When Should We Stop NA Therapy?

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TORONTO CENTRE FOR LIVER DISEASE

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HBV TAG Meeting

VELUT ARBOR ÆVO

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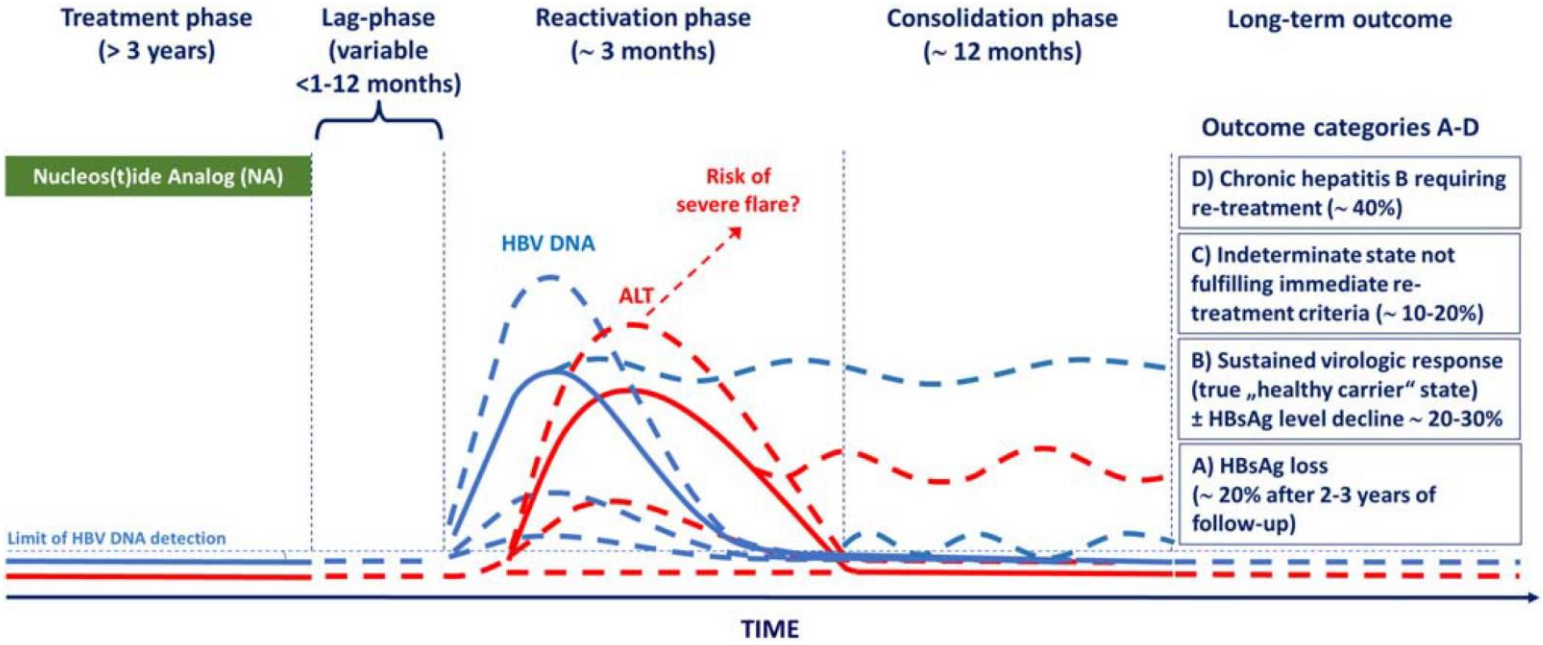
Why stop NA Therapy HBeAg negative CHB?
The good, the bad and the indeterminate outcome



Lampertico & Berg Hepatology 2018

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AASLD and EASL Guidance on NA Withdrawal

CHB treatment guidelines	EASL (2017)	AASLD (2018)
SOT HBeAg+ve	HBeAg seroconversion with >12 months of consolidation + HBVDNA neg	HBeAg seroconversion with >12 months of consolidation + HBVDNA neg
SOT HBeAg-ve	May be considered after 3 yrs viral suppression	May be considered after HBsAg loss

All guidelines recommend to consider stopping after in HBsAg loss and 12 months consolidation. No NA withdrawal recommended in cirrhosis.

1. EASL Clinical Practice Guidelines. J Hepatol 2017; 67: 370; 2. Terrault NA et al. Hepatology 2018;67: 1560; 3. Sarin SK et al. Hepatol Int 2015

Retrospective Cohort Studies: HBsAg Seroclearance after NA Withdrawal

Study	N	Tx duration	HBsAg loss	Incidence
Chan	53	27 mo	11/53	23% - 5 yrs
Hadziyannis	33	4-5 yrs	13/33	39% - 3 yrs
Chen	105	93 wks		30% - 6 yrs
Patwardhan	33	5.3 yrs	?	30% - 6 yrs
Hung	73	30 mo	20/73	46% - 6 yrs
Yao	119	151 wks	44/119	55% - 6 yrs
Berg	21 (42)	>4 yrs	4/21	19% - 144 wks
Jeng	691	156 wks	42/691	13% - 6 yrs
Papatheodoridis	57	5.3 yrs	12/57	25% 1.5 yrs

Prediction HBsAg loss in several studies: HBsAg level at stop below 100-1000 IU/mL

Courtesy F. Zoulim EASL PCG 2018; adapted from Jeng WJ et al. Hepatology 2018;68:425

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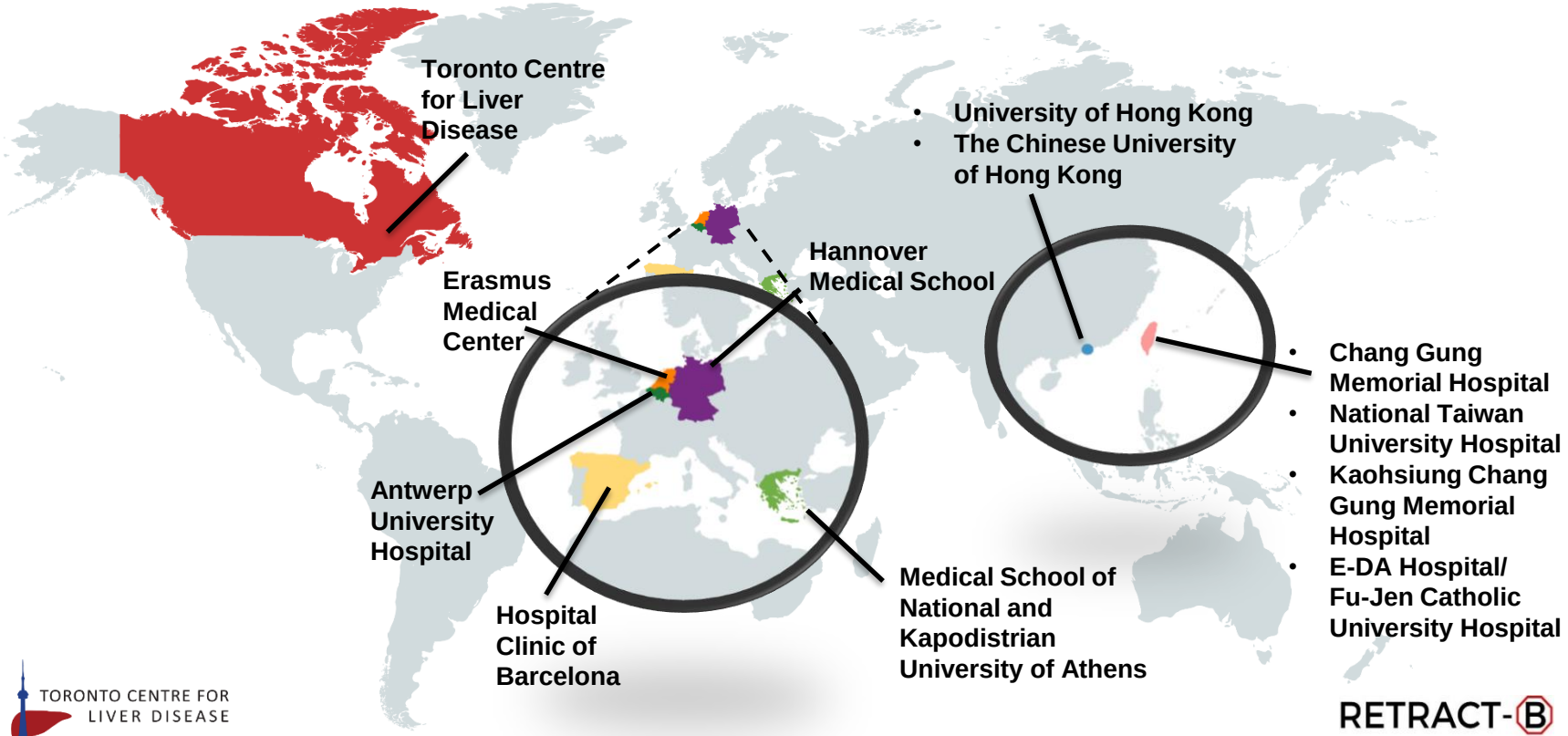
Retract-B Study

Global Cohort Stop Study n= 1541; 12 sites in 8 countries



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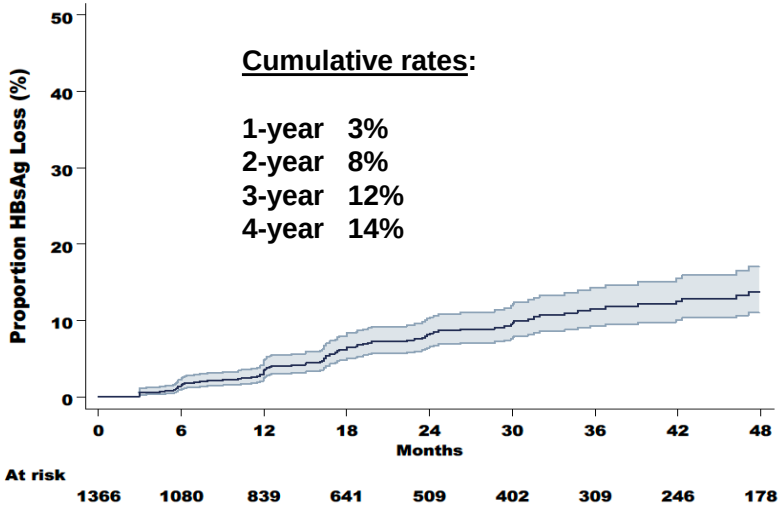
RETRACT-B
THE GLOBAL STUDY GROUP

– HBeAg negative at NA cessation: both HBeAg positive and negative at start of therapy
– Undetectable serum HBV DNA at NA cessation

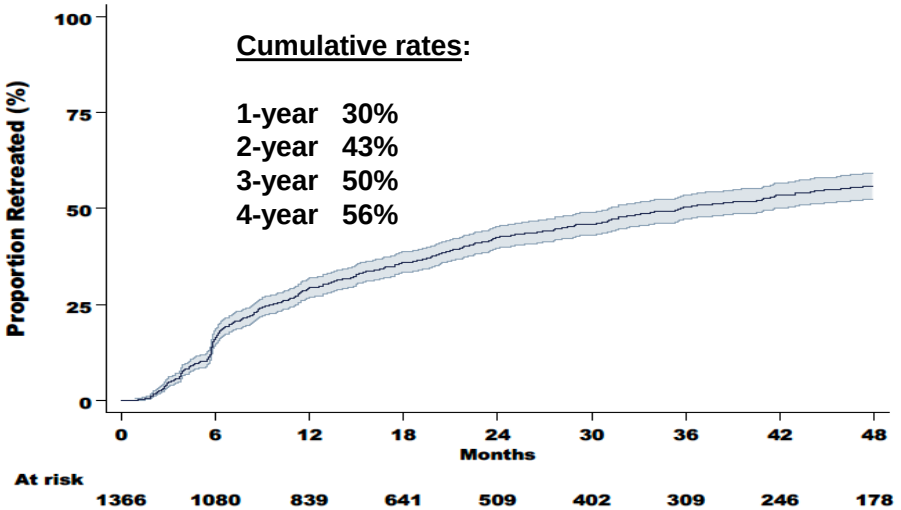
Hirode G, Janssen HL et al. AASLD 2020

Cumulative Rates of HBsAg Loss and Retreatment after NA Cessation

HBsAg Loss



Retreatment



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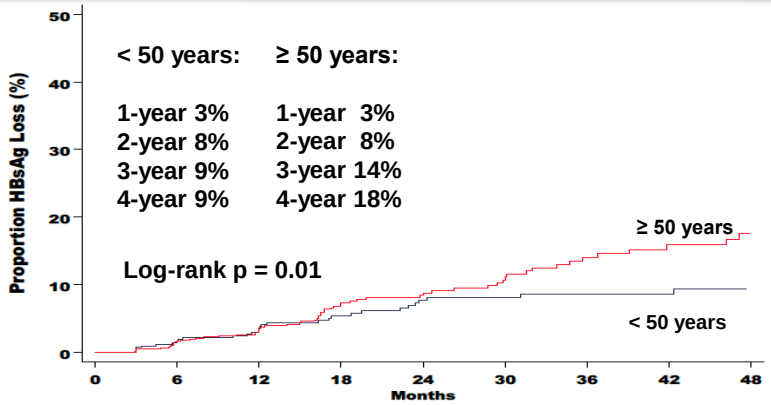
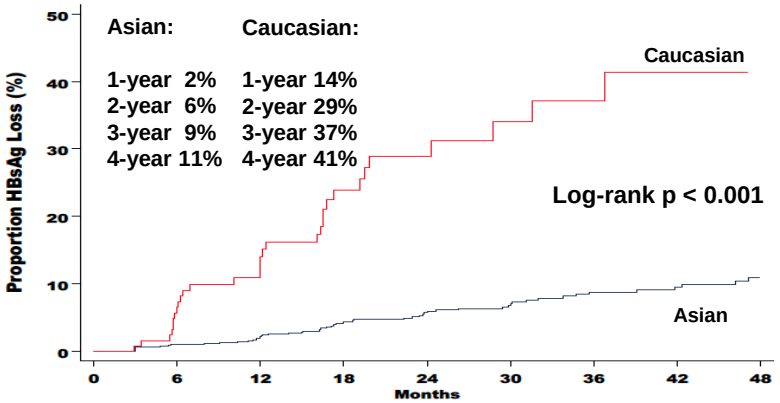
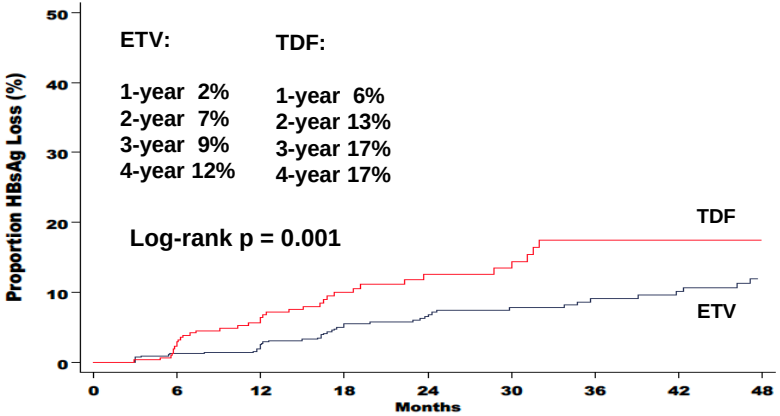
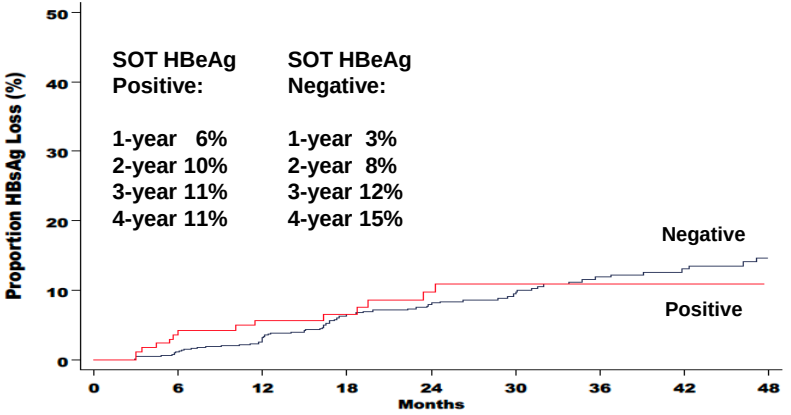
Hirode G, Janssen HL et al. AASLD 2020

Cumulative Rates of HBsAg Loss









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Hirode G, Janssen HL et al. AASLD 2020

Adverse Outcomes

	4-year Cumulative Rate (%)	Median Months from Baseline (IQR)
Virological relapse (HBV DNA ≥ 2000 IU/mL)	74	6 (4 – 12)
Combined relapse (HBV DNA ≥ 2000 IU/mL + ALT ≥ 2 x ULN)	56	8 (3 – 17)
ALT flare (≥ 5 x ULN)	33	10 (5 – 19)

- 15 (1%) patients experienced hepatic decompensation
- 12 (0.96%) patients died of which, 9/12 (75%) were reported as liver-related deaths

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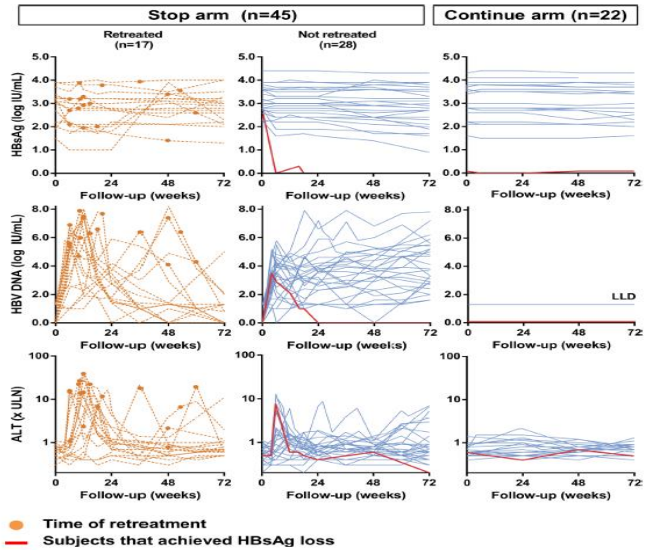
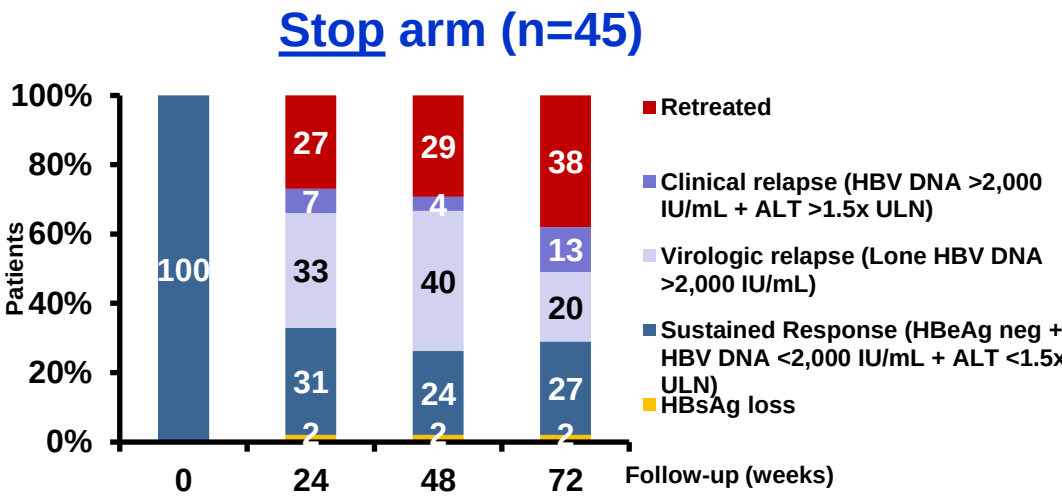
Hirode G, Janssen HL et al. AASLD 2020

NA discontinuation in HBeAg neg CHB
A RCT study – Toronto STOP study

67 NUC suppressed patients: age 50, 97% Asian, 92% HBeAg neg. ALT normal, DNA negative, HBsAg 3 log, duration of NUC 7 yrs, Fibroscan 5





Response Week 72: STOP VS Continue

HBsAg loss:	1 (2.2%) vs 1 (4.5%) p=NS
DNA <20 IU/ml:	1 (2.2%) vs 20 (91%), p<0.005
ALT <ULN:	21 (47%) vs 18 (82%), p=0.01
DNA+ALT:	13 (29%) vs 18 (82%), p<0.005

Liem KS, Janssen HL Gut 2019

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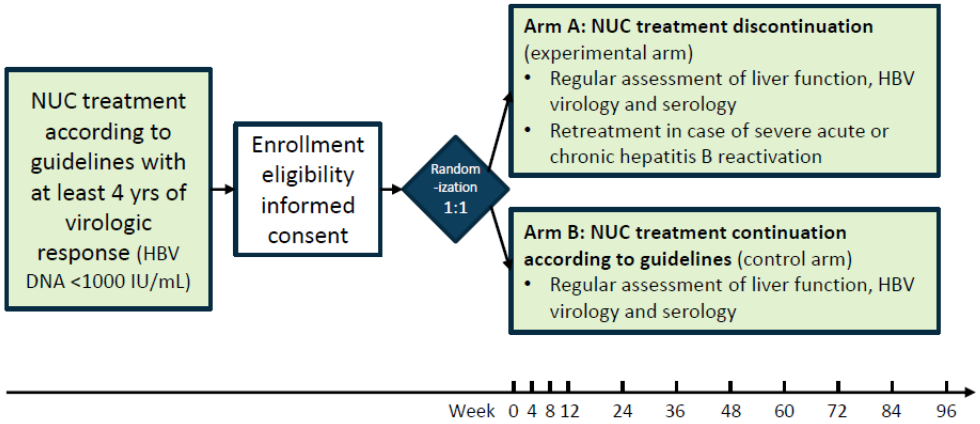
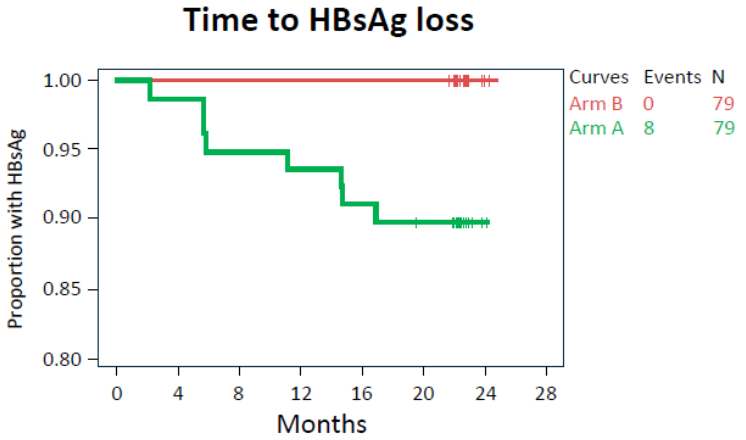
STOP NUC RCT in HBeAg Negative Patients

RCT in 158 patients, 80 % Caucasian, mostly treated with ETV and TDF





van Bommel et al. EASL 2020

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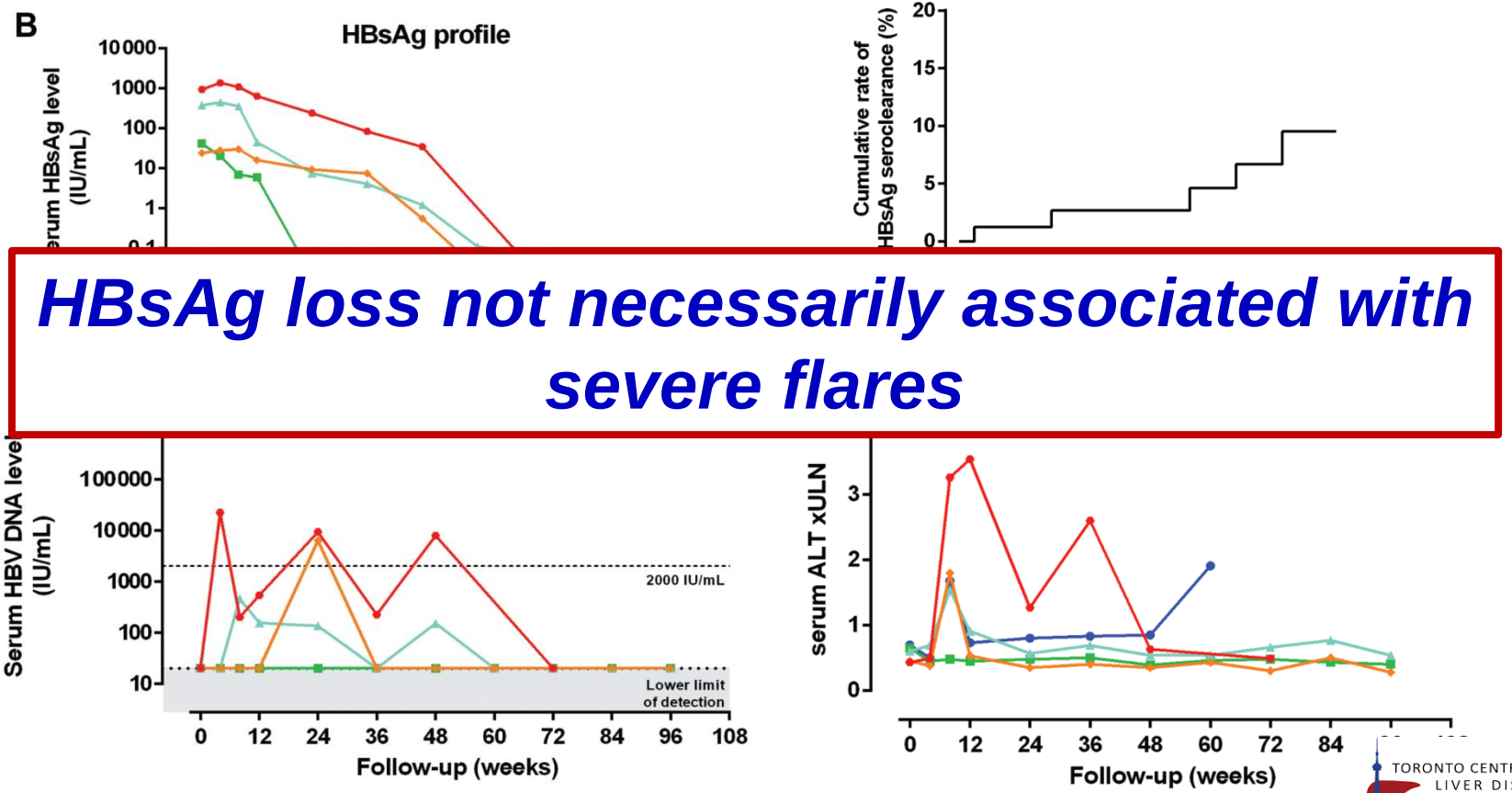
Risk Factors for Dangerous Withdrawal Flares

- Fibrosis state
- Retreatment policy
- Serological status: HBsAg < HBeAg neg < HBeAg pos
- Absence of anti-HBe
- Rise of HBV- DNA
- Amplitude/AUC of the flare
- Comorbidity

Profiles of HBVDNA and ALT in with HBsAg loss



HBsAg loss not necessarily associated with severe flares

Cao J et al. J Infect Dis 2017; 215: 581

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Retreatment criteria after NAs withdrawal in CHB

EASL, AASLD, APASL: No specific criteria

Indications for retreatment in patients with:

- Flares > 5-10x ULN +/- increase bilirubin and INR
- Persistent mild to moderate liver disease activity: ALT>2-3 x ULN & HBVDNA >2,000 IU/mL for ≥ 6 months
- HBeAg seroreversion
- Timing of retreatment is very difficult since viral rebound should be permitted but not at the costs of dangerous flares

Liaw Y-F, Hepatology 2021; Terrault NA, Lok, A, Janssen HL, NIDDK Hepatitis B Research Network (HBRN) 2021

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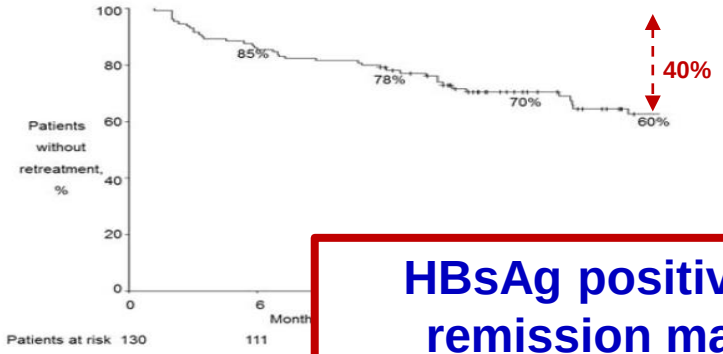
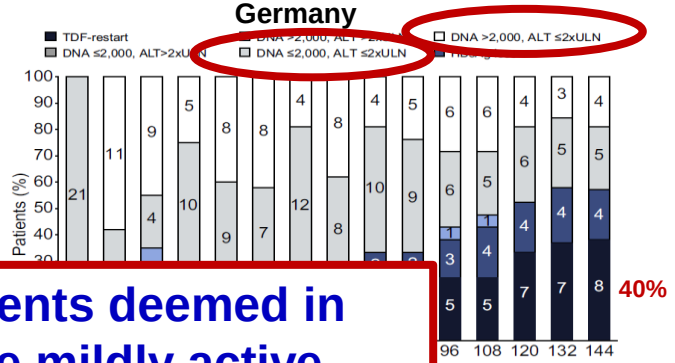
Retreatment Rates Continue to Rise over Time

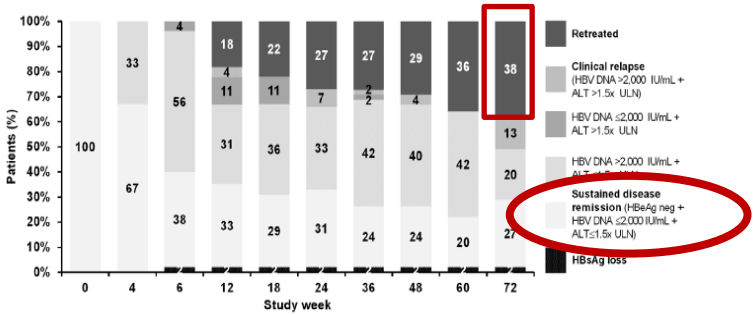
Greece and Taiwan



Germany



HBsAg positive patients deemed in remission may have mildly active disease not comparable to NA.



			Loss	
			Yes (n = 42)	
On treatment				
Nucleoside	587 (84.95%)	547 (84.3%)	40 (95.2%)	0.0712
Nucleotide	104 (15.05%)	102 (15.7%)	2 (4.8%)	
ETV	537 (83.78%)	504 (83.17%)	33 (94.29%)	0.0987
TDF	104 (16.22%)	102 (16.83%)	2 (5.71%)	
Time to normal ALT (weeks)	13.0 (0-157.0)	13.0 (0-157.0)	12.1 (2.0-124.7)	0.3032
Time to ud (weeks)	27.0 (4.0-165.9)	27.1 (4.0-165.9)	23.9 (4.0-56.0)	0.0016
Consolidation (weeks)	111.0 (48.0-385.4)	111.4 (48.0-385.4)	104.3 (51.1-308.0)	0.2483
Tx duration (weeks)	156.0 (60.9-429.6)	156.1 (60.9-429.6)	129.6 (75.0-312.7)	0.0005
HBsAg reduction (log)	−0.3 (−3.4 to 3.1)	−0.3 (−3.3 to 3.1)	−0.8 (−3.4 to 1.5)	0.0016
>1 log reduction	142 (20.55%)	124 (19.14%)	18 (41.86%)	0.0002
EOT age	55.2 (30.1-97.7)	55.3 (30.1-97.7)	53.9 (36.4-75.2)	0.1298
EOT HBsAg (IU/mL)	429.0 (0.1-28,109.0)	456.6 (0.7-28,109.0)	80.4 (0.1-1,913.6)	<0.0001
EOT HBsAg (Log_{10}IU/mL)	2.6 (−1.2 to 4.4)	2.7 (−0.2 to 4.4)	1.9 (−1.2 to 3.3)	<0.0001
Off therapy				
Follow-up duration (weeks)	155.1 (1.9-613.9)	150.3 (1.9-574.0)	268.6 (49.9-613.9)	<0.0001
VR	547 (79.16%)	527 (81.2%)	20 (47.6%)	<0.0001
CR	419 (60.64%)	408 (62.9%)	11 (26.2%)	<0.0001
Retreatment	281 (40.67%)	279 (43%)	2 (4.8%)	<0.0001
CR+ reTx+	269 (38.93%)	267 (41.14%)	2 (4.76%)	<0.0001
CR+ reTx−	150 (21.71%)	141 (21.76%)	9 (20.93%)	
CR− reTx+	12 (1.74%)	12 (1.85%)	0 (0%)	
CR− reTx−	260 (37.63%)	229 (35.34%)	31 (72.09%)	

Abbreviation: CR, clinical relapse; reTx, retreatment; Tx, treatment; ud, DNA undetectable; VR, virologic relapse.

Papatheodoridis G et al, Hepatology 2018; Berg T et al, J Hepatol 2017; Liem KS, Janssen HL et al, Gut 2019; Jeng WJ et al, Hepatology 2018

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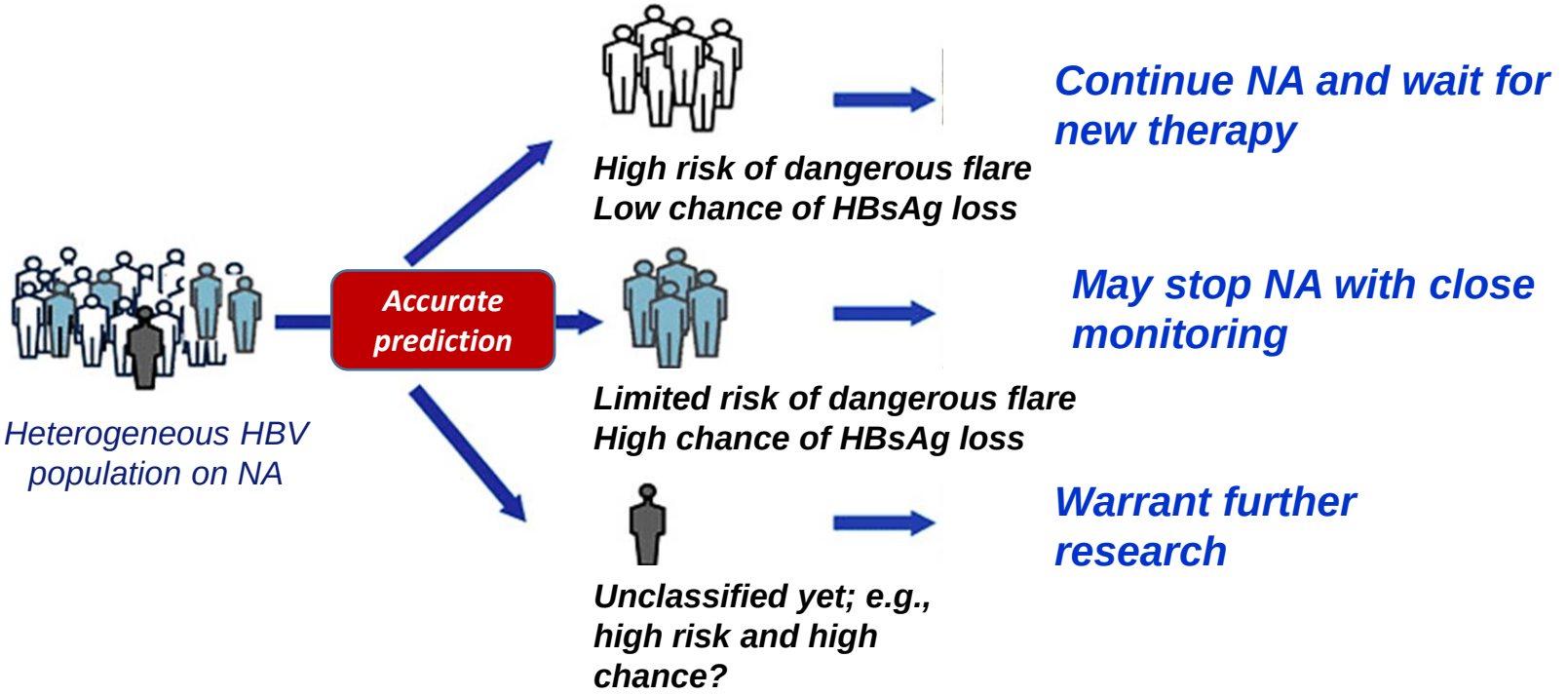
Individualized NA Withdrawal?



- *Decision to stop NA based on race and HBsAg level at EOT?*
- *Decision to retreat based on HBsAg/ALT kinetics?*

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Conclusion

NA Withdrawal in HBV

- HBsAg loss rates around 14% at 4 years after NA withdrawal
- Rate of HBsAg loss about 6 times higher among Caucasians vs Asians and about 22 times higher for those with EOT HBsAg level <100 IU/ml vs HBsAg level > 100 IU/ml
- Virological relapse in > 75%, ALT flares (5>ULN) in 33% and retreatment rate 56% at 4 years post NA withdrawal: increasing rates of retreatment with prolonged follow-up
- Many patients who remain HBsAg positive and are deemed in remission may have mildly active disease not comparable to NA. We need to assess the prognosis.
- Timing of retreatment is very difficult since viral rebound should be permitted but not at the costs of dangerous flares
- Individualized NA management:
  - NA stop based on race and EOT HBsAg level?
  - NA retreatment based on HBsAg/ALT kinetics?

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