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Controversy - To stop or not to stop NUCs?	
Tuesday January 15, 2019	Controversy
09:50 - 10:20	Amphi bleu

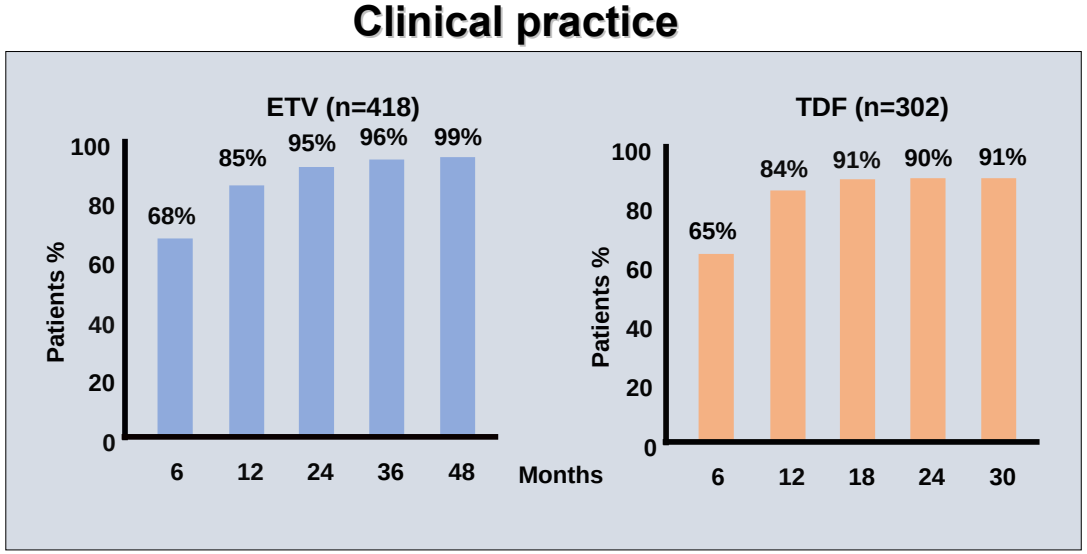
Antivirals for chronic HBV infection

	TDF	ETV	TAF
Advantages	• Potent antiviral activity • High barrier to resistance • HBV drug resistant patients • Pregnancy • No evidence of adverse outcomes in infants	• Potent antiviral activity • High barrier to resistance	• Potent antiviral activity • High barrier to resistance • HBV drug resistant patients • Potential no renal dysfunction and no bone alterations
Disadvantages	• TDF-associated renal dysfunction and/or osteoporosis/ osteomalacia,	• Genotypic resistance rates are higher in patients with pre-existing LAM-resistant CHB • Safety of ETV in pregnancy is unknown	

EASL 2017 CPG HBV, J Hepatol 2017

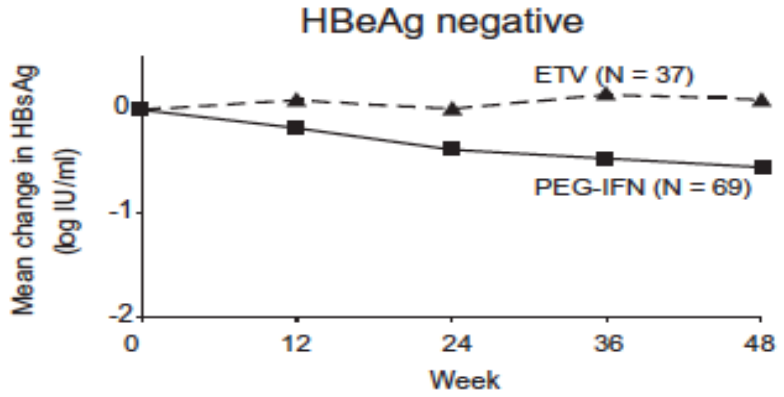
NAs therapy: current needs

Efficient control of HBV replication
NO FUNCTIONAL CURE



find more active direct anti-viral agents

Slow HBsAg decline during NAs therapy
NEED OF LIFE-LONG NAs ADMINISTRATION



Reijnders JGP et al J-Hepatol. 2011

shorten NAs therapy
by accelerating HBsAg clearance

NAS Discontinuation: What's EASL says

- NAs should be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion (Evidence level II-2, grade of recommendation 1).
- 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).
- Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term ($\geqslant$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).

EASL Recommendations 2017

GASTROENTEROLOGY 2012;143:629–636

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

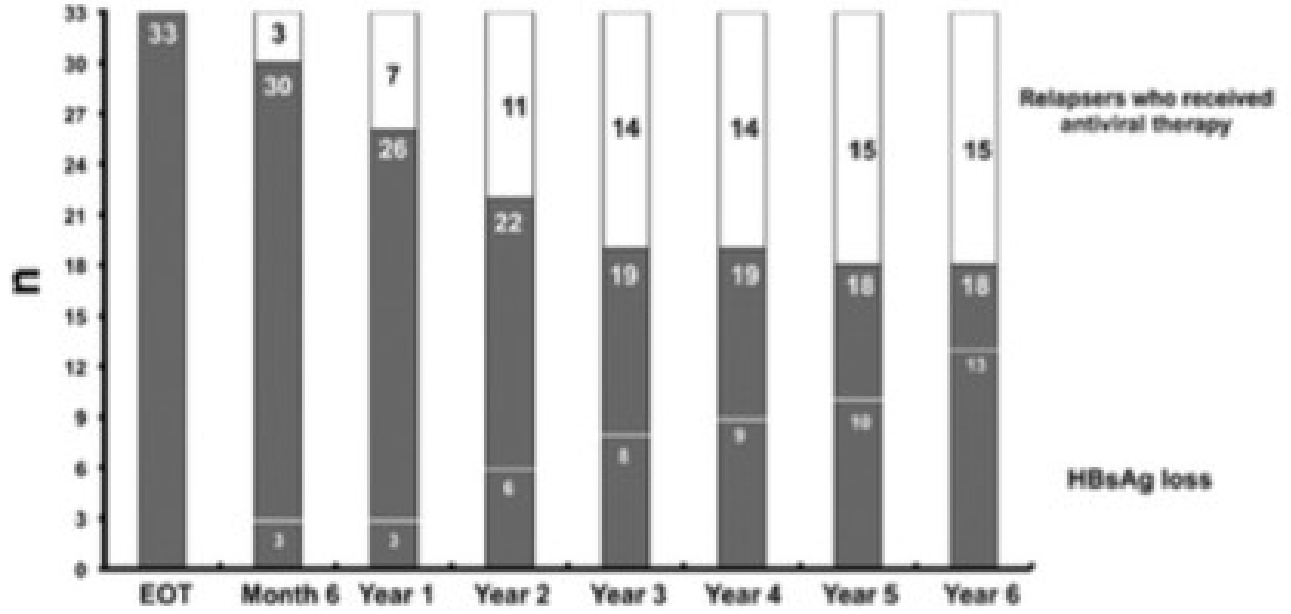


Figure 2. The number of patients who experienced a relapse and received antiviral therapy (relapsers) or lost HBsAg among the remaining patients during follow-up.

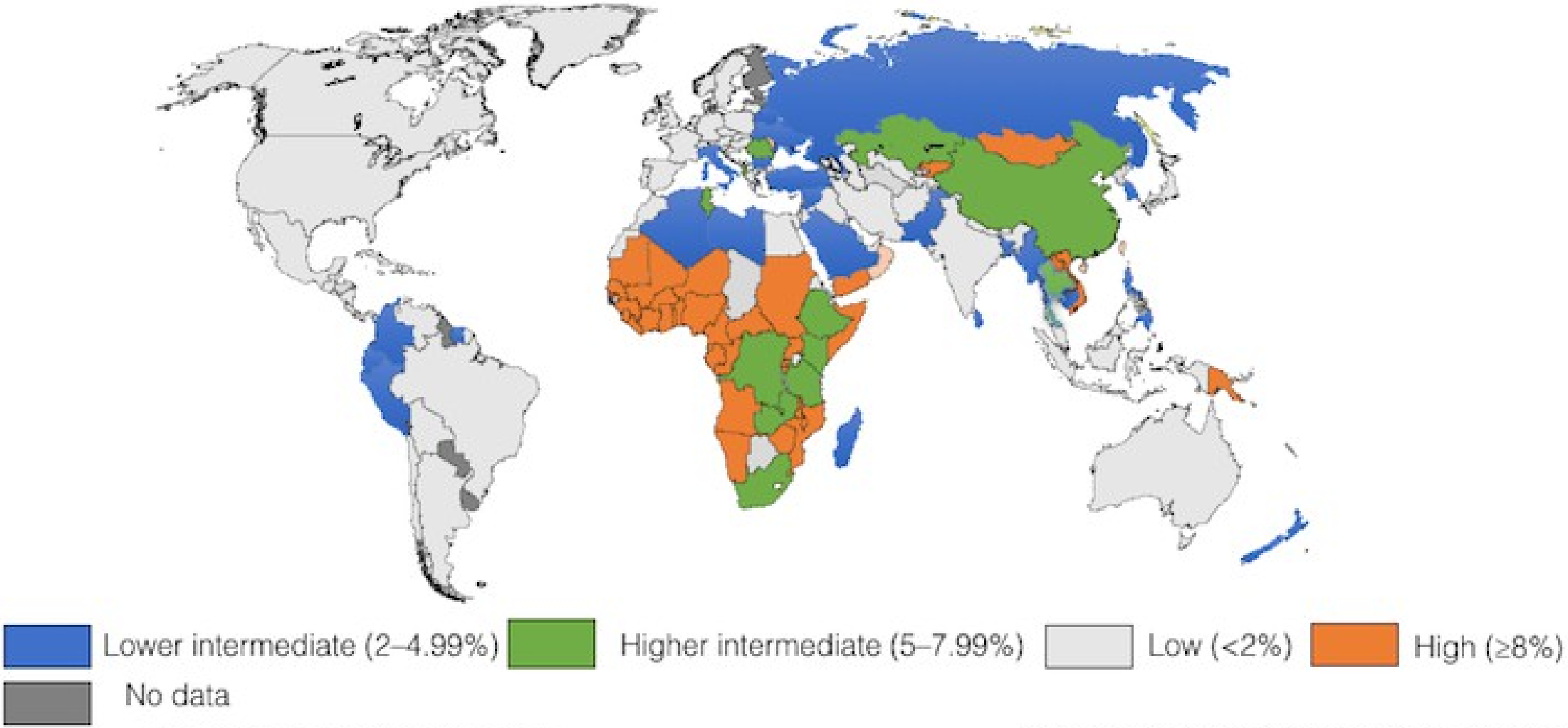
Hadziyannis SJ et al Gastroenterology 2012

Why discontinuing NAs?

1. Cost saving in countries where HBV is endemic
2. To prevent long term side effects in subgroup of patients including old patients and patients with childbearing potential

3. To induce immune clearance

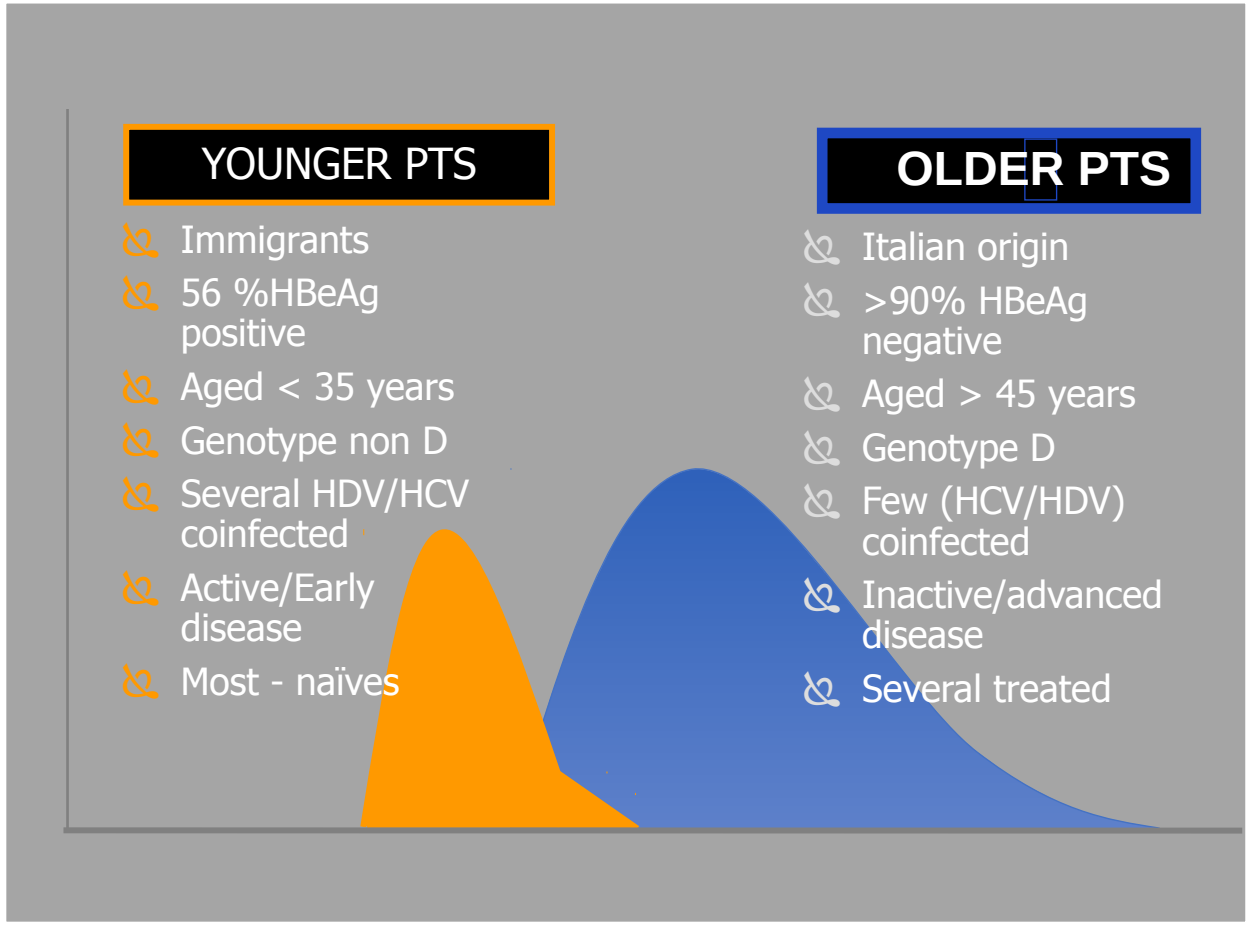
Estimates of worldwide CHB prevalence (HBsAg): a systematic review of data (1965-2013)



Schweitzer A, et al. Lancet 2015;17:386:1546–55

CHB: chronic hepatitis B; HBsAg: hepatitis B surface antigen

CHB and age-related issues back to the future



Antiviral Agent	FDA Pregnancy **Category**	Defects/Live Births When Exposed During First Trimester, %* (n/N)	Defects/Live Births When Exposed During Second/Third Trimester, %* (n/N)	Advantages/Disadvantages of Using During Pregnancy
Adefovir	C	(0/66)	(0/2)	∀ Not recommended
Entecavir	C	(2/66)	(0/2)	∀ Not recommended
Lamivudine	C	3.1 (149/4880)	2.9 (209/7327)	∀ Extensive human safety data ∀ Not a preferred first-line agent in treatment guidelines ∀ Associated with high rates of antiviral resistance
Telbivudine	B	(2/148)	(0/12)	∀ Positive human safety data; pregnancy class ∀ Fewer data than lamivudine or [enofovir]DF ∀ Not a preferred first-line agent in treatment guidelines ∀ Discontinued in the US
Tenofovir AF	NA	(1/25)	(0/22)	∀ Insufficient data to recommend in pregnancy
Tenofovir DF	B	2.3 (76/3342)	2.1 (31/1475)	∀ Preferred option ∀ Extensive human safety data, pregnancy class

Alberti A et al 2018

inPractice 2018

Why discontinuing NAs?

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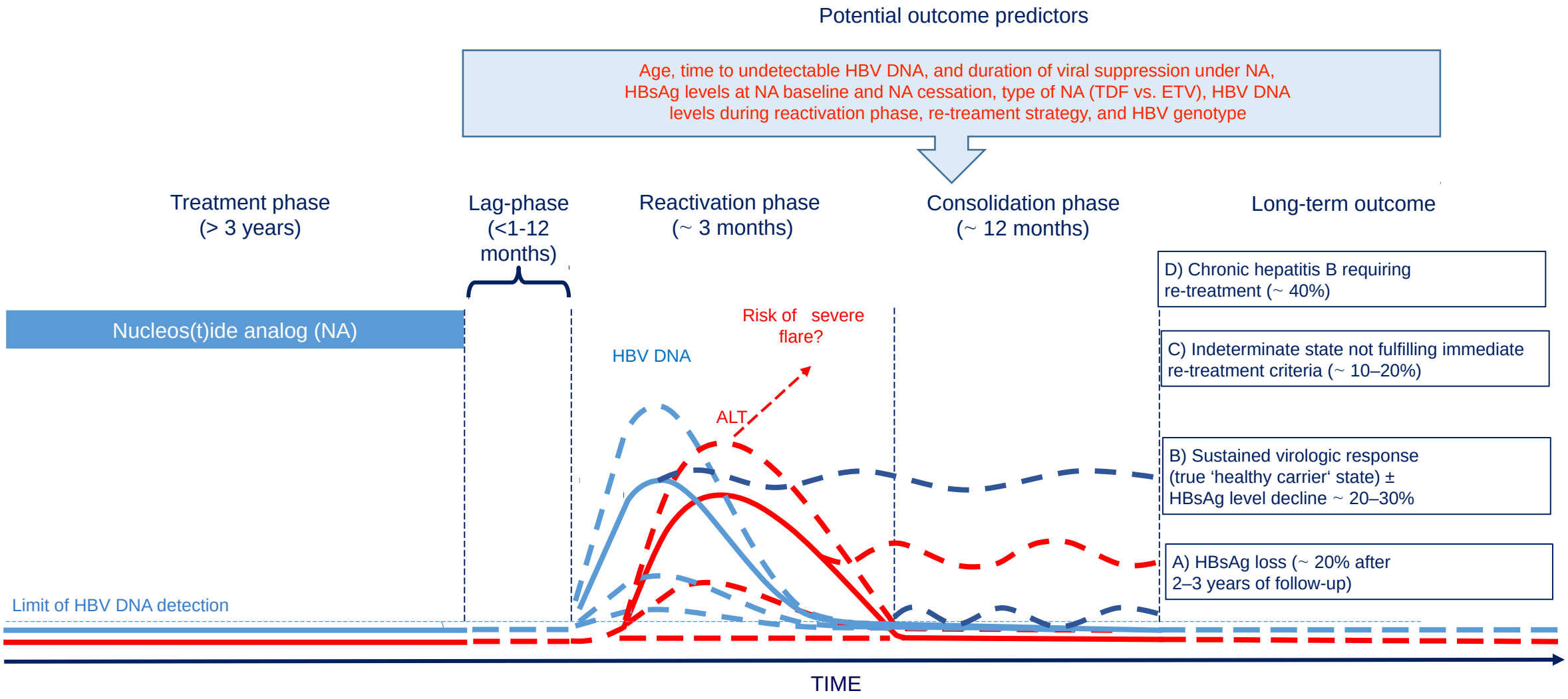
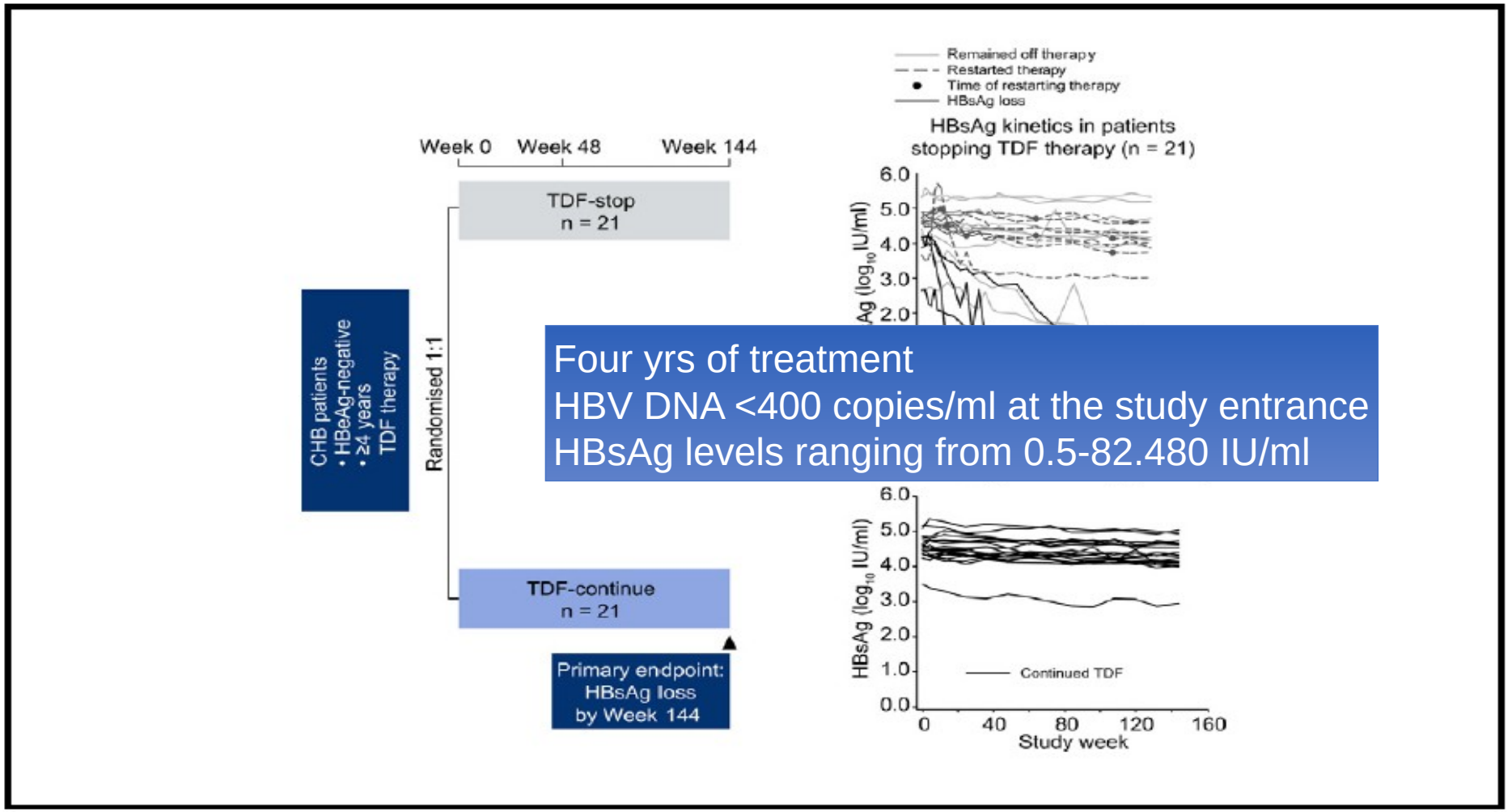
Typical Courses in HBeAg-ve patients after stopping NAs
THE GOOD, THE BAD, THE INDETERMINATE OUTCOME



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

HBsAg: hepatitis B surface antigen

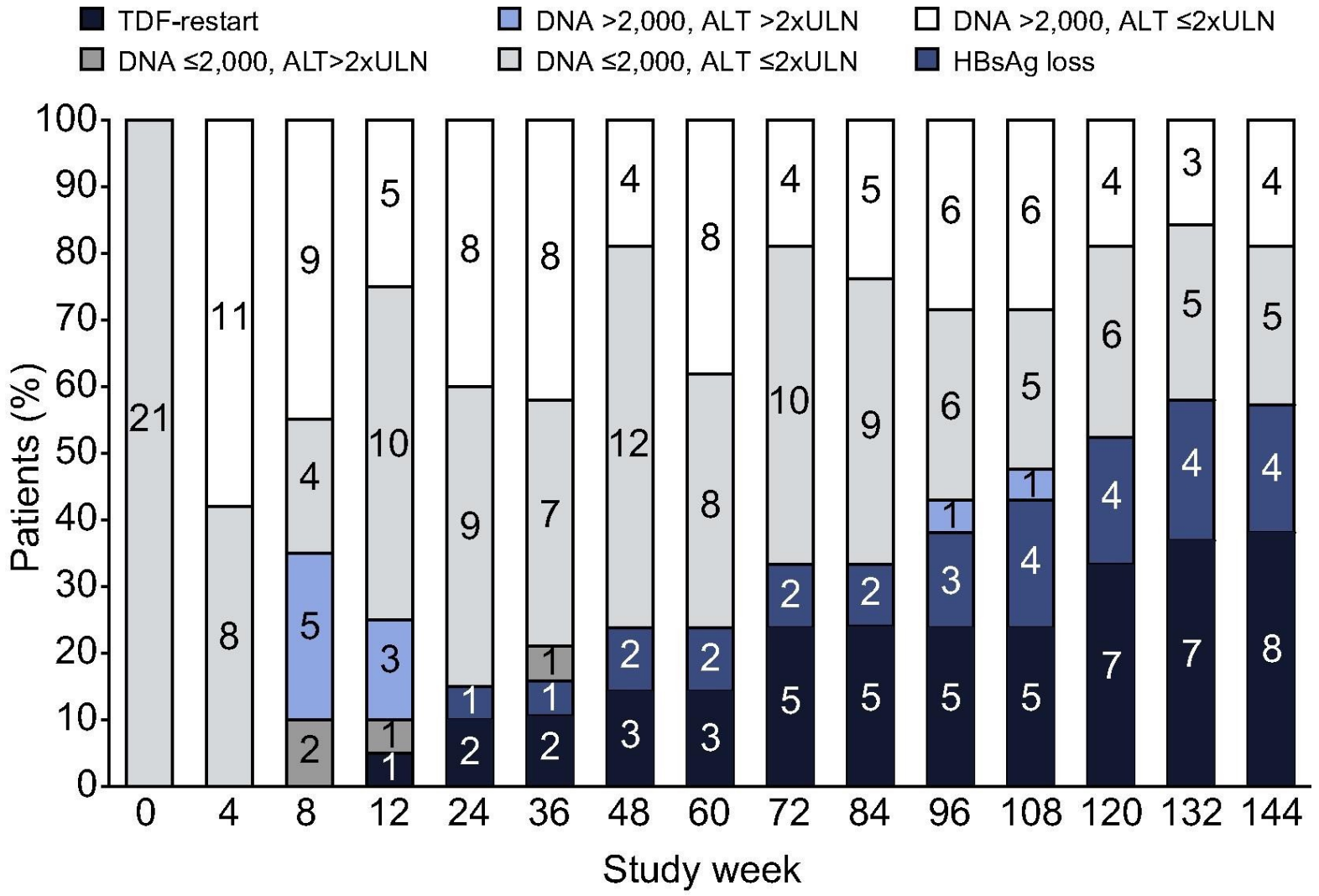
Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients – FINITE study



Of the patients who stopped TDF therapy, 62% remained off therapy to Week 144.
Four patients (19%) achieved HBsAg loss and three of them achieved HBsAg seroconversion.

Berg T et al. J Hepatol 2017

HBsAg loss after TDF Discontinuation in HBeAg-ve pts
19% HBsAg loss after 144 weeks of follow-up

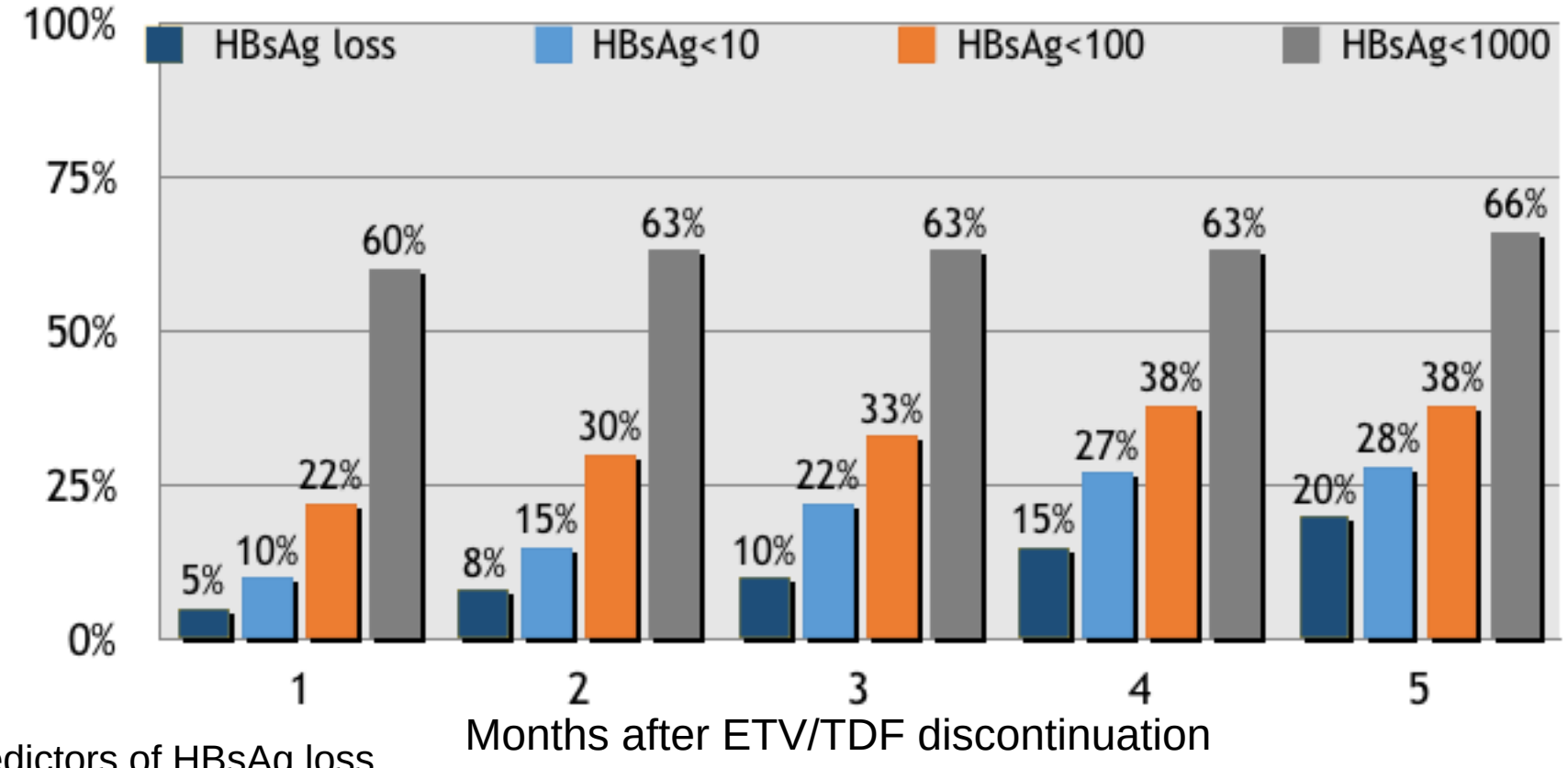


Berg T J Hepatol 2017

Rates and predictors of HBsAg loss after discontinuation of effective long-term ETV or TDF in non-cirrhotic HBeAg-ve pts: the DARING-B

60 HBeAg negative non-cirrhotic patients

Cumulative rates of undetectable or low levels of HBsAg



Prospective study

<u>Independent predictors of HBsAg loss</u>

HBsAg at month 0 (per 100 IU/ L)– adjusted HR 0.732 (0.587-0.913), P=0.006

IP-10 at month 1 (per 10 pgIU/L) - adjusted HR 1.163 (1.061-1.274), P=0.001

ALT at month 1 (per 10 IU/L) - adjusted HR 1.284 (1.089-1.512), P=0.003

Papatheodoridis M et al. ILC 2018;PS-159

NAs discontinuation: retrospective experiences in patients from ASIA

Source	Year	No	Cirrhosis	No Cirrhosis	Male (%)	Age (Yrs)	Tx duration	Follow-up Duration	HBsAg loss	Incidence
Chan	2011	53	18	35	81.1	56	27 mos	47 mos	11/53	5-yrs 23%
Patwardhan	2014	33	0	33	72.7	42	5.28 yrs	3 yrs	1/20	
Hung	2017	73	73	0	78.1	51.7	30.3 mos	66.8 mos	20/73	6 yrs 46.3%
Yao	2017	119	28	91	79	52	151.5 wks	6 yrs	44/119	6 yrs 54.9%

cidence and predictors of HBsAg sero-clearance after cessatio of NAs therapy in HBe Antigen-negative CHB

Prospective study

691 patients; 308 (44.6%) had cirrhosis

Tx duration 156 wks including consolidation tx of 111 weeks
Follow-up duration 155 wks
HBsAg loss 42/691
6-yr incidence 13%

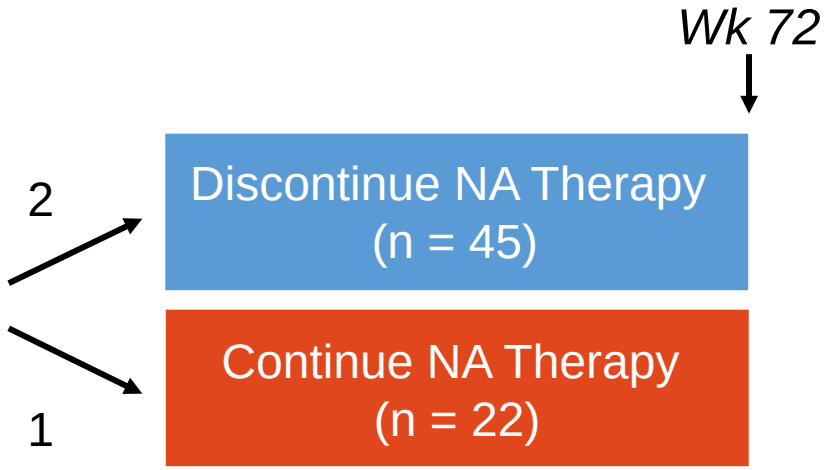
Estimated annual HBsAg loss 1.78%

Jeng WJ et al Hepatology 2018

STOP: Nucleos(t)ide Analogue Cessation in HBeAg-Negative Patients With CHB

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

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



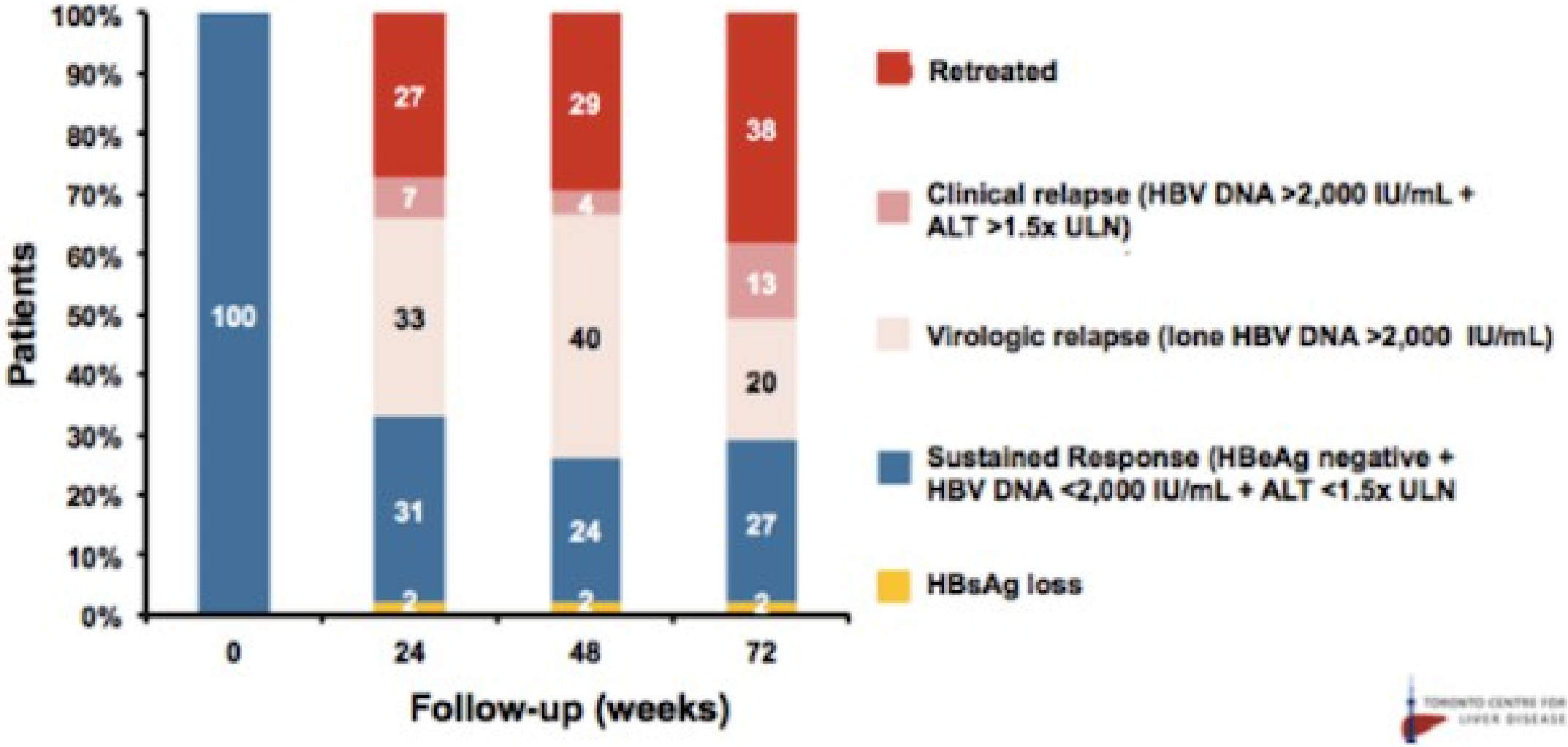
*If HBeAg+ at NA start, HBeAg seroconversion + undetectable HBV DNA ≥ 12 mos after seroconversion; if HBeAg-, undetectable HBV DNA ≥ 36 mos.

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.

Sustained response, retreatment & HBsAg loss in stop arm (n=45)



Who is eligible for NAs discontinuation?

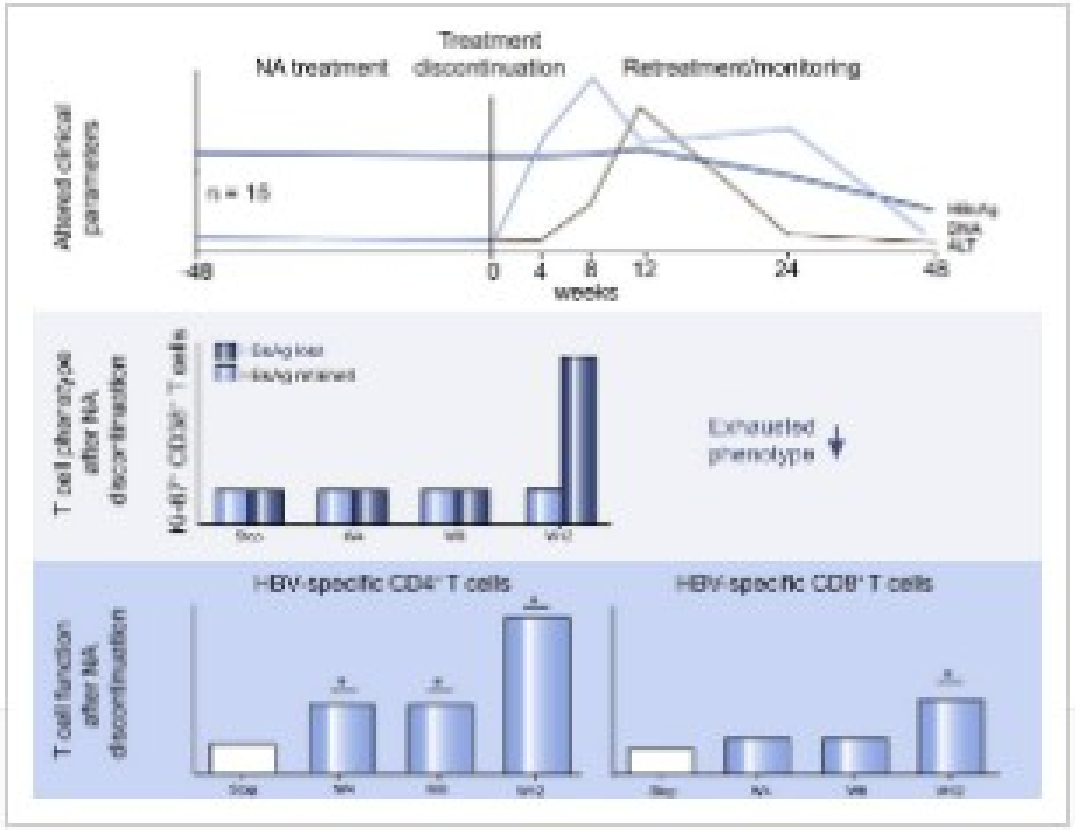
All guidelines exclude cirrhotics, but they provide different recommendations in HBeAg-ve pts

CHB Tx guidelines	EASL 2017	AASLD 2018	APASL 2015
HBeAg+ve	HBeAg seroconversion with 12 mos of consolidation + undetectable HBV DNA	HBeAg seroconversion with 12 mos of consolidation + undetectable HBV DNA	HBeAg seroconversion and after at least 1 yr of additional therapy
HBeAg -ve	may be considered after 3 yrs viral suppression	indefinite (may be considered after HBsAg loss)	-HBsAg seroconversion or HBsAg loss >1 yr -Rx for at least 2 yrs with HBV DNA undetectable on 3 separate occasions 6 months apart

Hepatitis B virus-specific T cell responses after stopping NAs therapy in HBeAg-negative CHB

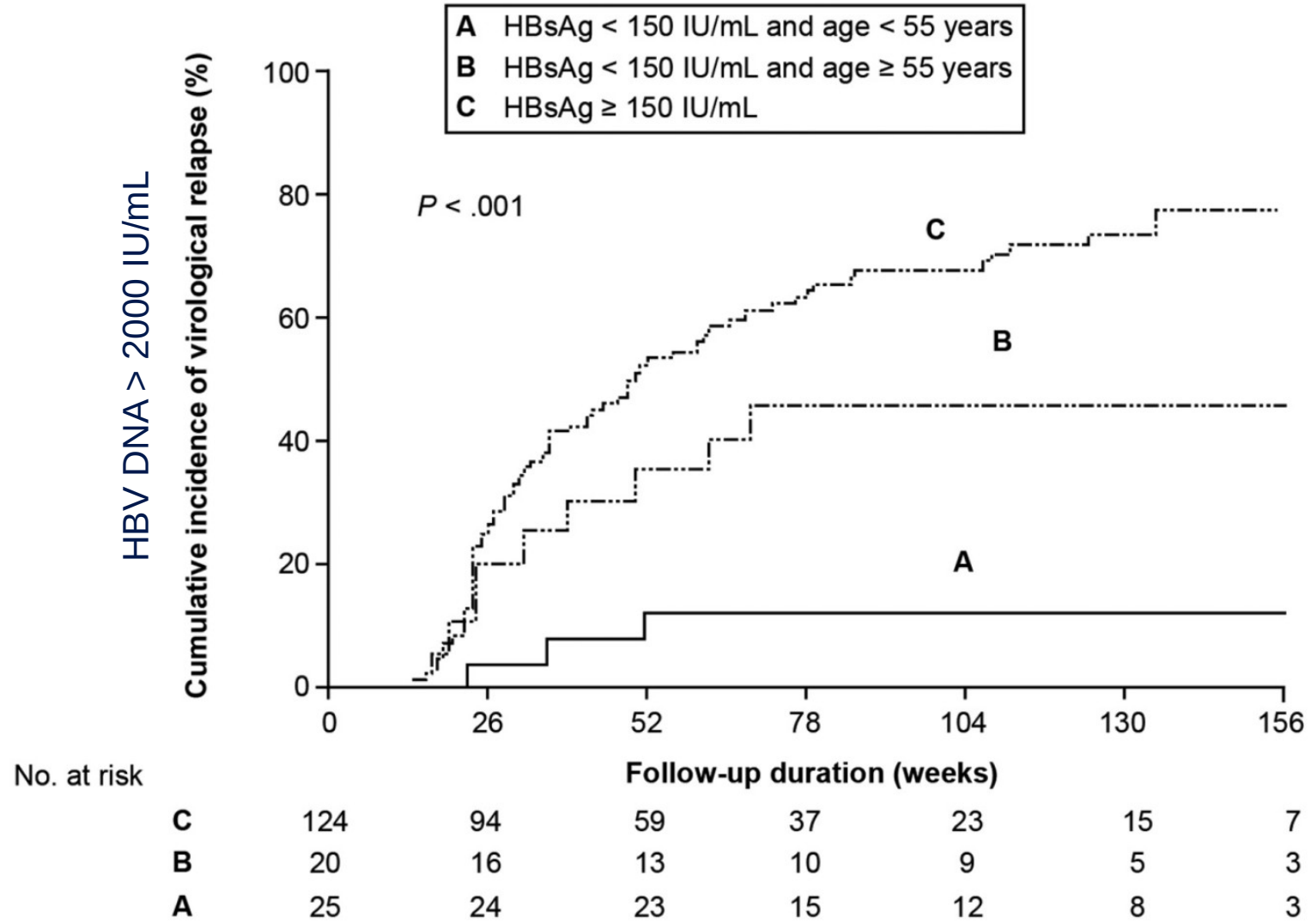
rological relapse may trigger immune responses and increase HBsAg los

Graphical abstract



Rinker F et al J Hepatol 2018

Risk factors of relapse in HBeAg-negative patients (N=169)
Age and end-of-treatment HBsAg level matter



High HBsAg

Low HBsAg and age ≥ 55 years

Low HBsAg and age < 55 years

30% HBsAg loss

Chen C-H et al. Clin Gastroenterol Hepatol 2015; 13: 1984

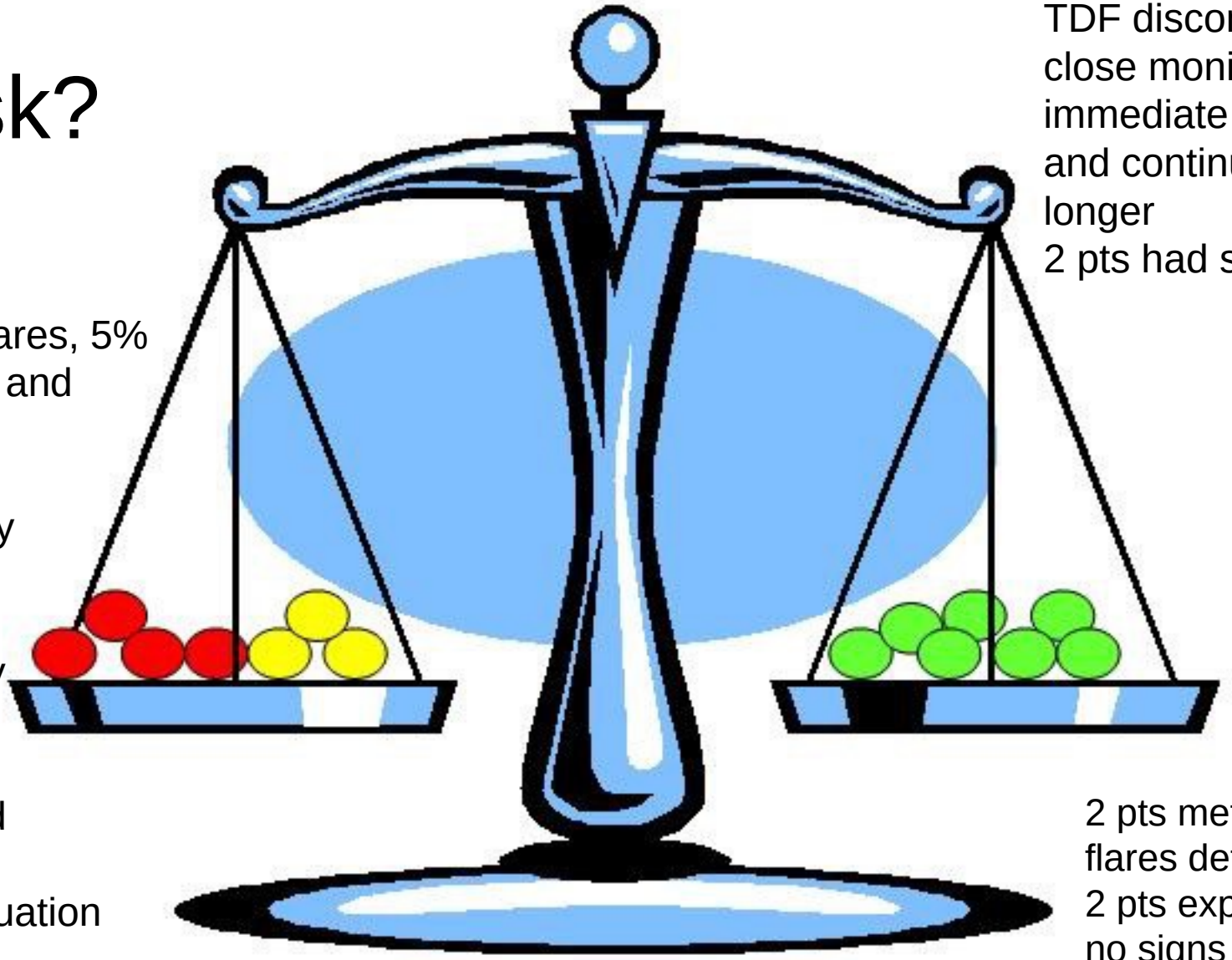
Predictors of Relapse After NA Cessation in CHB

- Unmet need for biomarkers to assess risk of treatment withdrawal
- -Data from multiple small prospective studies support use of HBcrAg and/or HBsAg to predict risk of relapse

Prospective Study/Authors	Findings
Hsu (N = 135)	✦ HBcrAg, HBsAg independently predict off-treatment clinical relapse, can be combined with age, ALT, and TDF use in novel risk score
Papatheodoridis DARING-B (N = 60)	✦ HBsAg loss associated with lower levels of HBsAg at ETV/TDF d/c ✦ HBcrAg levels at d/c, 1 mo before retreatment predict probability of retreatment
Seto (N = 103)	✦ Significantly lower HBV reactivation rate in patients with BL HBsAg ≤ vs > 10 IU/mL ✦ Lower BL HBcrAg level associated with reduced HBV reactivation rate in patients with BL HBsAg > 20 IU/mL
Carey (N = 15)	✦ HBcrAg or pregenomic HBV RNA at TDF d/c may predict significant ALT flares necessitating retreatment

1. Hsu. AASLD 2018. Abstr 397. 2. Papatheodoridis. AASLD 2018. Abstr 408. 3. Seto. AASLD 2018. Abstr 417. 4. Carey. AASLD 2018. Abstr 530.

Any Risk?



With lamivudine discontinuation,17% flares, 5% of whom with jaundice and clotting factor <50%

Deaths reported mostly in cirrhotic pts

Flares may occur early

ALT 5x or 10x reported in up yo 22% of cases 24 mos after discontinuation

Hankoop P et al Hepatology 2000;
Papatheodoridis G et al Hepatol 2018;
Chen C-H 2018;

TDF discontinuation well tolerated close monitoring means starting immediate ALT evaluation bimonthly and continue after 24 wks or longer
2 pts had severe ALT increase

Berg T et al J Hepatol 2017

2 pts met criteria for hepatic flares definition (ALT>10 UNL)
2 pts experienced ALT increase
no signs of decompensation
no deaths

;

Buti M et al. Lancet Gastroenterol & Hepatology in press

Re-treatment related issues

Is re-treatment response compromised? No, HBV DNA levels decline after re-treatment
When to re-start treatment?

Direct Bilirubin levels increasing greater than 1.0 mg/dl from baseline or
Bilirubin elevated >3 mg/dl in 2 consecutive assessments or
INR>1.3 or
Clinical decompensation regardless of ALT/HBVDNA levels

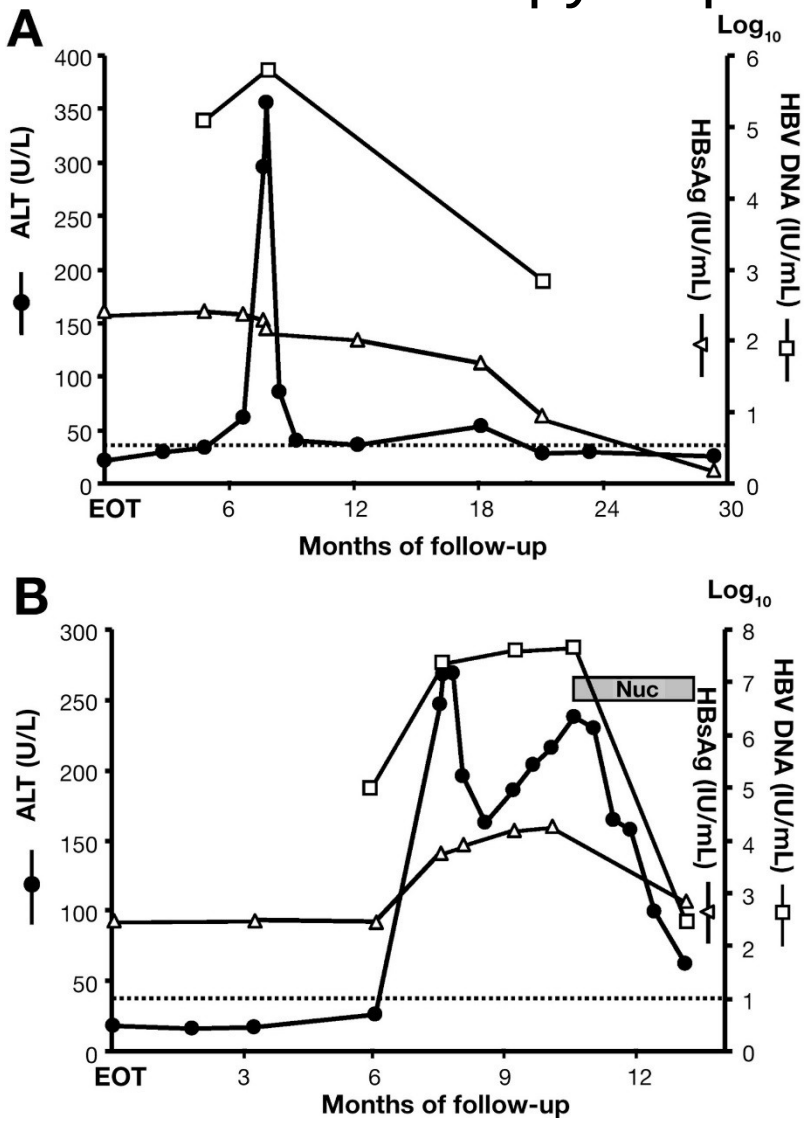
HBV DNA >10.000 UI/ml and ALT >1000 U/L

HBV DNA >10.000 UI/ml and 3 ALT values >300 U/L over 4 weeks

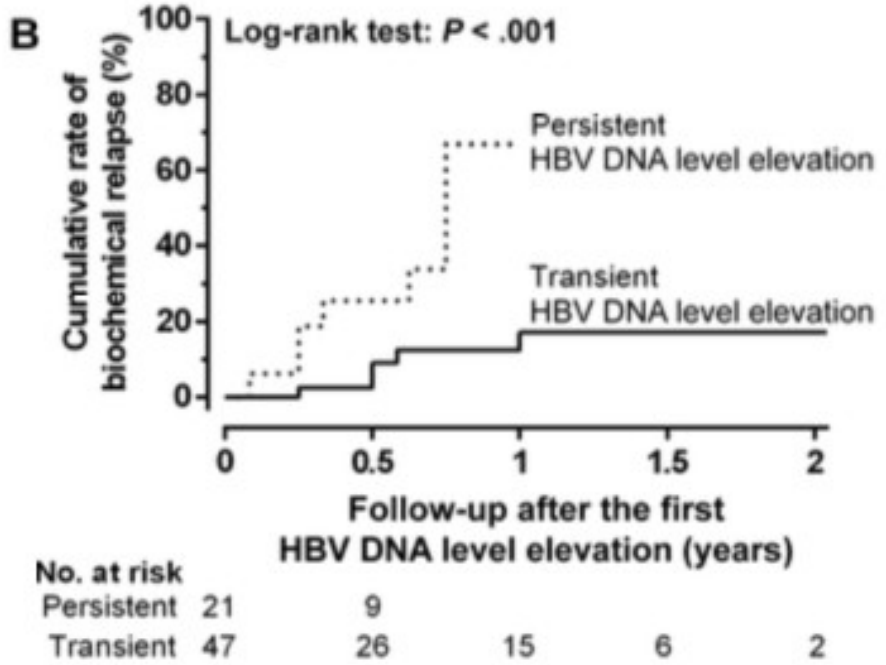
HBV DNA >10.000 UI/ml and 3 ALT values >150 U/L over 12 weeks

Early re-treatment reduces chances of HBsAg loss

HBsAg and HBV DNA Kinetics in Re-treatment Decision for Off-Therapy Hepatitis B Flare in HBeAg-Negative Patients



Liaw Y-F et al Gastroenterology 2018 154, 2280-2281



Cao J et al J Infect Dis 2017

Conclusions

As therapy can be discontinued in selected subgroups of HBeAg-ve non cirrhotic patients with undetectable HBV DNA for at least three yrs during Tx, only if they are able to adhere to a strict monito rogram

Withdrawal of NAs frequently results in ALT flares and HBV DNA rebound: early, close and long term monitorin mandatory for safe and effective NAs discontinuation

irological and biochemical flares are often transient and may represent a trigger for inducing long-term immune control

aucasian race, younger age and low baseline HBsAg levels at the stop of NAs seem to be ssociated with viral clearance