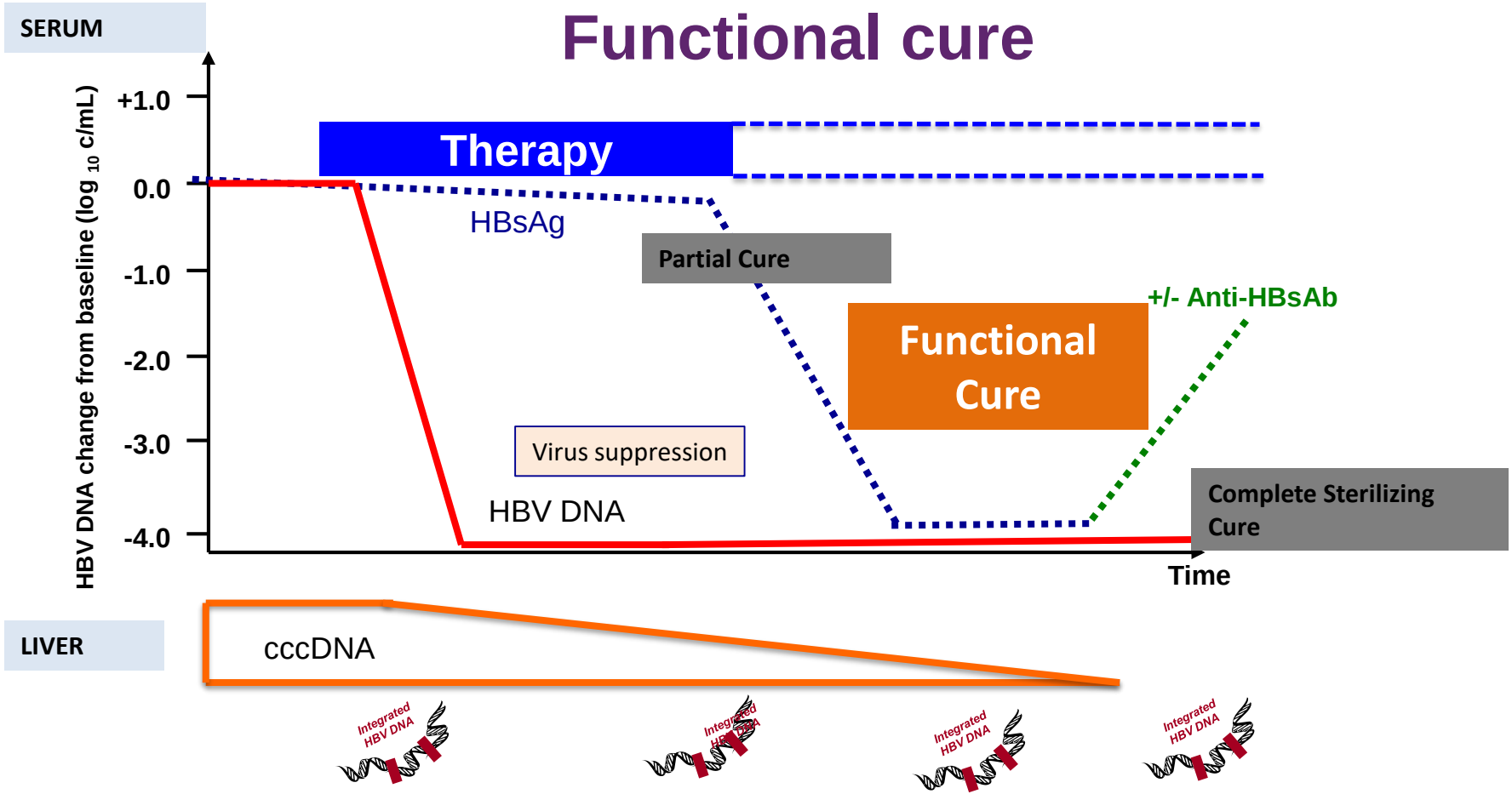
- Real world data in 1,075 HBeAg negative patients in Taiwan: 13% in 6 years (estimated annual incidence **1.78%**)

Papatheodoridis M, *et al. EASL*. 2018; #PS-159; Berg T, *et al., J Hepatol* 2017;67:918-27; Papatheodoridis G, *et al. Hepatology* 2016;63:1481-92; Jeng WK, *et al. Hepatology* 2018;68:425-34; van Bommet F, et al. EASL 2020 #LB006; Garcia-Lopez M, et al. EASL 2020 #AS003 .

Functional Cure

Is it needed?

Functional cure



Lok AS, et al. Hepatology 2017;66:1296-1313.

Do we still need functional cure?

- Inactive carriers
  - Low HBV DNA, low HBsAg, absence of significant fibrosis
  - Low risk of HCC

- NA treated patients with viral suppression
  - Low risk of cirrhosis progression and HCC

- Stop NA in patients with low HBsAg
  - Predicts inactive disease and HBsAg loss

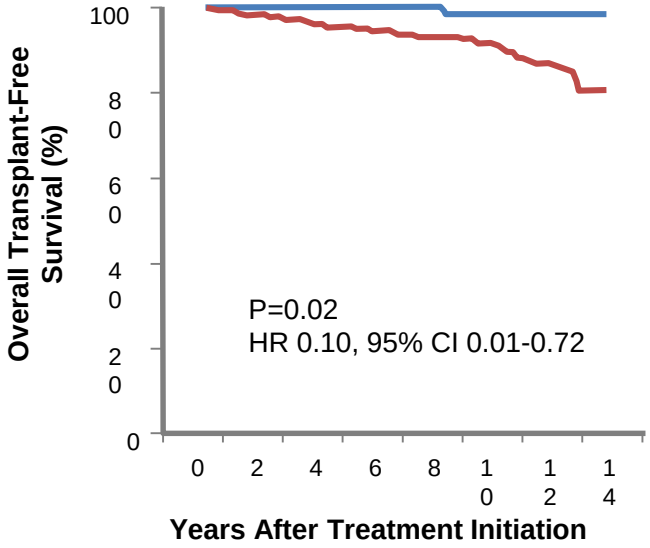
HBsAg seroclearance and undetectable HBV DNA is the ultimate goal

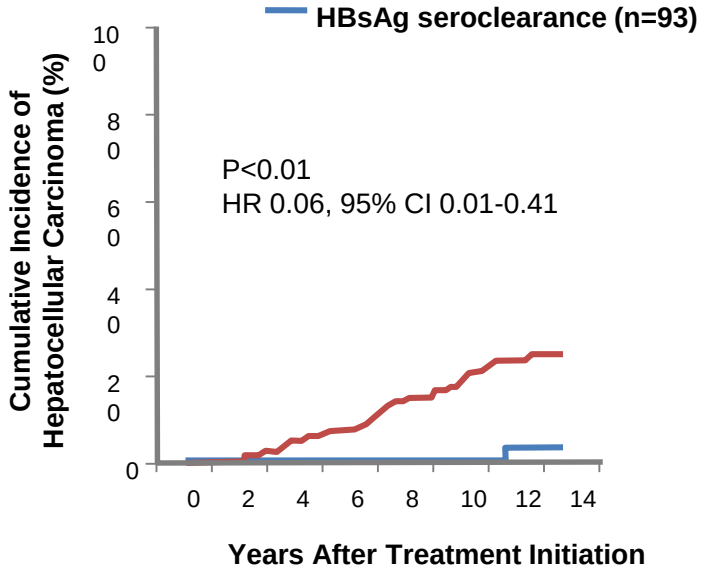
- Patients in REVEAL-HBV study
- Predominantly HBeAg negative, non-cirrhotic patients with normal ALT
- Total 48,149 person-years of follow-up

HBV biomarkers	N	HCC	HCC incidence per 100000 person year	Adjusted HR	Life-time HCC risk
HBV DNA UD + HBsAg loss	516	8	94	1.0	4.0%
HBV DNA UD, no HBsAg loss	635	11	106	1.53	6.6%
HBeAg negative, HBV DNA +	1351	65	294	3.99	14.2%
HBeAg seroconversion, HBV DNA +	151	22	904	15.13	80.1%

Liu J, et al. Gut 2014;63:1648-57.

HBsAg loss improves survival and lowers HCC incidence in patients who are on OAV treatment





5409 consecutive CHB patients from Korea treated with LAM or ETV
110 achieved HBsAg seroclearance (0.33% annual seroclearance rate).

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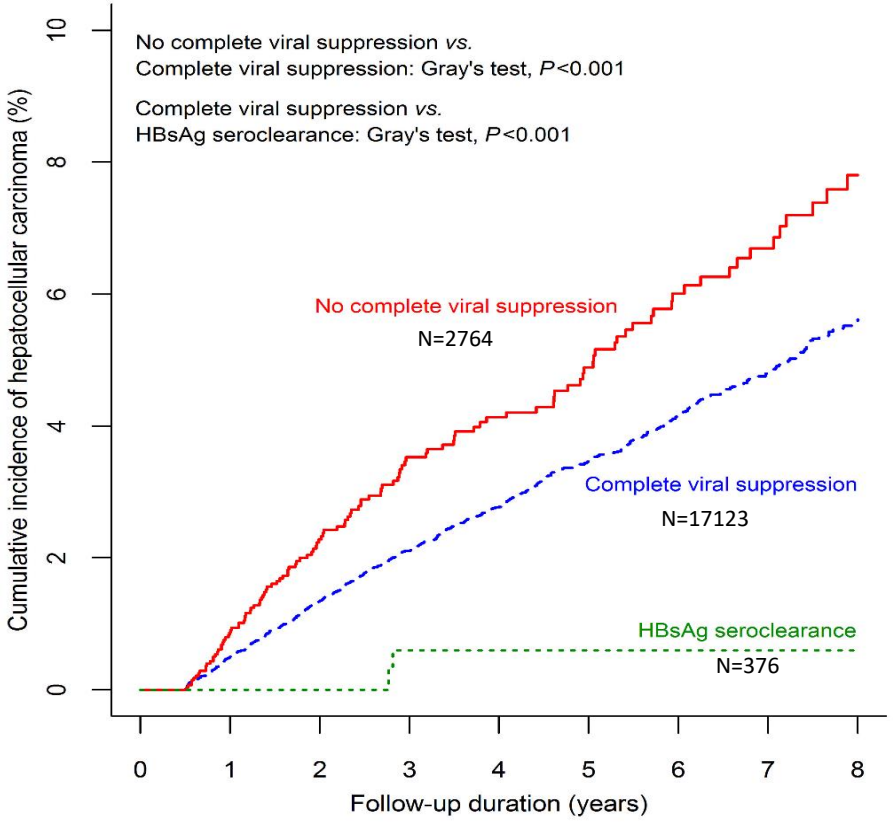
Kim GA et al. *Gut* 2014;63:1325-1332.

HBsAg seroclearance further reduces HCC in patients with complete viral suppression



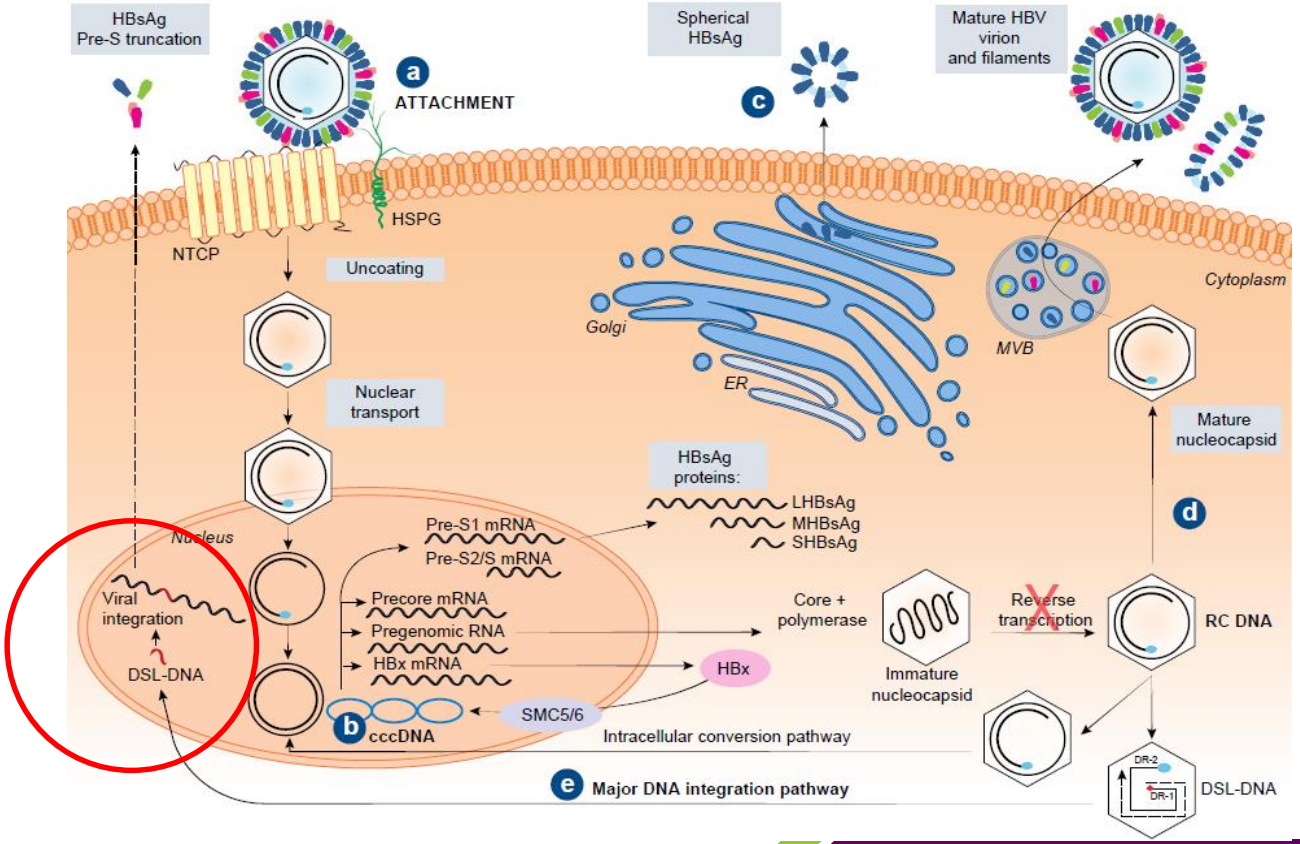
20,263 ETV/TDF treated CHB patients in Hong Kong

- 11% cirrhosis
- FU 4.8 (2.8-7.0) years

	aHR	*P*
Complete viral suppression	Referent	
No Complete viral suppression	1.69	<0.001
HBsAg seroclearance	**0.24**	**0.04**

Yip TC, et al. J Hepatol. 2019 Mar;70(3):361-370.

HBsAg seroclearance indicates clearing of cccDNA + intrahepatic integrated HBV DNA



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Cornberg M, … Chan HL. J Hepatol 2017;66:398-411

Insights into controversies of CHB treatment

- **Immune tolerant patients**
  - HBeAg positive, HBV DNA >7 log IU/ml, normal ALT, no significant liver injury
  - Treatment not urgent and not now

- **Inactive carrier**
  - HBeAg negative, HBsAg <1000 IU/ml, normal ALT, no significant liver injury
  - Low risk group, probably no additional benefit from further HBV DNA suppression by NA therapy

Insights into controversies of CHB treatment

- **Stop NA in HBsAg positive patients**
  - Can tolerate flare, which may lead to HBsAg loss in HBeAg-negative Caucasian patients
  - HBsAg <100 IU/ml have lower risk of relapse and higher chance of HBsAg loss

- **Functional cure**
  - HBsAg loss indicates immune clearance of both cccDNA and intrahepatic integrated HBV DNA
  - Further reduces HCC risk as compared to inactive carriers and NA suppressed patients
  - Should be the goal of future HBV therapy