OVERVIEW OF STOPPING NUCS IN CURRENT CLINICAL PRACTICE

Grishma Hirode, MSc

Toronto General Hospital
University Health Network
University of Toronto, Canada

TORONTO CENTRE FOR LIVER DISEASE

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Current clinical practice

- Main goals of nucleos(t)ide analogue (NUC) therapy for chronic hepatitis B (CHB) patients:
  - Long-term HBV DNA suppression
  - HBeAg loss, with or without anti-HBe seroconversion, in HBeAg positive CHB patients
  - ALT normalization
  - HBsAg loss, with or without anti-HBs seroconversion → optimal endpoint!
  - Improve survival and quality of life by preventing disease progression and HCC

- Current guidelines:
  - The Asian Pacific Association for the Study of the Liver (APASL) 2016
  - The European Association for the Study of the Liver (EASL) 2017
  - The American Association for the Study of Liver Diseases (AASLD) 2018

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Stopping NUC therapy

PRO

- Life-long therapy not required
  - Financial benefits?
  - Adherence/compliance?
- No NUC-related long-term side-effects or safety concerns
- Higher rates of HBsAg loss
  - On-therapy (annual incidence) ~1%[1,2]
  - Off-therapy (cumulative incidence) 0-55% over follow-up durations of 0.5-8 years[3,4]

CON

- NUCs are cheap in most regions, safe and effective, improve long-term outcomes, and monitoring is simple
- Prediction of response after stopping unclear:
  - Strict and frequent monitoring required
  - Non-compliance can result in severe or fatal flares
  - Costs?
- While for those who remain HBsAg positive, disease remission may be achieved, long-term HBV DNA undetectability may not be achieved
  - Risk of progression of fibrosis

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1. Yeo YH, et al. Gastroenterology 2019;156:635–646;10:1–98
2. Zhou K, et al. J Hepatol. 2017;67(2):370–98
3. Liem, et al. Gastroenterology 2020;158(5):1185-1190
4. Jeng et al. Hepatology 2018;68(2):425-434

Stopping guidelines: HBeAg positive patients

APASL 2016[1]	EASL 2017[2]	AASLD 2018[3]
HBsAg loss OR HBeAg seroconversion + Consolidation ≥12 months + Undetectable HBV DNA	HBsAg loss OR HBeAg seroconversion + Consolidation ≥12 months + Undetectable HBV DNA + No cirrhosis	HBsAg loss OR HBeAg seroconversion + Consolidation ≥12 months + Undetectable HBV DNA + No cirrhosis

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1. Sarin SK, et al. Hepatol Int. 2016;10:1–98
2. Lampertico P, et al. J Hepatol. 2017;67(2):370–98
3. Terrault NA, et al. Hepatology. 2018;67:1560–99

Stopping guidelines: HBeAg negative patients

APASL 2016[1]	EASL 2017[2]	AASLD 2018[3]
HBsAg loss + Consolidation ≥12 months or anti-HBs+ OR NUC therapy ≥24 months + Undetectable HBV DNA on three occasions 6 months apart + No cirrhosis	HBsAg loss OR May be considered in selected patients given the following: Viral suppression ≥36 months + No cirrhosis + Guaranteed post-NUC monitoring	HBsAg loss OR Compelling rationale

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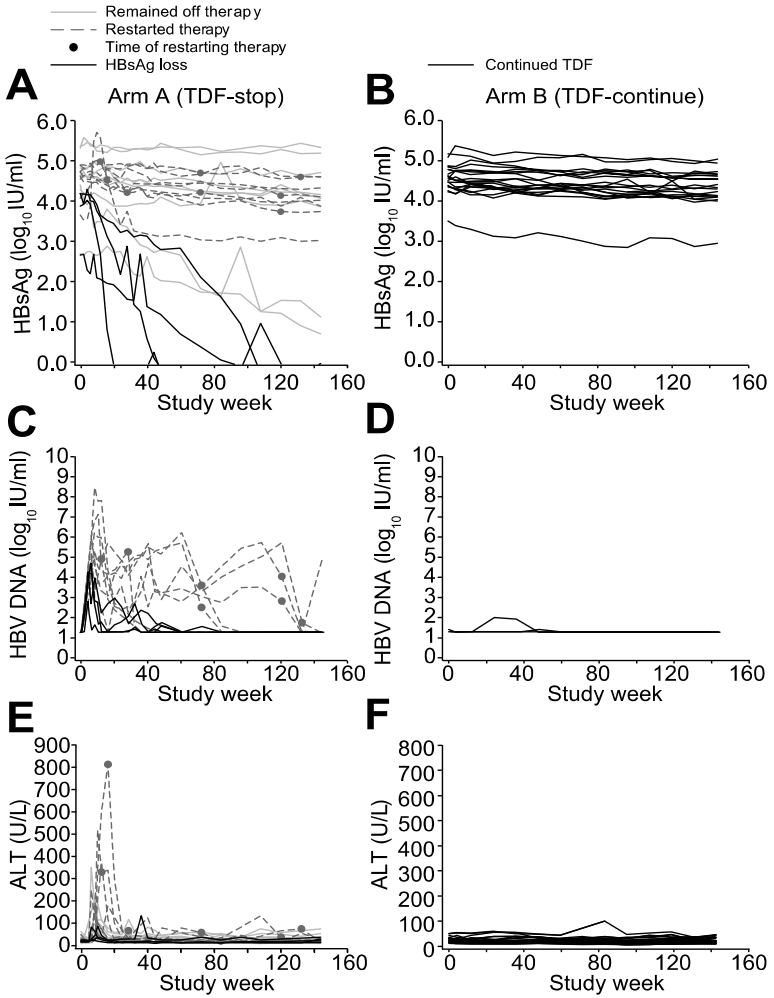
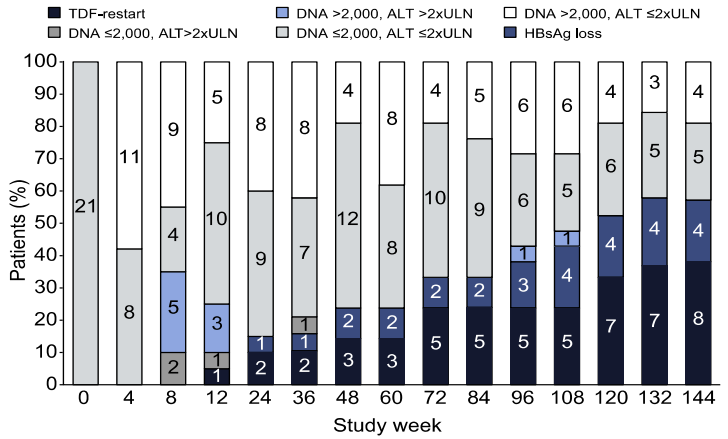
1. Sarin SK, et al. Hepatol Int. 2016;10:1–98
2. Lampertico P, et al. J Hepatol. 2017;67(2):370–98
3. Terrault NA, et al. Hepatology. 2018;67:1560–99

RCT: FINITE study

- **42 virally suppressed HBeAg negative patients** (21 stop, 21 continue):
  - 88% Caucasian
  - 100% TDF
  - Mean Fibroscan 5.6 kPa
- **Primary endpoint**:
  - HBsAg loss at 144 weeks
- **Conclusions**:
  - Higher HBsAg loss in stop arm at 144 weeks
  - No serious adverse events
  - Highly controlled cohort under strict observation!



	Stop vs. Continue	p
HBsAg loss at 144 weeks	19% vs. 0%	0.02



- **Retreatment criteria**:
  - ALT flares
  - Clinical relapse
  - Decompensation

For patients who fulfilled any of these criteria, TDF was restarted at the discretion of the investigator

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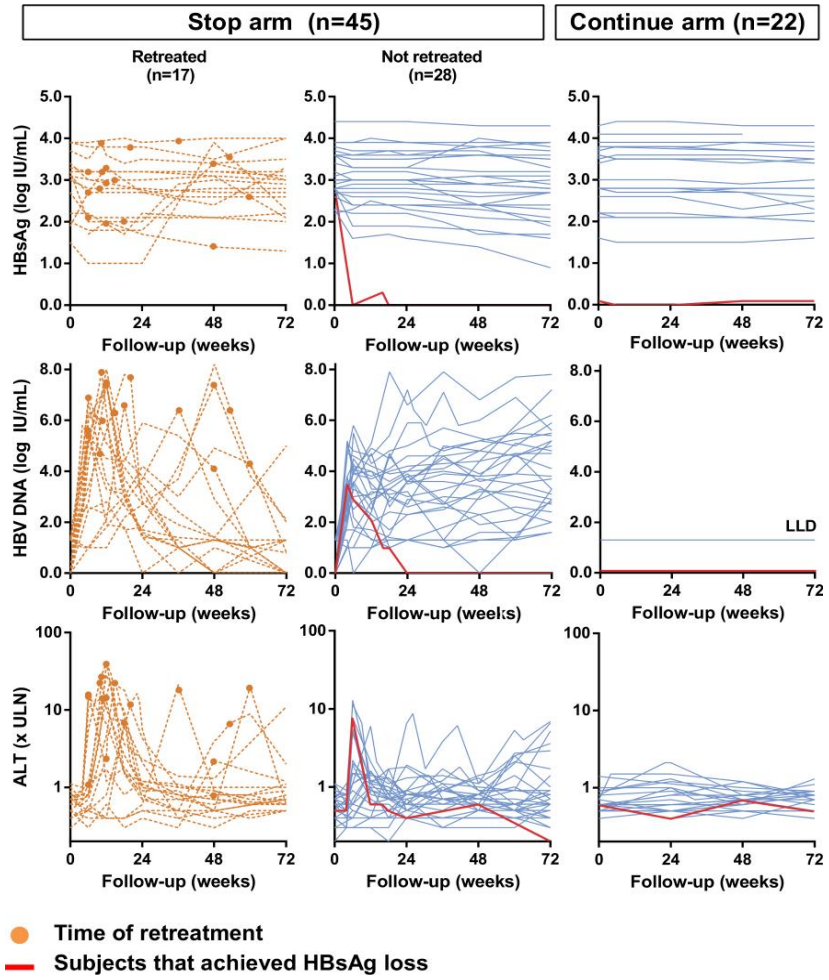
Berg T, et al. J Hepatol 2017;67:918–924

RCT: TORONTO STOP study

- **67 virally suppressed HBeAg- patients** (45 stop, 22 continue):
  - 97% Asian
  - 7% ETV, 93% TDF
  - Mean Fibroscan 5 kPa
- **Primary endpoint**:
  - Sustained response (HBV DNA <2000 IU/mL) at 48 weeks
- **Conclusions**:
  - NUC withdrawal has marginal benefits in Asians
  - No serious adverse events



Response at 72 weeks:

	Stop vs. Continue	p
HBsAg loss	2.2% vs. 4.5%	1.00
HBV DNA <20 IU/mL	2.2% vs. 91%	< 0.005
ALT ≤ULN	47% vs. 82%	0.01
ALT ≤ULN + HBV DNA <2000 IU/mL	29% vs. 82%	< 0.005
Retreated	38% vs. N/A	

- **Retreatment criteria**:
  - HBeAg seroreversion
  - Clinical relapse

Final decision was at the discretion of the treating physician

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Liem KS, et al. Gut 2019;68:2206–2213

RCT: Stop-NUC trial

- **158 HBeAg negative patients** (79 stop, 79 continue):
  - 80% Caucasian
  - 39% ETV, 51% TDF
  - Mean Fibroscan 5.7 kPa

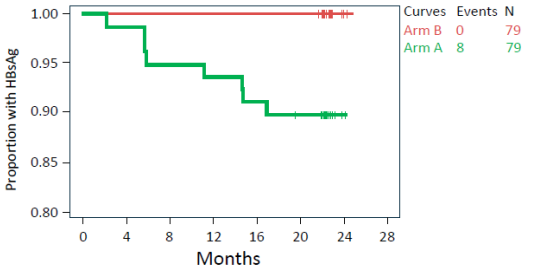
- **Primary endpoint**:
  - HBsAg loss at 96 weeks

- **Conclusions**:
  - Higher HBsAg loss in stop arm at 96 weeks
  - End of therapy HBsAg <1000 U/mL predictive of HBsAg loss
  - No serious adverse events
  - ALT flares respond well to retreatment
  - Long-term monitoring is crucial

HBsAg loss

		Baseline HBsAg <1000 U/mL	Baseline HBsAg [illegible]	p-value
HBsAg loss	No	18 (72%)	53 (98.1%)	0.001
	Yes	7 (28%)	1 (1.9%)	

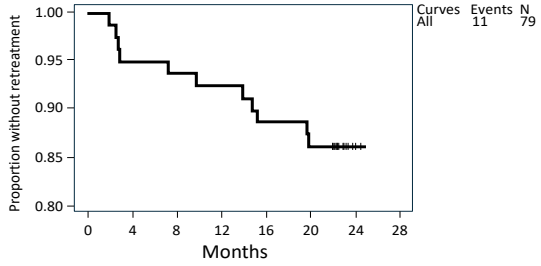
Time to HBsAg loss



Results at Week 96: NUC stopping arm

	n (%)
HBsAg loss	8 (10.3)
No retreatment indicated	53 (67.9)
Retreatment indicated	6 (7.7)
Retreatment initiated	11 (14.1)
Total	78 (100)

Time to retreatment



- **There were six main retreatment criteria**:
  - ALT flares (3)
  - Decompensation (1)
  - *Physician discretion* (2)

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van Bommel et al. EASL 2020

Cohort studies

Source	Number of patients	Race/ ethnicity	Pre-therapy HBeAg	HBsAg loss incidence
Chan	53	Asian	Neg	23% at 5 years
Hadziyannis*	33	Caucasian	Neg	39% at 5.5 years
Chen	188	Asian	Pos / Neg	24% at 6 years
Patwardhan*	33	N/A	Neg	N/A
Chi*	94	Mixed	Pos / Neg	3.1% annual rate
Hung*	73	Asian	Neg	47% at 6 years
Yao	119	Asian	Neg	55% at 6 years
Cao	82	Asian	Pos / Neg	10% at 2 years
Van Hees*	62	Mixed	Pos	N/A
Jeng*	691	Asian	Neg	13% at 6 years
Papatheodoridis*	57	Caucasian	Neg	25% at 1.5 years
Su*	100	Asian	Neg	0% at 2 years
Chen*	411	Asian	Pos / Neg	N/A

* *Reports number of complications off-therapy*

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1. Chan et al., Antivir Ther 2011. 2. Hadziyannis et al., Gastro 2012. 3. Chen et al., J Hepatol 2014. 4. Patwardhan et al., Aliment Pharmacol Ther 2014. 5. Chi et al., Aliment Pharmacol Ther 2015. 6. Hung et al., J Viral Hepat 2017. 7. Yao et al., Sci Rep 2017. 8. Cao et al., J Infect Dis 2017. 9. Van Hees et al., Aliment Pharmacol Ther 2017. 10. Jeng et al., Hepatol 2018. 11. Papatheodoridis et al., Antivir Ther 2018. 12. Su et al., J Infect Dis 2018. 13. Chen et al., Clin Microbiol Infect 2018.

RETRACT-B study

Update on the RETRACT-B study design and protocol presented at the HBV forum in 2019

- **Study design**: Retrospective cohort study (N = 1,556)

- **Study population**: CHB patients who discontinued NUC therapy from participating centers across North America, Europe, and Asia

  - Inclusion:

    - Virally suppressed at NUC withdrawal
    - HBeAg negative at NUC withdrawal: both HBeAg positive and negative at start of therapy

  - Exclusion:

    - Coinfection: HCV, HDV, and/or HIV
    - HCC diagnosis prior to stopping NUCs
    - Pegylated interferon therapy within 12 months prior to stopping NUCs

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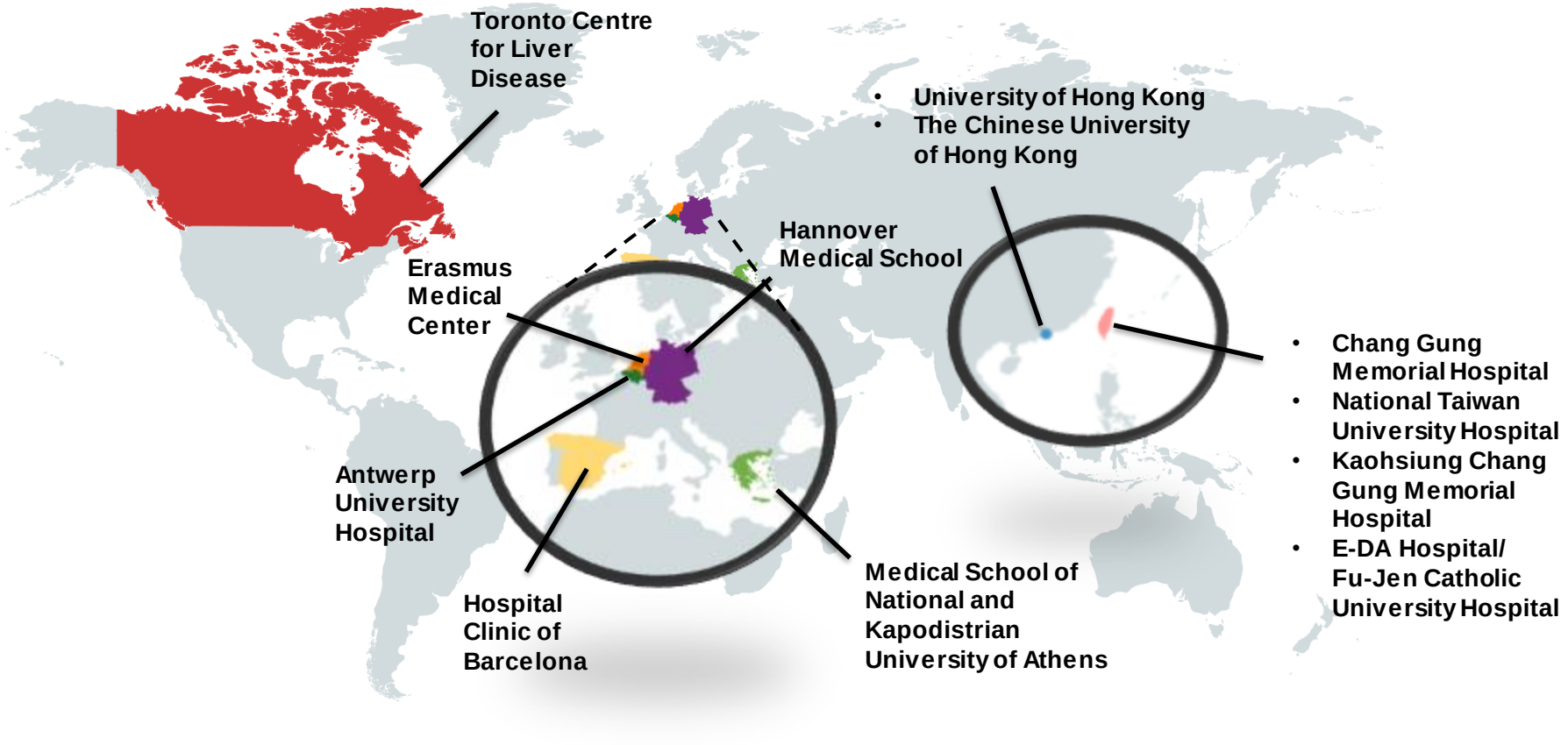
Hirode et al. EASL 2021

RETRACT-B study: Global, multi-center cohort



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RETRACT-B study: Characteristics

	Total Cohort (N = 1,556)
Age at NUC withdrawal: < 50 years / ≥ 50 years, %	37 / 63
Sex: Male / Female, %	72 / 28
Race/ethnicity: Caucasian / Asian / Other, %	11 / 88 / 1
NUC prior to withdrawal: ETV / TDF, %	63 / 29
Total NUC duration, *years*, median (IQR)	3.0 (3.0 – 4.0)
Start of therapy HBeAg status: Negative / Positive, %	84 / 15
At NUC withdrawal	
Cirrhosis status: Non-cirrhotic / Cirrhotic, %	88 / 12
HBsAg, log_{10} *IU/mL*, mean ± SD	2.6 ± 0.8
ALT x ULN, median (IQR)	0.6 (0.4 – 0.8)
During off-therapy follow-up	
Number of follow-up visits, median (IQR)	6 (3 – 9)
Time between visits, *months*, median (IQR)	2.8 (2.0 – 5.0)
Total follow-up time, *months*, median (IQR)	19.4 (8.0 – 39.8)

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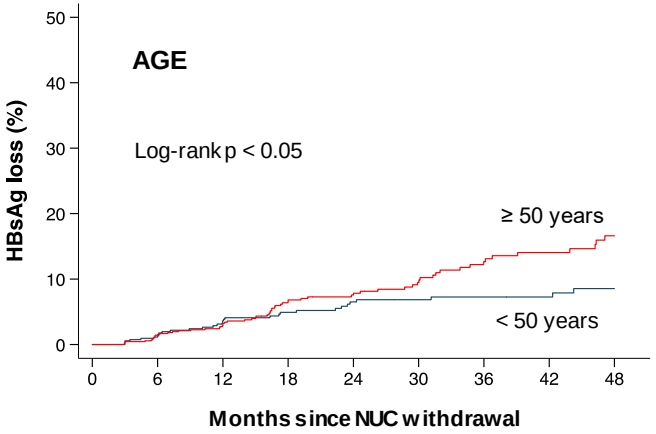
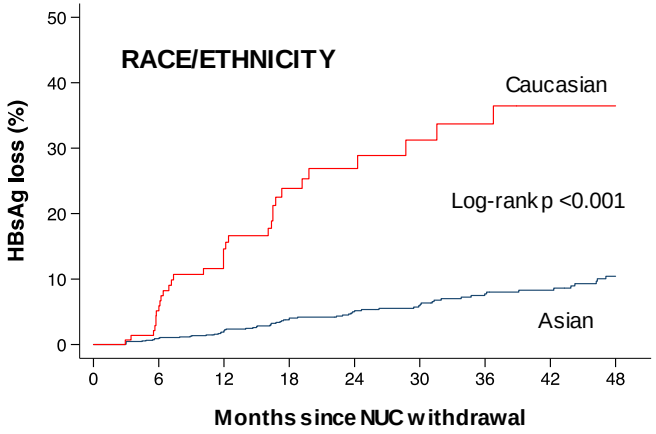
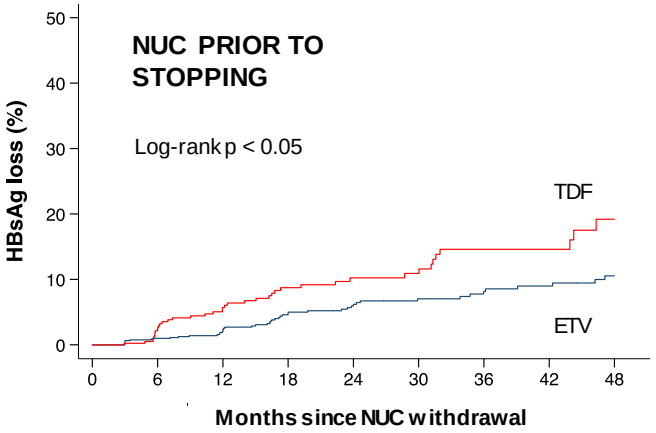
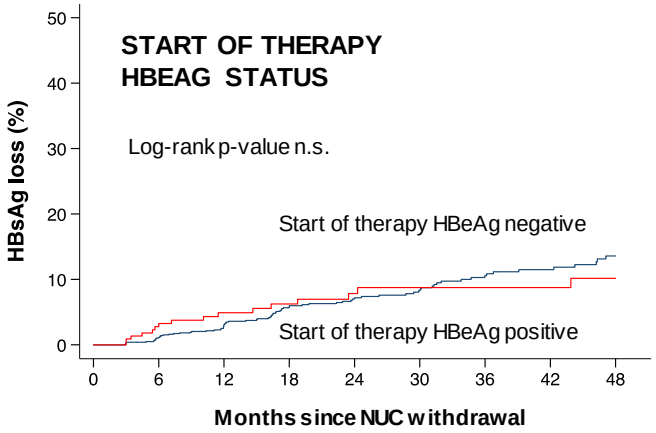
Hirode et al. EASL 2021

RETRACT-B study: HBsAg loss









- Cumulative incidence of HBsAg loss:

  3% at 1 year
  7% at 2 years
  10% at 3 years
  13% at 4 years

- Adjusted HBsAg loss ~6 times higher among Caucasians vs. Asians (p <0.001)

- Adjusted HBsAg loss ~22 times higher among patients with end of therapy HBsAg ≤100 IU/mL vs. >100 IU/mL (p <0.001)

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RETRACT-B study: Results

	4-year cumulative incidence (%)
Virological relapse (HBV DNA ≥2000 IU/mL)	83
Clinical relapse (HBV DNA ≥2000 IU/mL + ALT ≥2 x ULN)	55
ALT flare (≥5 x ULN)	31

- Cumulative incidence of retreatment was 30% at 1 year and 56% at 4 years off-therapy
- 19 patients developed hepatic decompensation:
  - Cumulative incidence of hepatic decompensation was 1% at 1 year and 2% at 4 years off-therapy
  - Higher among patients diagnosed with cirrhosis at any time point prior to NUC withdrawal
  - Higher among start of therapy HBeAg positive patients
- 16 patients developed HCC:
  - Cumulative incidence of HCC was 0.4% at 1 year and 1% at 4 years off-therapy
- 14 (1%) patients died among the total cohort

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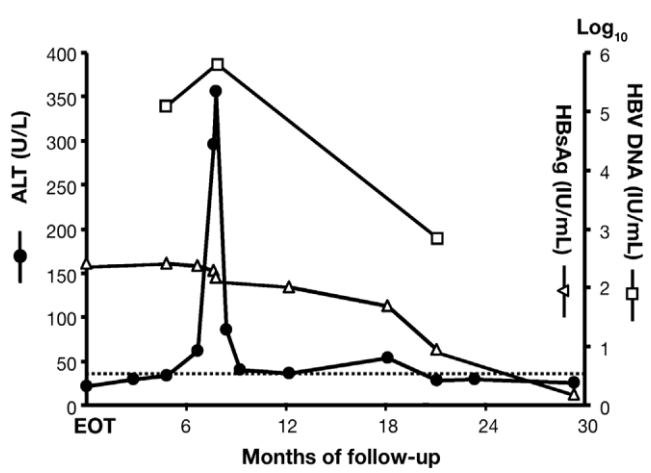
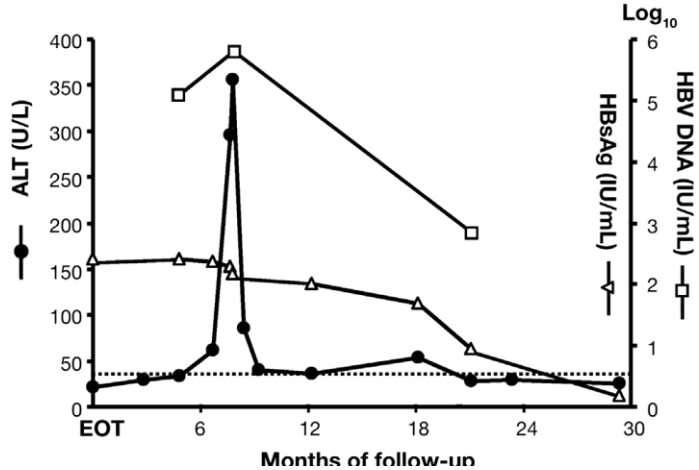
What we know: Flares

- Risk of severe ALT flares after NUC withdrawal may be associated with severity of virological relapse[1]
- An ALT flare may not be a prerequisite for HBsAg loss,[2] and may result in complications if not retreated

Host-dominating or "effective" flare[3]



Virus-dominating or "ineffective" flare[3]



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1. Papatheodoridis GV et al. 2018;68(2):415-424
2. Cao J et al. J Infect Dis 2017; 215: 581
3. Liaw YF, Hepatology 2021;73(2):843-852

What we know: Complications

- Case reports of patients who developed off-NUC complications, or descriptive information within a larger study
- Few studies comparing incidence of liver-related complications on- and off-NUC therapy
  - Most with small sample sizes
  - Most show no difference in HCC incidence
- However, rates of hepatic decompensation and HCC cannot be compared across studies due to differences in baseline criteria
  - Need a well-designed large and long-term RCT to answer this question!

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What we know: Retreatment

- Current decisions on when to retreat largely based on physician discretion
- Virological relapse after stopping is universal → poor criterion
- No retreatment criteria outlined in any of the three guidelines!
- Decision on when to retreat is crucial:
  - Not to early → to potentially achieve HBsAg loss
  - Not too late → to prevent liver-related complications

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Conclusion

- Most existing studies are small, single-site studies that did not correct for selection or measurement bias

- Larger studies on stopping NUCs are from Asia which are not seldom driven by local policies and reimbursement criteria

Future direction:

  - Better understanding of viral and host factors involved in the pathogenesis of CHB
  - Identification of novel biomarkers and predictors of response after NUC withdrawal
  - Off-NUC flare management strategies
  - Standardization of stopping and retreatment criteria, and monitoring frequencies
  - New antivirals and therapeutic strategies, including combination therapies → more RCTs!

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