

Stopping NA Treatment

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NA Stopping Rules for HBV therapy – Current Guidelines

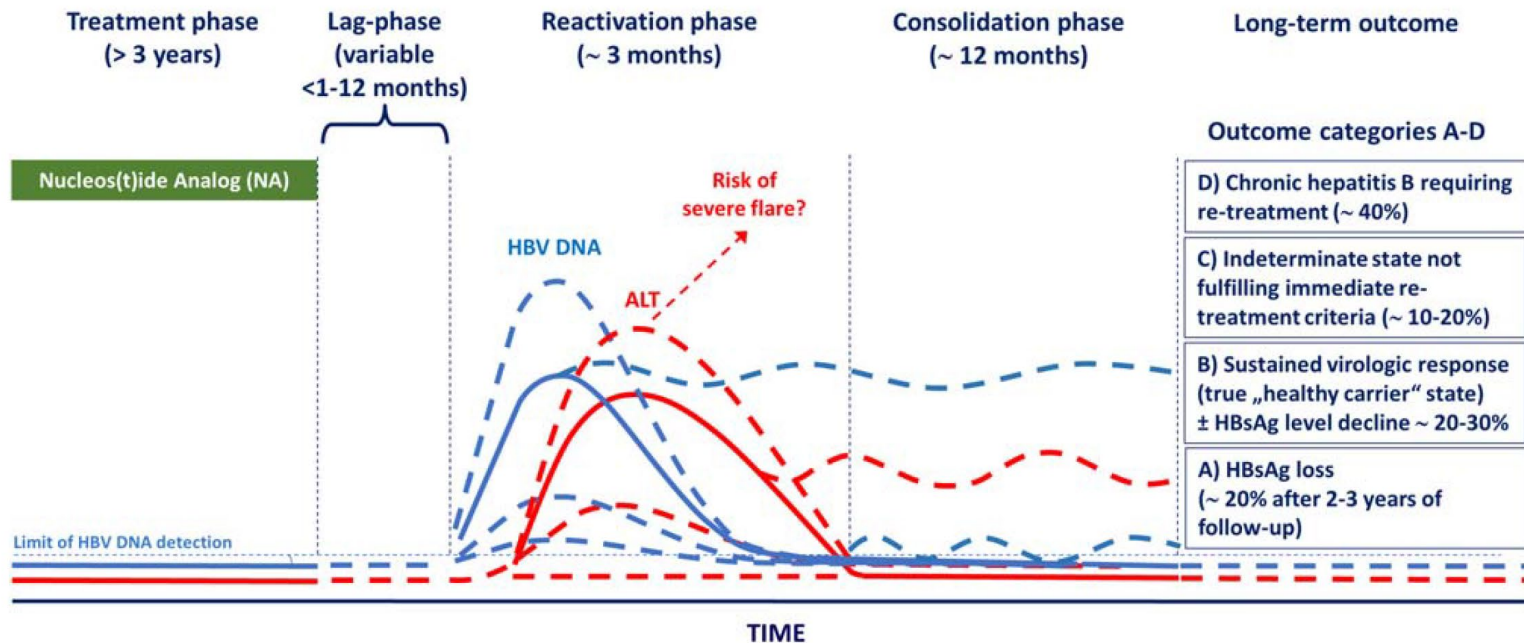
CHB treatment guidelines	EASL (2017)	AASLD (2018)	APASL (2015)
HBeAg+ve	HBeAg seroconversion with 12 months of consolidation + undetectable HBV DNA	HBeAg seroconversion with 12 months of consolidation + undetectable HBV DNA	HBeAg seroconversion and after at least 1 year (preferably 3 years) of additional therapy;
HBeAg-ve	In 2012: Indefinite In 2017: may be considered after 3 yrs viral suppression	Indefinite (discontinuation may be considered after HBsAg loss)	1. HBs seroconversion or HBsAg loss + \geq 1yr consolidation 2. Rx for at least 2 yrs with negative HBV DNA on 3 separate occasions, 6 months apart.

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

All guidelines exclude cirrhosis

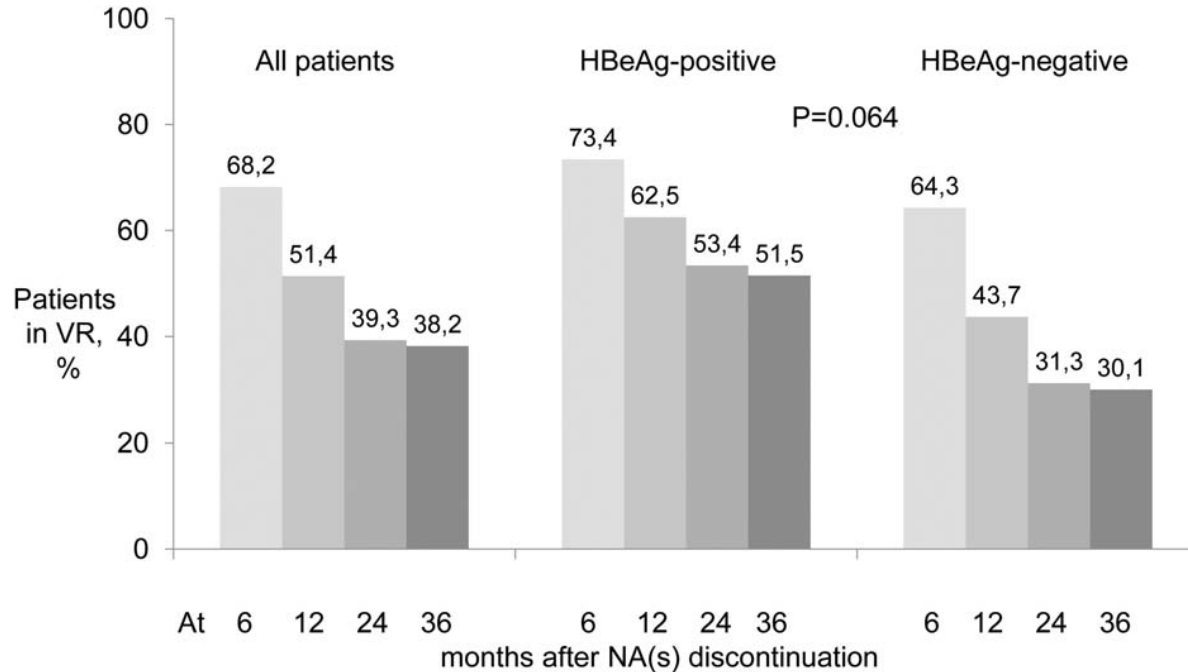
Why stop NA Therapy HBeAg negative CHB?

The good, the bad and the indeterminate outcome



Rates of virological remission after NAs discontinuation

SOT HBeAg+ (n= 733;14 studies) and SOT HBeAg- (n=967;17 studies)



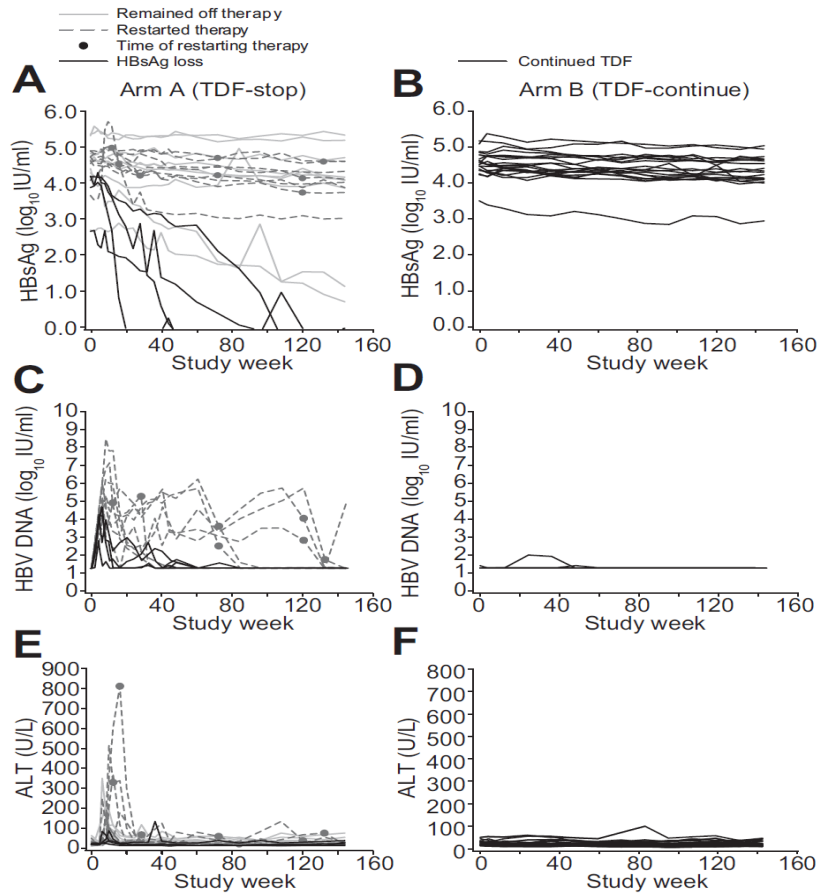
Posttreatment VR was defined by serum HBV DNA levels <20,000 IU/ml

Summary of studies HBsAg seroclearance after stop NA

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

*** Estimated Annual HBsAg loss of 1.78%**

Finite Study: RCT Stopping TDF after long-term viral suppression in HBeAg (-) patients



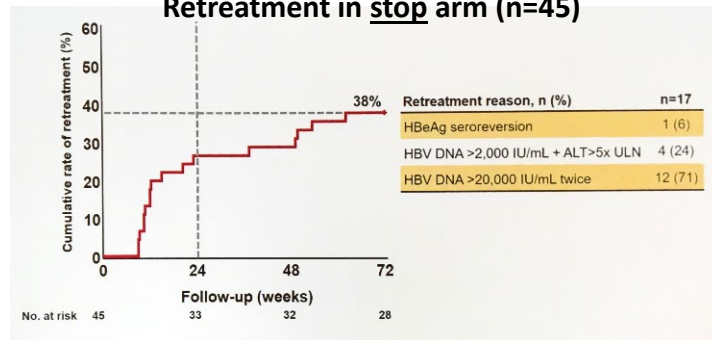
- 62% remained off treatment to wk 144
- Four patients (19%) HBsAg loss and three of them seroconversion
- Discontinuation was well tolerated

Stop Study: RCT Stopping NA after long-term viral suppression in HBeAg (-) patients

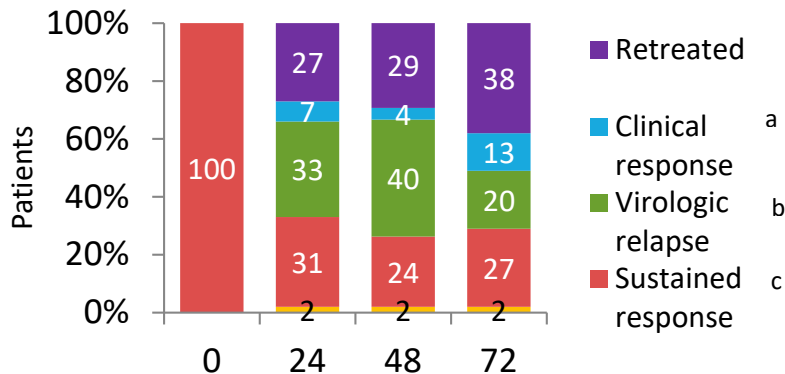
Primary endpoint and HBsAg loss

n (%)	Stop (n=45)	Continue (n=22)
HBV DNA <2000 IU/mL at Wk 48	11 (24)	21 (95)
HBsAg loss at Wk 48	1 (2)	1 (5)

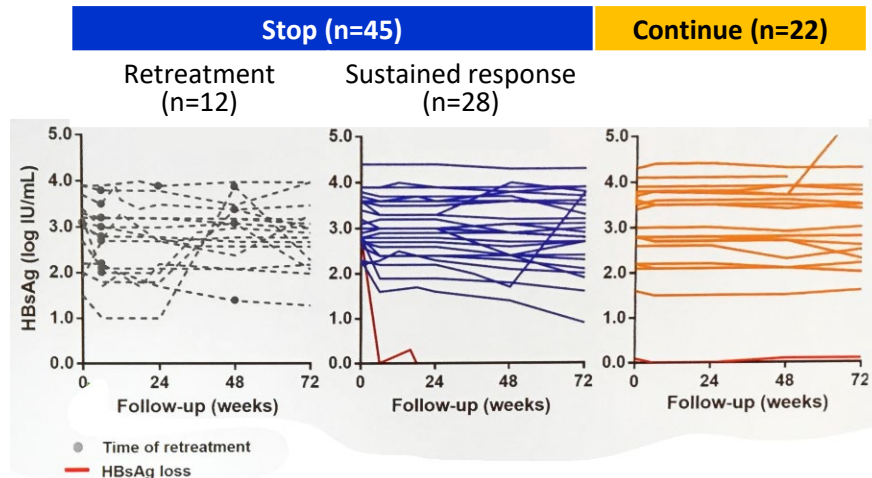
Retreatment in stop arm (n=45)



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



Limited HBsAg decline in all groups



^aHBV DNA >2000 IU/mL + ALT >1.5x ULN

^bone HBV DNA >2000 IU/mL

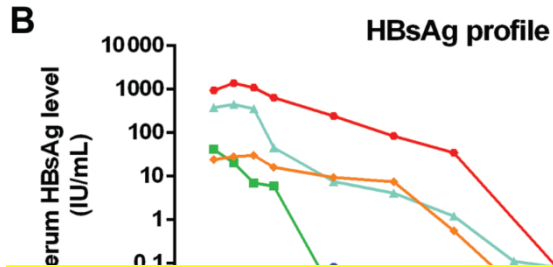
^cHBeAg -ve + HBV IU/mL DNA <2000 IU/mL + ALT <1.5x ULN

Outcome Predictors of NA Discontinuation

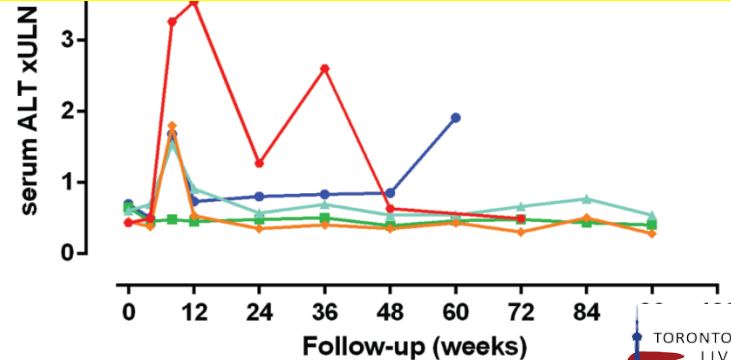
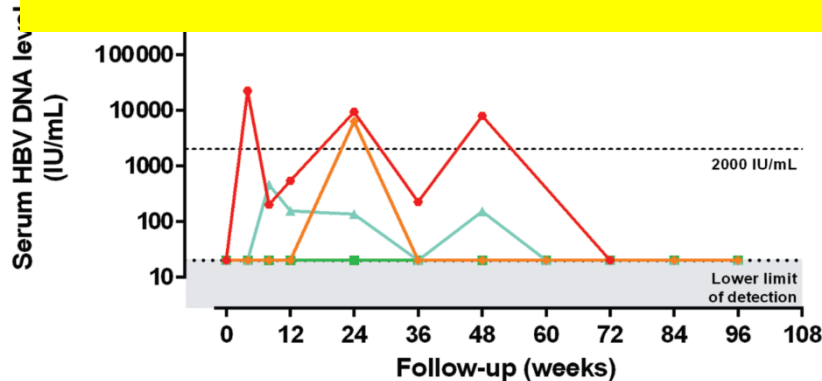
- Age, Race, HBV Genotype
- Time to undetectable HBV DNA
- Duration of viral suppression under NA
- HBsAg levels at NA baseline and at NA stop
- Type of NA: Tenofovir vs Entecavir?
- HBV-DNA levels during reactivation
- Re-treatment strategy

Most studies: HBsAg level at stop below 100-1000 IU/mL

Profiles of HBVDNA and ALT in with HBsAg loss

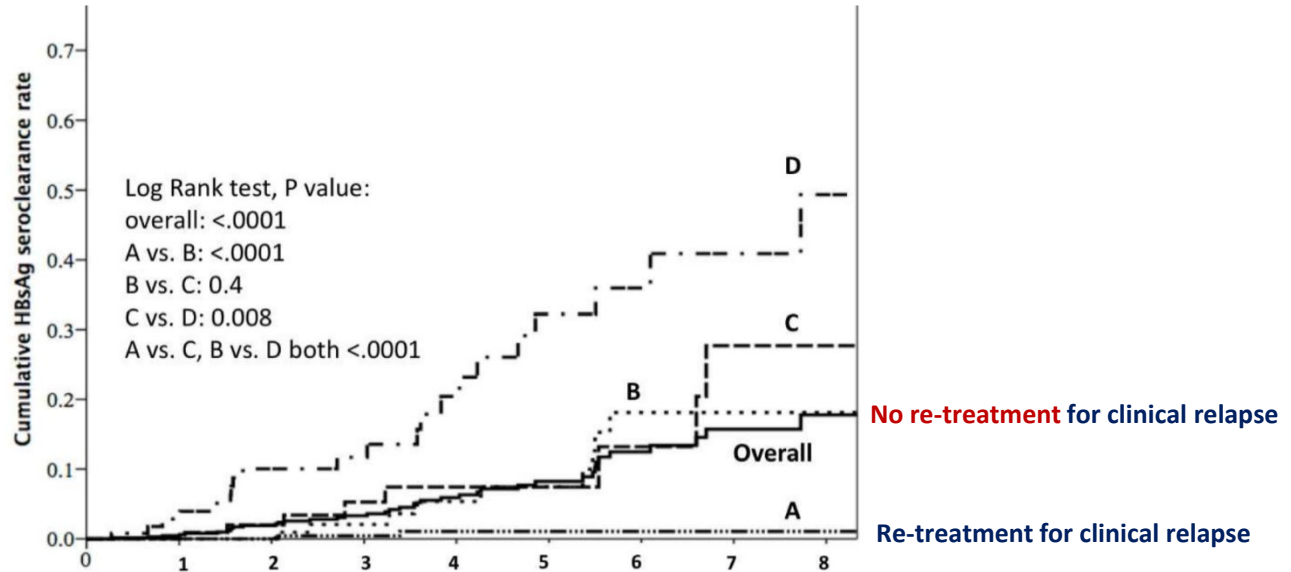


HBsAg loss not necessarily associated with severe flares



Stopping NA therapy in HBeAg-negative patients: Early re-treatment for clinical relapse reduces chance for HBsAg loss

Cumulative HBsAg loss after stopping NA



Virologic and biochemical relapse rates based on different cut-off levels: Risk of severe flares

Months After NA Discontinuation	HBV DNA									
	>2000 IU/mL				>20,000 IU/mL				>100,000 IU/mL	
	ALT > ULN	ALT >2x ULN	ALT >2x ULN on ≥ 2 occasions	ALT > ULN on ≥ 3 occasions	ALT > ULN	ALT >2x ULN	ALT >5x ULN	ALT >10x ULN	ALT >2x ULN	ALT >3x ULN
3	28%	23%	2%	5%	19%	18%	13%	10%	15%	12%
6	36%	29%	4%	9%	25%	23%	16%	11%	18%	14%
12	48%	38%	11%	15%	35%	30%	18%	11%	26%	20%
18	50%	42%	14%	22%	39%	34%	20%	12%	31%	25%
24	55%	42%	16%	25%	44%	38%	22%	12%	33%	27%

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 of the flare
- AUC of the flare
- Comorbidity

Reported fatal outcomes due to hepatic flares and decompensations after stopping NA

Study	Hepatic decompensation	Case fatality rate (death)	Presence of cirrhosis
Lim SG et al. 2002	n.a.	2 case reports	Yes
Jeng JW et al. 2018 (HBeAg negative, 45% cirrhosis)	9/308 pts with cirrhosis (3%) 9/691 overall (1.3%)	3/308 pts with cirrhosis (1%) 3/691 overall (0.4%)	Yes
Kuo YH et al. 2010	n.a.	1/401 (0.2%)	Yes
Chen C-H et al. 2018 (HBeAg negative, no cirrhosis)	2/263 (0.8%)	0/263 (0%)	No
Van Hees S et a. 2018 (HBeAg pos. with seroconversion)		1/62 (1.6%)	Yes (probable)
Chen C-H et al. 2018 (HBeAg positive, no cirrhosis)	3/148 (2%)	1/148 (0.7%) (HBeAg reversion after stopping)	No

Retreatment Policy

NIDDK Hepatitis B Research Network (HBRN)

- Any one of the three criteria: INR ≥ 1.3 , total bilirubin ≥ 3.0 mg/dL, direct bilirubin ≥ 1.0 mg/dL regardless of HBV DNA or ALT level
- Any clinical decompensation, regardless of HBV DNA or ALT level
- HBV DNA $> 10,000$ IU/mL and ALT > 1000 U/L
- A total of one HBV DNA value $> 10,000$ IU/mL and three ALT values > 300 U/L over 4 weeks
- A total of one HBV DNA value $> 10,000$ IU/mL and three ALT values > 150 U/L over 12 weeks
- HBeAg seroreversion

Conclusions

- Withdrawal of NA frequently results in a virologic and biochemical relapse
- Flares observed after NA discontinuation are often transient and likely represent a trigger for inducing a long-term HBV-specific immune control in a subset of patients
- Rates of HBsAg loss vary widely in different studies, may be higher in Caucasian patients and those with HBsAg < 100 IU/ml at treatment stop
- Flares with liver decompensation have been, mainly observed in patients with cirrhosis
- For safe and effective outcome of NA discontinuation, re-treatment should be initiated timely enough to prevent harm for the patient, but HBV DNA and ALT elevations should be tolerated to some extent to establish loss of HBsAg