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For now, do not stop NUCs

PHC 2019

R. PARANÁ
Federal University of Bahia, Brazil
HUPES-University Hospital
Gastro-Hepatology Unit

Disclosure

PI: Clinical Trials

-ABBVIE

-INTERCEPT

-GILEAD

-Novartis

-BMS

Speaker: Zambon

CNPq-Brasilian Agency of Research

Are there reasons to stop NUCs ?

No

- **High Genetic Barriers**
- **Good Efficacy**
- **Good Tolerance**
- **Generic brings lower price (accessibility)**
- **No need to check Fibrosis stage**
- **Lower risk of HCC and decompensation**
- **Low HBsAg Clearance rate**

Yes

- Resistence in Non-TDF therapy
- Cost
- Potential AE (Bone and Kidney)
- Putative CD8 immune response restauration
- Adherance
- Long term therapy and additional benefits are not well defined

Hepatitis B:
Why should we stop NUCs ?

- Evidence **against treatment discontinuation** in three patient populations:
  - HBeAg-positive patients
  - HBeAg-negative patients
  - HBeAg-positive or negative patients with cirrhosis

Safety of NA discontinuation in patients with cirrhosis

Clinical Event	Risk
Decompensation	0.8% (2/243)
Jaundice	2.5% (6/243)
Death	0.4% (1/243)

Meta-analysis

Papatheodoridis et al. Hepatology 2016;63:1481-1492

APASL stopping rule for HBeAg neg cirrhotic patients

Clinical Event	Risk
Severe flares	16.2% (15/94)
Decompensation	8.2% (8/94)
Death	1.1% (1/94)

Chang et al. Clin Gastroenterol Hepatol 2015;13:979-986

Guideline recommendations on stopping NUC therapy

Guideline	HBeAg positive	HBeAg negative	Cirrhosis
AASLD 20161	• HBeAg seroconversion with ≥12m consolidation therapy and normal ALT with undetectable HBV DNA • HBsAg loss	• HBsAg loss	• Not recommended
EASL 20122	• HBeAg seroconversion with 12 months consolidation therapy	• No recommendation	• Not recommended
APASL 20153	• HBeAg seroconversion with undetectable HBV DNA > 12 months, preferably 3 years	• HBsAg loss with annti HBs seroconversion, OR • HBsAg loss after 12 months consolidation therapy OR • 2 years undetectable HBV DNA , 3 separate occasions 6 months apart	• Can consider in compensated cirrhosis with careful monitoring plan
ALEH/ SBH	Consolidated AgHbe seroconersion Normal ALT Undetetable HBV-DNA	**HBsAg Loss + HBV-DNA Undetetable for 12 mo**	Not recommended

1 Terrault NA et al. Hepatology. 2016;63:261–283; 2 EASL, J Hepatol. 2012;57:167–185; 3 Sarin et al, Hepatol Int.2016;10:1–98.

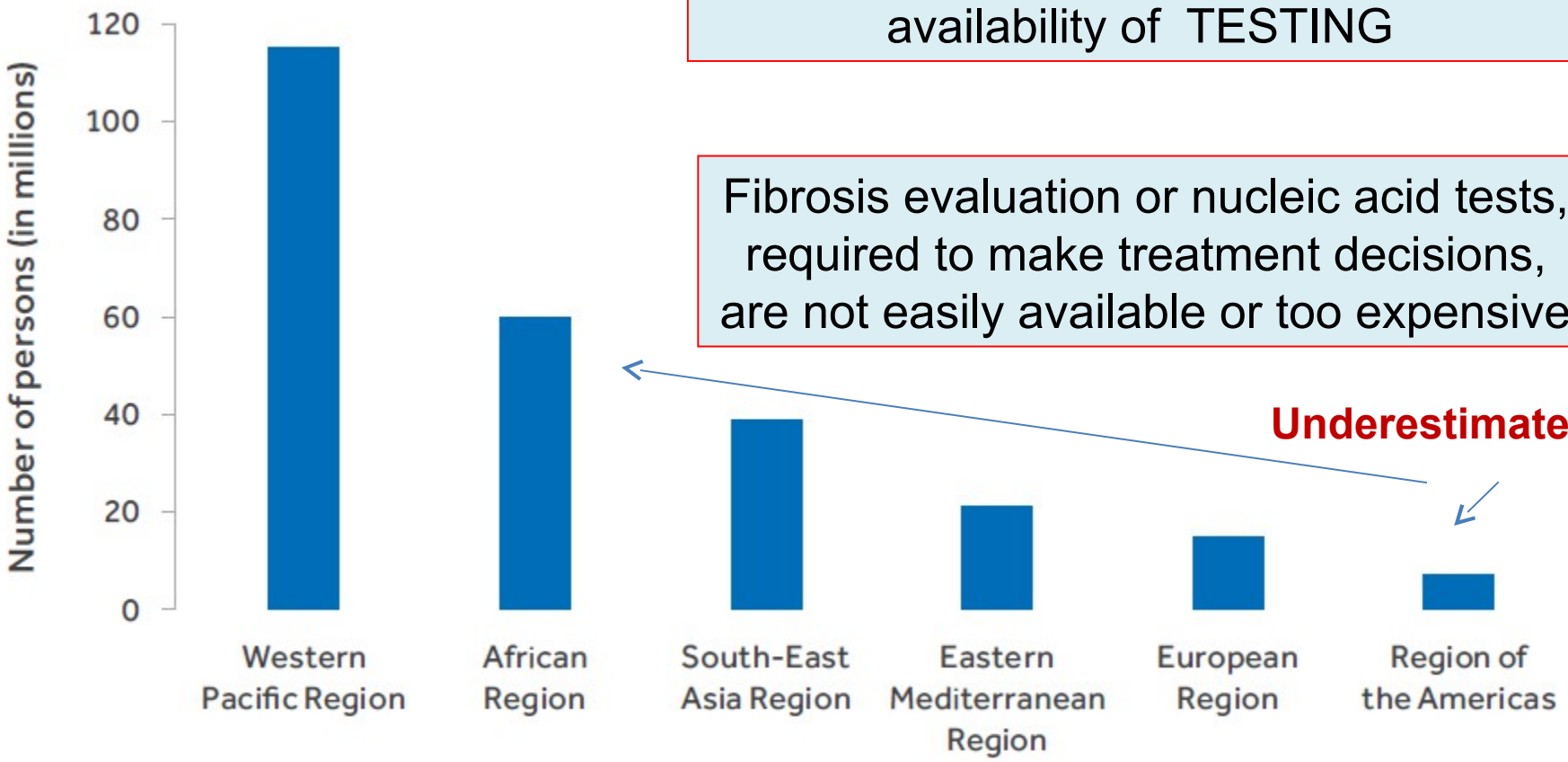
WHO HBV Guideline : Stop treatment

Estrategy	Category	Nota
	http://www.who.int/hiv/pub/hepatitis/hepatitis-b-guidelines/en/	
Term therapy	Cirrhotics	Keep
Descontinuation	No cirrhosis	APRI < 2
	close Follow up reactivation	
	HBeAg sueroconversion	1 year of consolidation HBeAg /anti HBe
	ALT persistently normal and HBV DNA persistently undetectable	
	HBsAg loss	**HBV-DNA undetectable Reliable Lab test**
retreatment	Reactivation	ALT / HBV DNA

Prevalence of HBV infection (HBsAg) in the general population by WHO region

Low-income countries → limited availability of TESTING

Fibrosis evaluation or nucleic acid tests, required to make treatment decisions, are not easily available or too expensive

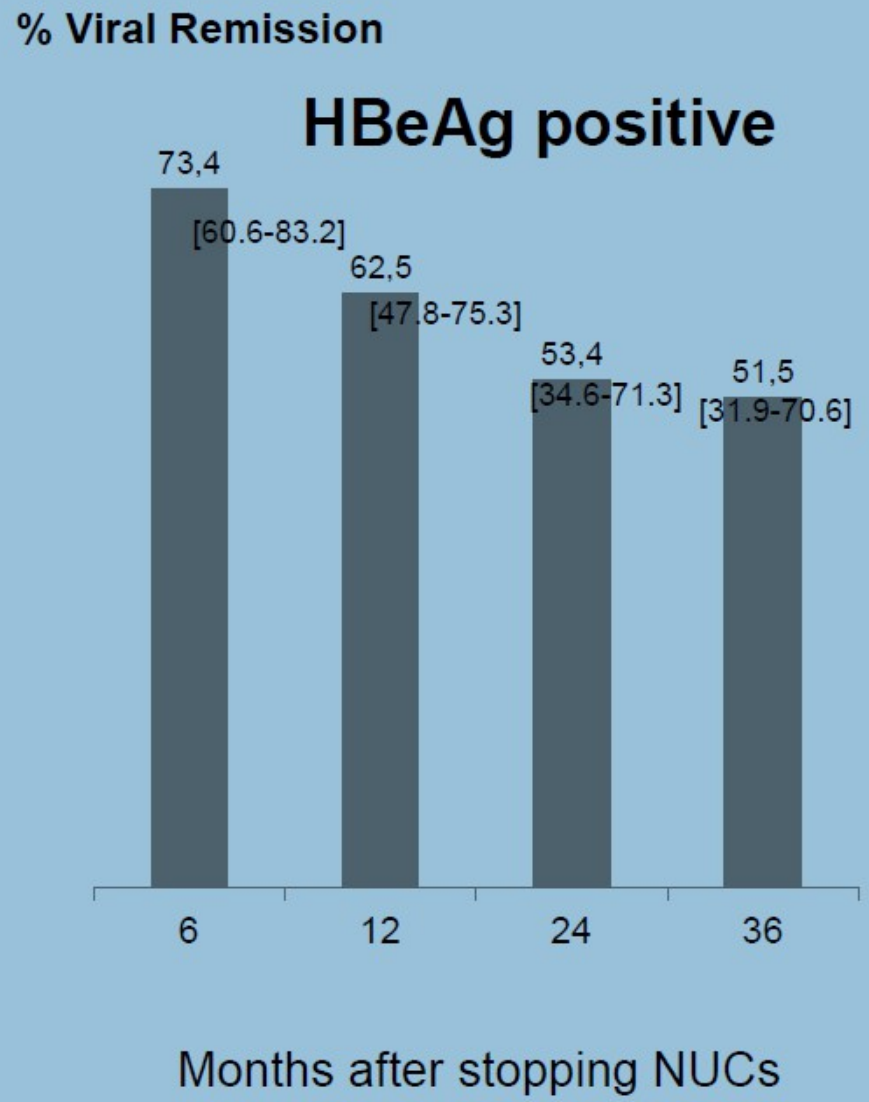


WHO GLOBAL HEPATITIS REPORT, 2017

Adapted from Gadano

NUCs Discontinuation in HBeAg positive patients

Meta-analysis - Durable viral remission after stopping NUCs in HBeAg positive CHB



- Viral Remission:
  - HBV DNA ≤ 2 x 104 IU/ml
- Biochemical Remission
  - ALT< ULN (14 studies)
  - ALT<1.25xULN (1 study)
  - ALT<2xULN (6 studies)

Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

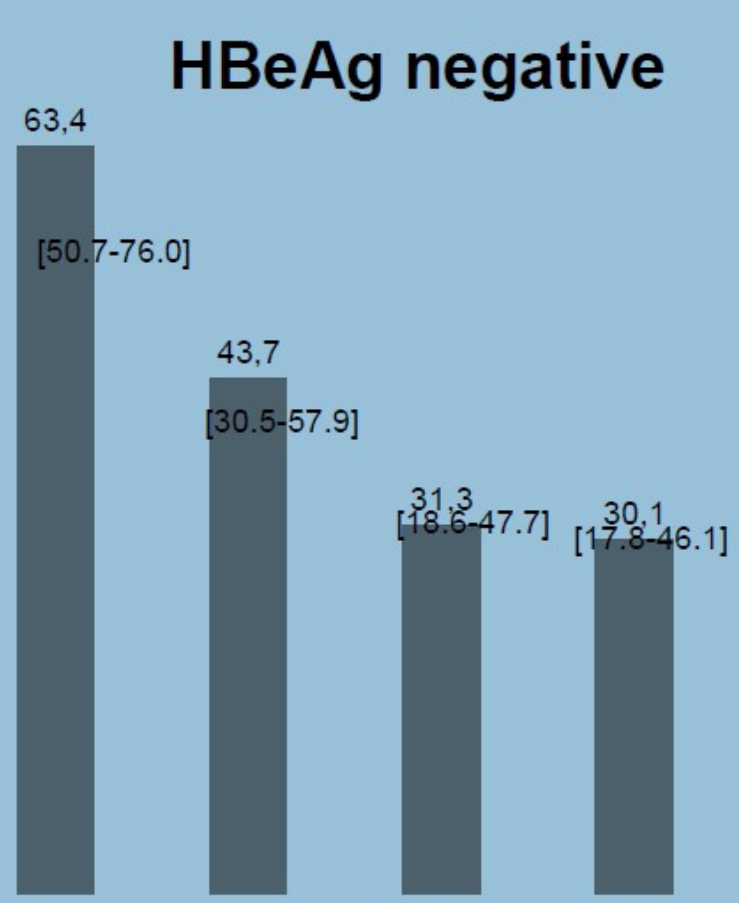
Meta-analysis - Factors associated with durable VR at 12 Months After stopping NUCs: HBeAg positive CHB

Characteristic	Prob of durable response	Odds Ratio	P value
HBeAg-positive patients			
VR defined by HBV DNA			0.289
<200 IU/mL	42.0 (16.6-72.4)	1	
<2000 IU/mL	71.2 (52.2-84.8)	3.41 (0.74-15.71)	
<20,000 IU/mL	63.1 (32.8-85.7)	2.37 (0.39-14.33)	
Duration of on-NA VR			0.544
<12 months	53.2 (27.4-77.4)	1	
12-24 months	72.0 (49.2-87.2)	2.26 (0.52-9.84)	
>24 months	60.3 (27.1-86.1)	1.33 (0.22-7.98)	
Duration of consolidation therapy after HBeAg seroconversion			0.928
<12 months	62.6 (38.5-81.8)	1	
≥12 months	64.1 (42.2-81.3)	1.06 (0.28-4.02)	

Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

HBeAg negative CHB

Meta-analysis - Durable viral remission after stopping NUCs in HBeAg negative CHB



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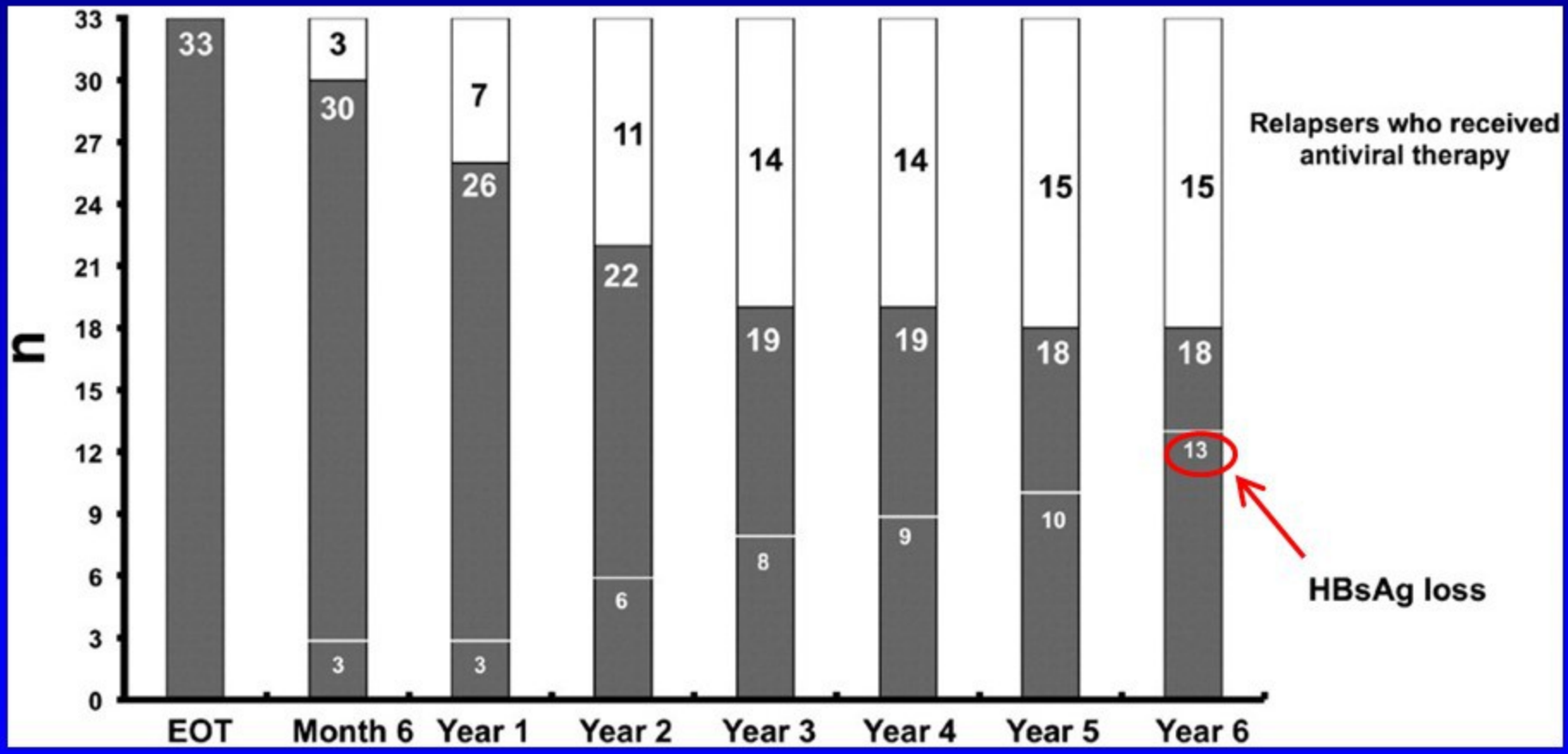
Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

Meta-analysis - Factors associated with durable VR at 12 Months After stopping NUCs: HBeAg neg CHB

Characteristic	Prob of durable response	Odds Ratio	P value
HBeAg-negative patients			
VR defined by HBV DNA			0.513
<200 IU/mL	29.3 (10.8-58.7)	1	
<2000 IU/mL	48.0 (30.6-65.9)	2.24 (0.53-9.41)	
Duration of on-NUC VR			0.005
<24 months	35.6% (24.6-48.2)	1	
>24 months	75.0% (51.1-89.6)	5.45 (1.68-17.70)	

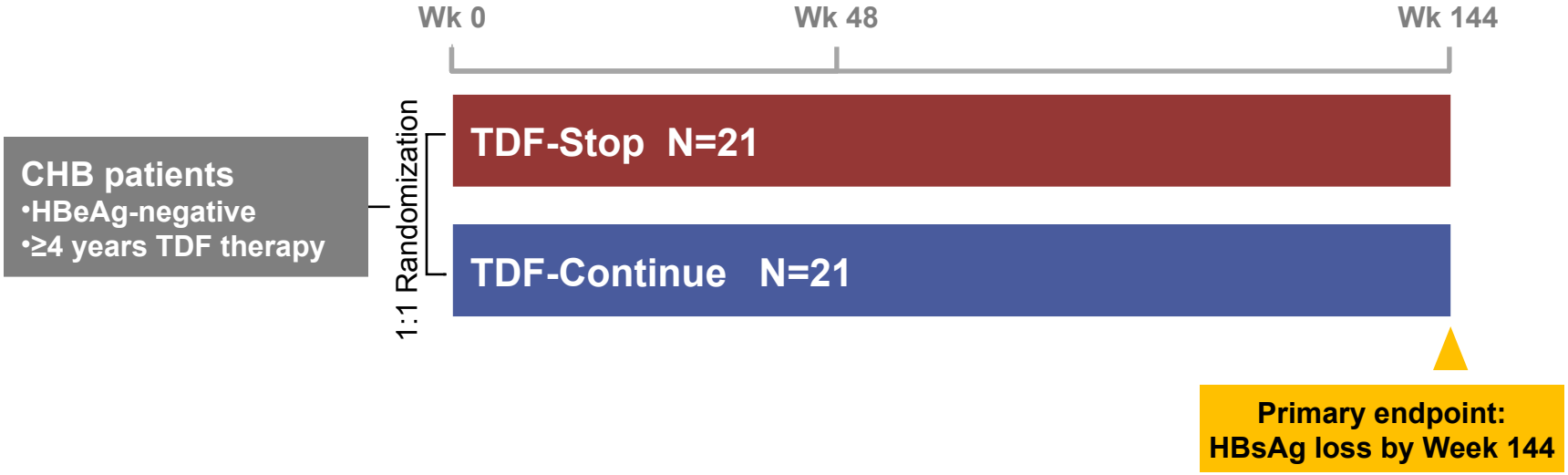
Papatheodoridis G et al, Hepatology 2016; 63(5): 1481-92

High Rate of Sustained Response and HBsAg Loss After 4-5 Years Adefovir Treatment in HBeAg- Patients



Hadziyannis S, Gastroenterol 2012; 143: 629

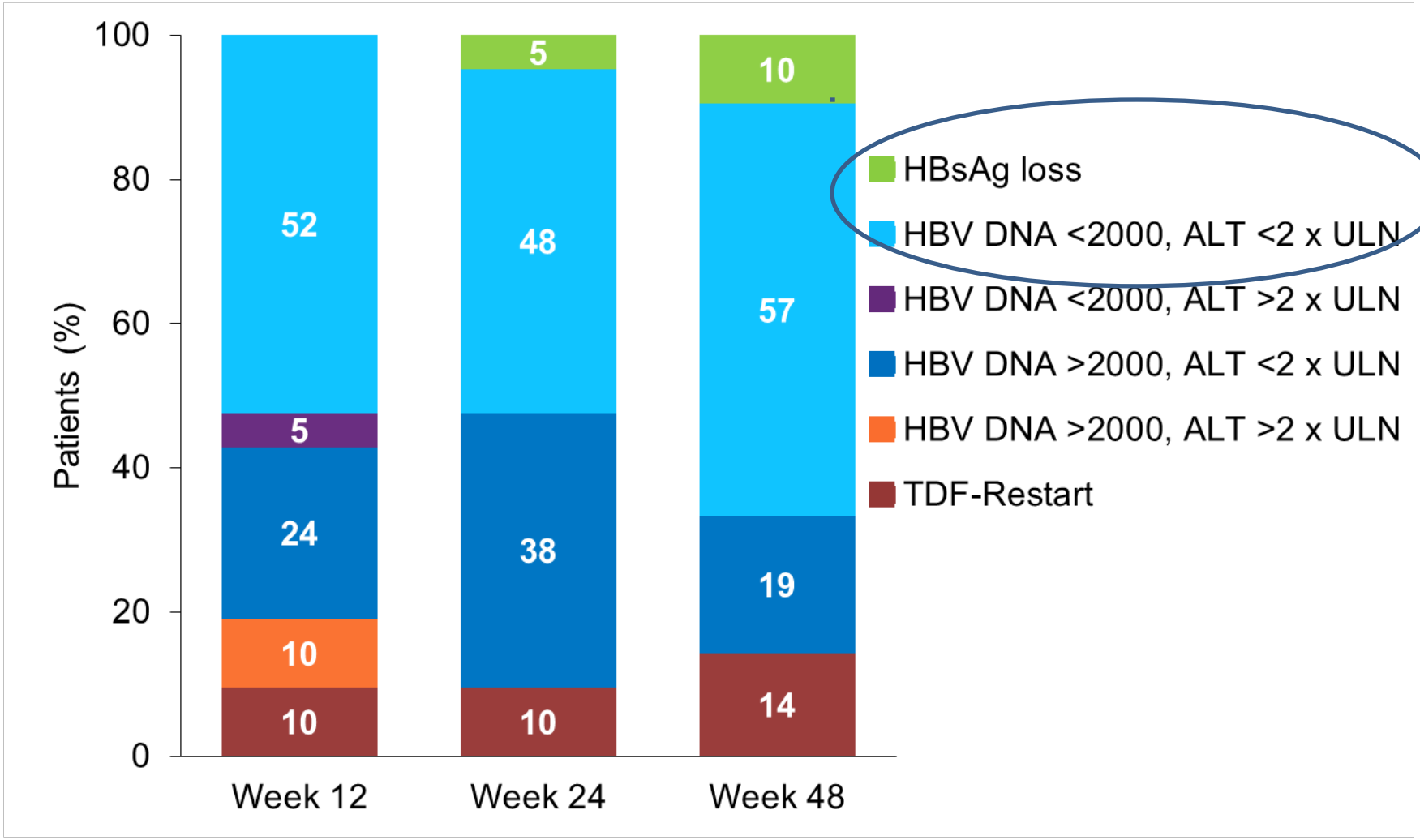
Stopping TDF After Long-Term Virologic Suppression in HBeAg-Negative CHB: Week 48 Interim Results From an Ongoing Randomized, Controlled Trial ("FINITE CHB")Study Design



- Open-label, multicenter, randomized, controlled trial
- HBeAg-negative at TDF initiation and randomization
- HBV DNA <400 copies/mL for ≥3.5 years before randomization
- No cirrhosis (Fibroscan ≤10 kPa), normal ALT, HBeAg-, anti-HBe+, HBsAg+
- No history of decompensated liver disease

Berg T et al. 2017

TDF Cessation
HBsAg loss, HBV DNA, ALT, TDF-Restart in 21 Patients



Berg T et al. EASL 2015

Study weekness

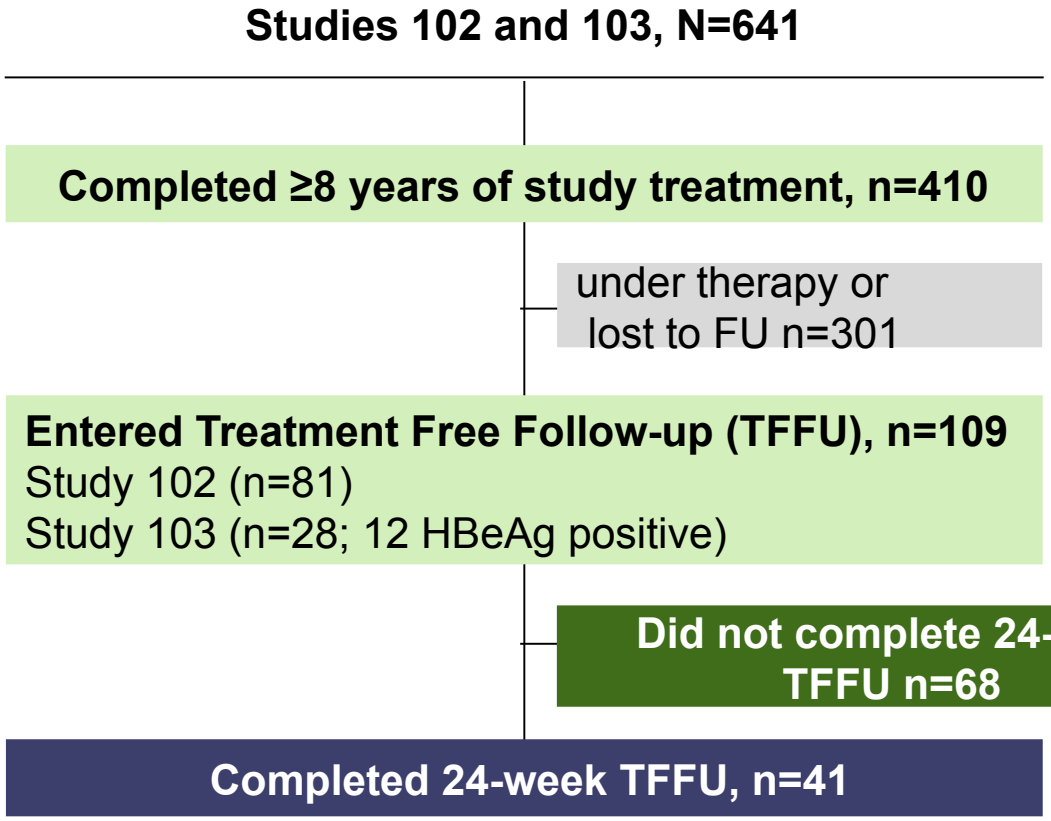
Small number of patients

Retreatment criteria

Most Gen D

Randomized Trial, but not enough to define recommendations

TDF Cessation after 8 years of therapy

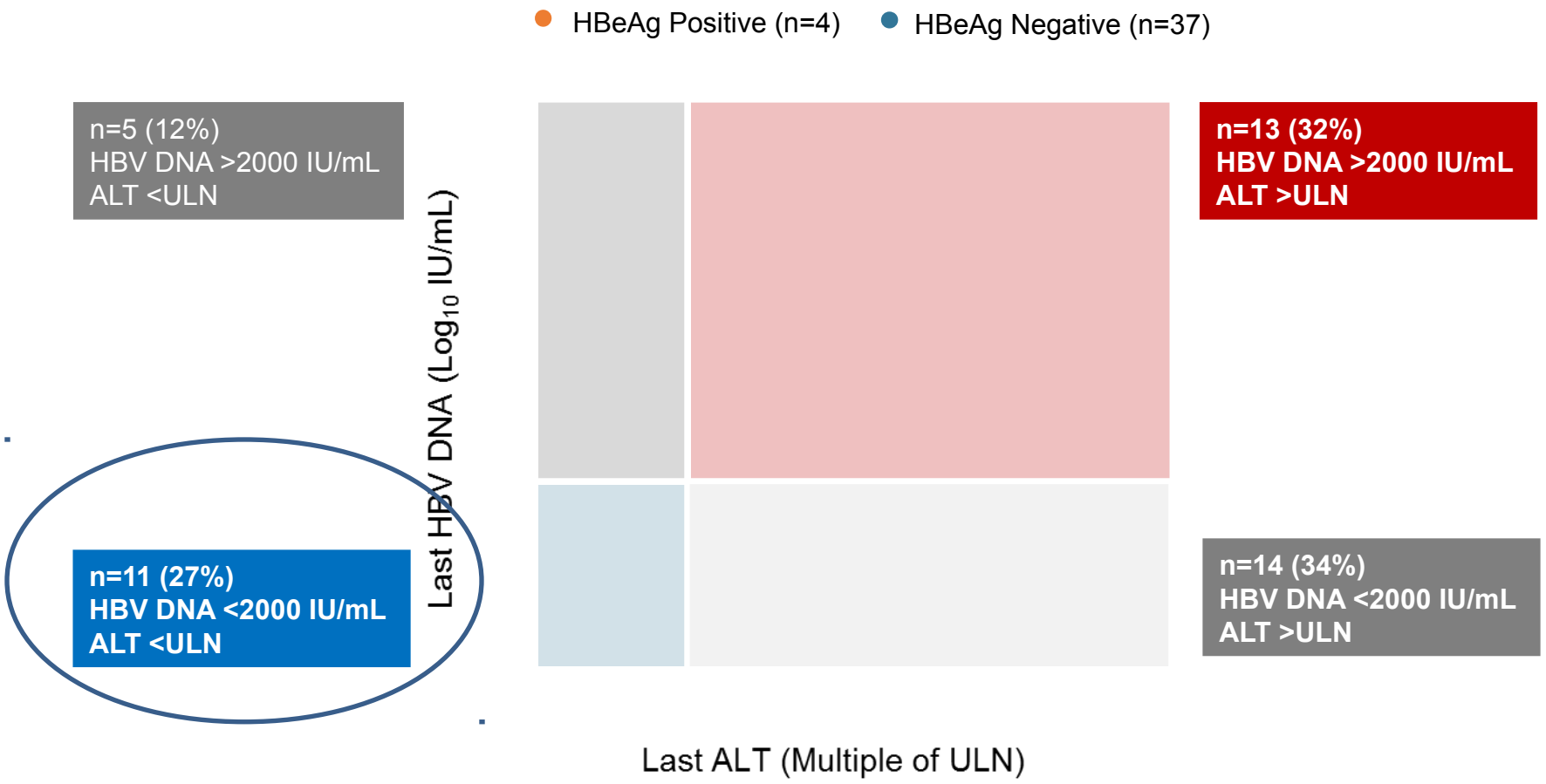


Mean age, year (SD)	46 (10)
Male, n (%)	35 (85)
Asian race, n (%)	20 (49)
A	4 (10)
B	10 (24)
C	7 (17)
D	18 (44)
Ishak F5-F6, n (%)	9 (22)
HBeAg positive, n (%)	7 (17)
ALT ≤ULN, n (%)	3 (7)

Buti M et al.AASLD 2015.

Week 24 HBV DNA and ALT

24-week TFFU Completers (n=41)



3 Patients with HBsAg loss

Buti M et al.AASLD 2015.

Predictors of HBV DNA <2000 IU/mL

24-week TFFU Completers (n=41)

	Univariate		Multivariate	
	Odds Ratio (95% CI)	p-Value	Odds Ratio (95% CI)	p-Value
Negative vs positive HBeAg (at 24-week TFFU)	16.3 (0.6, 458.5)	0.10	1.10 (0.01, 154.34)	0.97
HBV DNA $\log_{10}$ IU/mL (at baseline)	0.45 (0.24, 0.83)	0.01	0.60 (0.30, 1.18)	0.14
Genotype				
A vs Other	2.29 (0.22, 24.08)	0.49	0.36 (0.07, 1.74)	0.20
B vs Other	0.37 (0.09, 1.58)	0.18		
C vs Other	0.93 (0.18, 4.84)	0.93		
D vs Other	1.21 (0.34, 4.25)	0.77		
Age <40 vs ≥40 years (at EOT)	0.09 (<0.01, 2.76)	0.16	0.27 (<0.01, 108.02)	0.67

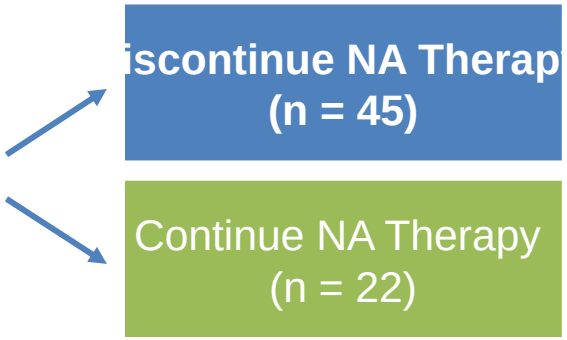
- p >0.2 in univariate and not included in multivariate: race, gender, last on-treatment BMI and HBV DNA, cirrhosis status at baseline or Week 240, baseline HBsAg level

Buti M et al.AASLD 2015.

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

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

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)

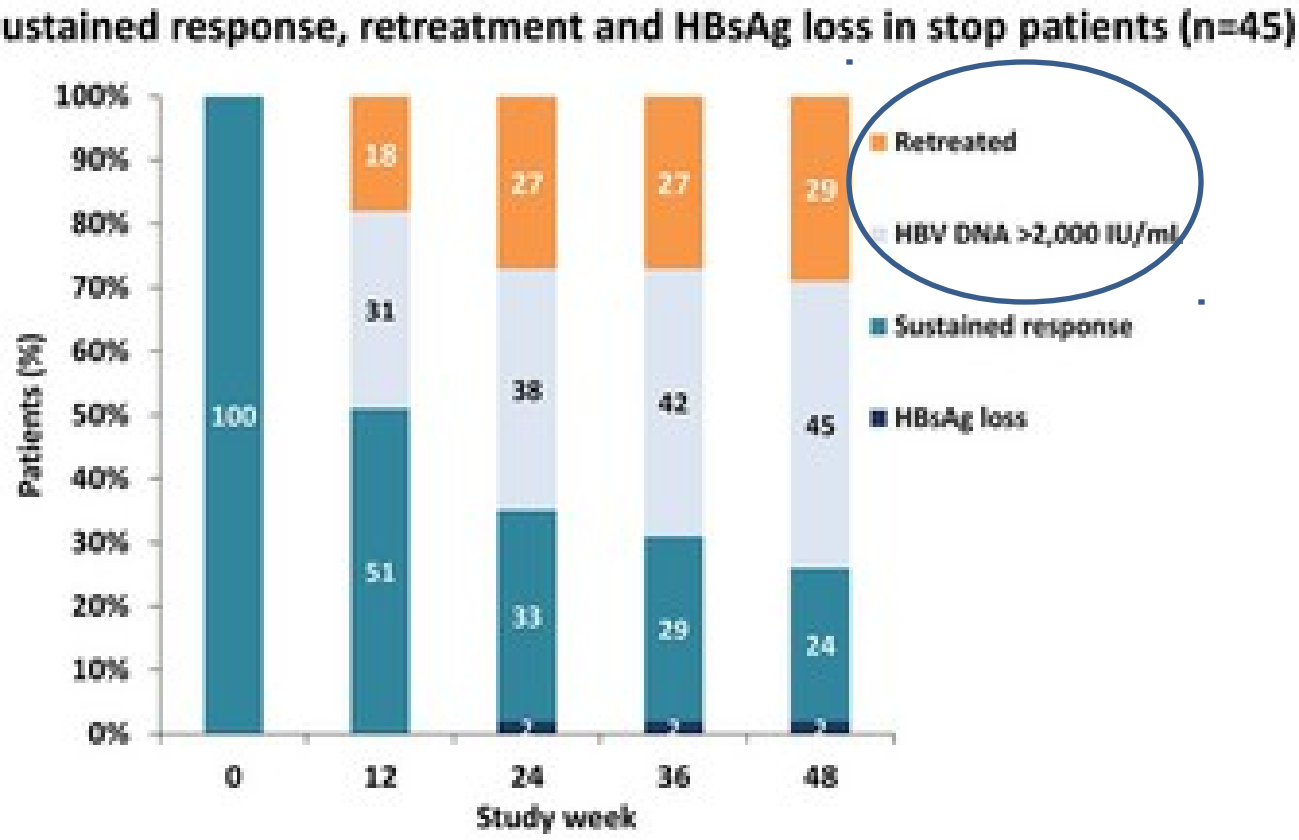


Primary endpoint: HBV DNA < 2000 IU/mL at Wk 48

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

Limited Sustained Response and Lack of HBsAg Decline after Stopping Long‐Term Nucleos(t)Ide Analogue Therapy in Hbeag Negative Patients with Chronic Hepatitis B: Results of a Prospective, Randomized, Open‐Label Phase IV Trial



Liem et al abs 286 AASLD 2018

Durability of Nucleos(t)ide Analogues Treatment in Patients With Chronic Hepatitis B

I-Cheng Lee, MD, PhD, Cheuk-Kay Sun, MD, Chien-Wei Su, MD, PhD, Yuan-Jen Wang, MD,

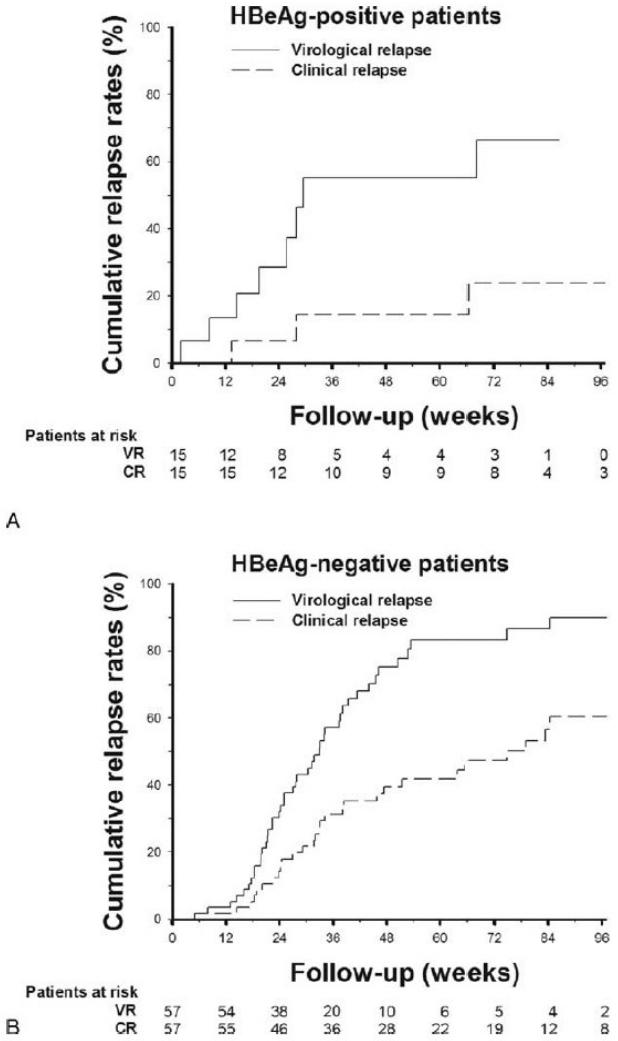


FIGURE 2. Cumulative rates of VR and CR after cessation of nucleos(t)ide analogues in patients with chronic hepatitis B and achieving APASL treatment endpoint. (A) VR and CR rates in HBeAg-positive patients. (B) VR and CR rates in HBeAg-negative patients. CR = clinical relapse, VR = virological relapse.

TABLE 3. Univariate Analyses of Factors Associated With Virological and Clinical Relapses in 15 HBeAg-positive CHB Patients Achieving APASL Treatment Endpoint

		Virological Relapse			Clinical Relapse		
		HR	95% CI	*P*	HR	95% CI	*P*
Age, y	>40 vs ≤40	2.227	0.518–9.570	0.282	0.484	0.044–5.364	0.554
Sex	Male vs female	1.475	0.293–7.432	0.638	0.217	0.019–2.419	0.214
NUCs	ETV vs LAM/ADV/Ldt	0.394	0.093–1.672	0.207	0.456	0.041–5.103	0.524
Treatment duration	157 weeks vs >157 weeks	0.502	0.115–2.186	0.358	2.523	0.228–27.873	0.450
Baseline HBV DNA, IU/mL	$>10^5$ vs $\leq 10^5$	1.005	0.188–8.544	0.996	0.129	0.008–2.111	0.151
EOT HBsAg, IU/mL	>100 vs ≤100	22.393	0–6.96×10^9	0.801	22.647	0–2.79×10^{11}	0.792
	>200 vs ≤200	22.393	0–6.96×10^9	0.801	22.647	0–2.79×10^{11}	0.792
	>500 vs ≤500	27.147	0.002–319004	0.490	25.971	0–4.56×10^{11}	0.787
	>1000 vs ≤1000	1.951	0.334–11.386	0.458	0.013	0–1.36×10^5	0.598

CHB = chronic hepatitis B, CI = confidence interval, EOT = end of treatment, HBV = hepatitis B virus, HR = hazard ratio, NUCs = nucleos(t)ide analogues.

Retrospective study
Treatment with
LAM
ADV
ETV
TDF

Risks of Stopping NUCs

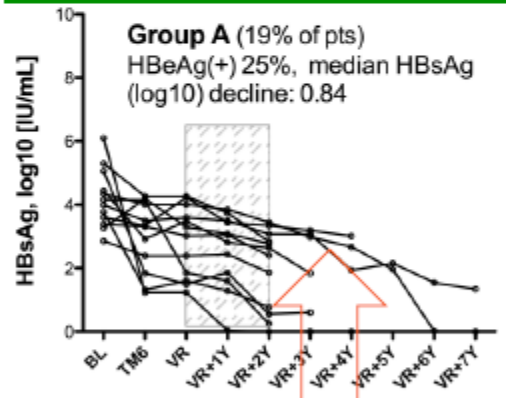
- **Viral Relapse**
- **ALT flare**
- **Clinical relapse, defined by ALT elevation and Viral relapse**
- **Hepatic Decompensation**
- **Unknown impact on HCC incidence?**

qHBsAg as a predictor of HBsAg seroclearance during NUC therapy

Different HBsAg decline pattern: Most patients show no significant HBsAg decline during NUC therapy

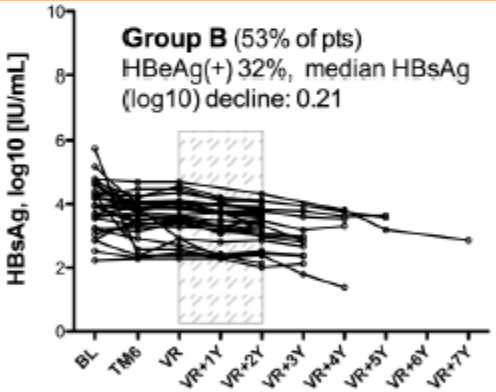
19%

A) >0,5-log decline
6 months after VR



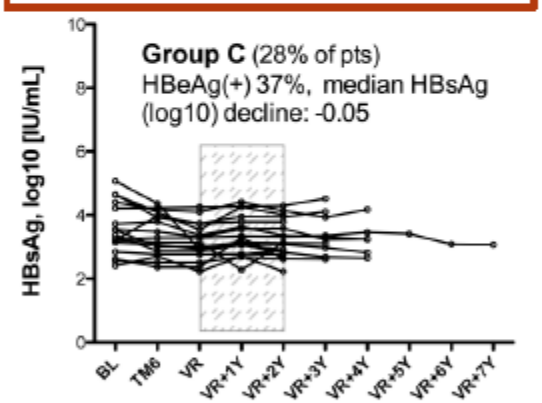
53%

B) 10%-0,5-log decline
6 months after VR



28%

C) <10% Abfall
6 Monate nach VR



Which is the CO velue of HBsAg to predict sustained viral supression?

Are these the best candidates for stopping Tx?

Jaroszewicz et al., Antiviral Therapy 2011

Not Available in many countries

How about qHBsAg as a tool for stopping NUCs in HBeAg negative patients ?

Study	n	qHBsAg cutoff	Sensitivity	Specificity	AUROC
Chen	105	<117 IU/ml	95%	76%	0.91
Chan	53	<100 IU/ml	78%	96%	0.91
Hadziyannis	39	<1000 IU/ml	?	?	?

How low ?
How long?

→ Still not ready for decision making…

[1]Chen et al, J Hepatol 2014;61:515-22, [2]Chan et al, Antivir Ther 2011;16:1249-57, [3]Hadziyannis et al, Gastroenterol 2012;143:629-36

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	Findings
(N = 135)[1]	▪ HBcrAg, HBsAg independently predict off-treatment clinical relapse, can be combined with age, ALT, and TDF use in novel risk score
DARING-B (N = 60)[2]	▪ 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
(N = 103)[3]	▪ 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
(N = 15)[4]	▪ HBcrAg or pregenomic HBV RNA at TDF d/c may predict

1. Hsu

CONCLUSIONS (I)

1. **Stopping NUCs may be beneficial in some well selected non cirrhotic patients, mainly HBeAg + ones, but it is not clearly known the predictors of VR, so far**
2. **There are no consensus on stopping NUCs among all Associations (EASL/ALEH/AASLD/APASL)**
3. **There are no good predictors of HBs Ag clearance**
4. **kinetic of HBV DNA relapse seems to be different : faster after Tenofovir (> 70 % wk 12) but slower with Entecavir (< 10 % wk 12)**

CONCLUSIONS (II)

Stopping NUCs during the treatment of chronic hepatitis B should be avoided until we are aware about the predictors of response. In addtion, more randomized trials with a larger number of patients with different genotypes, including asian and non-Asian patients and differentiating patients using ETV and TDF, are needed

Take home message

We have many things to stop before we worry about stopping NUCs:

- **Relapse of Fascism**
- **The commercial war**
- **European separatist movements**
- **The Brexit**
- **The wall USA / Mexico**
- **Corruption in Latin America**
- **The racism**
- **Religious intolerance**

Salvador, Bahia

Amazonia

OBRIGADO
THANK YOU
MERCI