CLDF

Chronic Liver Disease Foundation

3RD ANNUAL LIVER CONNECT CONFERENCE

Accredited by:

PURDUE UNIVERSITY

Presented by:

CLDF

Chronic Liver Disease Foundation

CLDF

Chronic Liver Disease Foundation

3RD ANNUAL

LIVER CONNECT

CONFERENCE

HBV/HDV-ACT Connect
(ADVANCING CURATIVE TREATMENTS)

Stopping All Therapy in HBV Clinical Trials: What Should Be the Criteria for Discontinuation

Nezam H. Afdhal M.D, DSC

Charlotte and Irving Rabb Professor of Medicine,

Harvard Medical School,

Chief of Gastroenterology, Hepatology and Nutrition,

Beth Israel Deaconess Medical Center, Boston

Disclosures

Scientific Advisory Boards: Gilead, Janssen, Merck, Takeda, Ligand, Shionogi, GSK, EchoSens, SonicIncytes, Axcella

Stock and Options: F-Star Therapeutics, Allurion

Executive Roles: Director, Liver Institute for Education and Research

The Controversy: Can You Stop NA Treatment: Current Guidelines on When to Stop the Treatment

HBeAg-positive

Prerequisite: HBeAg seroconversion

AASLD[1]:

- Consider to stop after **≥ 1-year consolidation** if not cirrhotic
- Alternatively, treat until **HBsAg loss**

EASL[2]:

- Discontinued after **≥ 1-year consolidation** if not cirrhotic

APASL[3]:

- Can be stopped after ≥ 1-year but **preferably 3-year consolidation**

HBeAg-negative

AASLD[1]:

- **Indefinitely**, unless there is a compelling rationale
- May be considered with **HBsAg loss**

EASL[2]:

- Discontinued after **HBsAg loss**
- In selected non-cirrhotic patients, **≥ 3 years of virological supression**

APASL[3]:

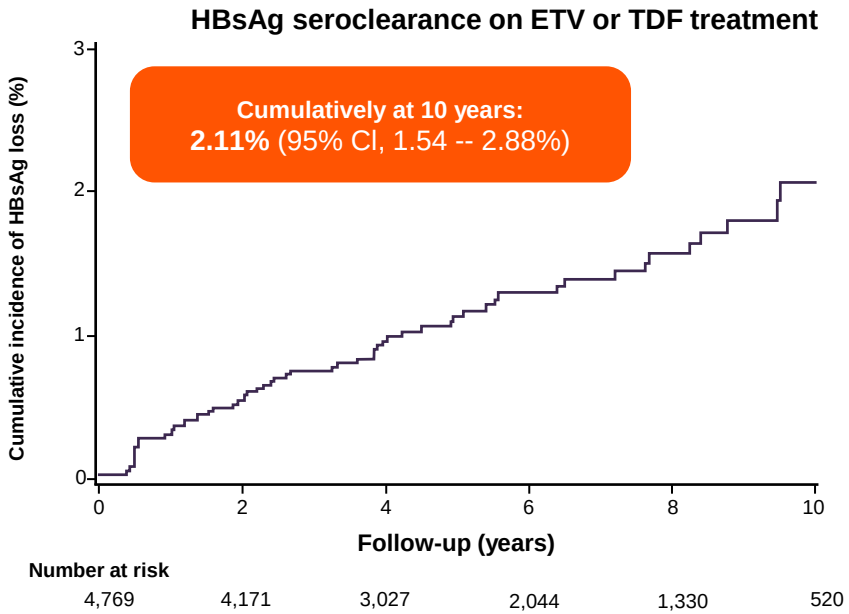
- **HBsAg loss** with anti-HBs conversion or ≥ 1-year post-HBsAg consolidation
- After **≥ 2-year virological supression**

AASLD, American Association for the Study of Liver Diseases; APASL, Asian Pacific Association for the Study of the Liver; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; anti-HBs, hepatitis B surface antibody.

1. Lampertico P, et al. *Journal of Hepatology*. 2017;67(2):370–398; 2. Terrault NA, et al. *Hepatology*. 2018;67:1560-1599;
3. Sarin SK, et al. *Hepatology International.* 2016;10(1):1–98.

HBsAg Loss Rarely Occurs During NA Therapy

From an international real-world cohort of 4,769 CHB patients treated with TDF or ETV and observed for 26,614.47 person-years



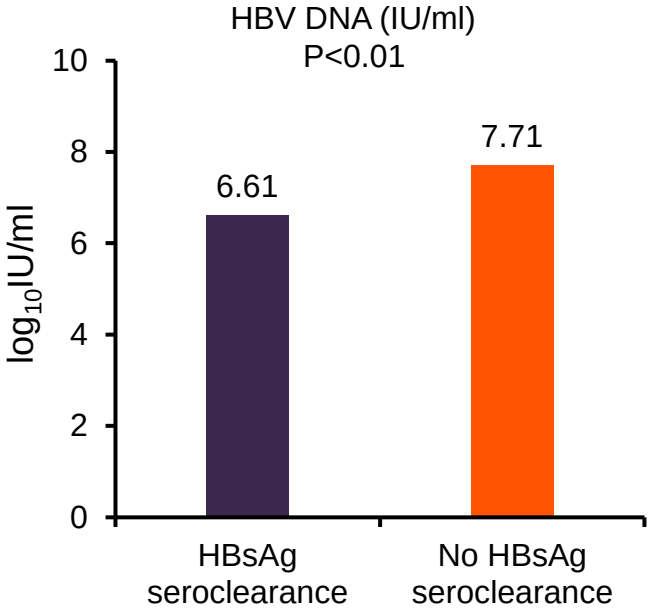
Treatment Years	Incidence (95% CI), %	
	Annual	Cumulative
0–1	0.30 (.18–.50)	0.30 (.18–.51)
1–2	0.23 (.12–.43)	0.53 (.35–.79)
2–3	0.23 (.12–.44)	0.76 (.54–1.06)
3–4	0.21 (.10–.45)	0.96 (.70–1.31)
4–5	0.18 (.08–.43)	1.14 (.85–1.53)
5–6	0.13 (.04–.41)	1.27 (.95–1.70)
6–7	0.11 (.03–.42)	1.38 (1.03–1.84)
7–8	0.19 (.06–.60)	1.57 (1.18–2.09)
8–9	0.27 (.09–.82)	1.83 (1.37–2.46)
9–10	0.29 (.07–1.14)	2.11 (1.54–2.88)

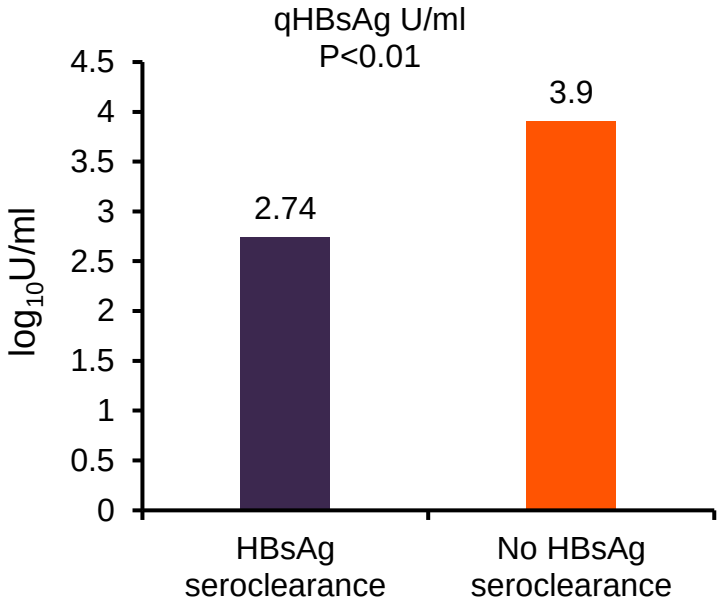
On average, 0.22% (95% CI, 0.17--0.28%) per year)

CHB, chronic hepatitis B; CI, confidence interval; ETV, entecavir; HBsAg, hepatitis B surface antigen; NA, nucelos(t)ide analogue; TDF, tenofovir disoproxil fumarate.

Hsu YC, et al. Incidences and determinants of functional cure during entecavir or tenofovir disoproxil fumarate for chronic hepatitis B. *J Infect Dis.* 2021. DOI:10.1093/infdis/jiab241 reproduced by permission of Oxford University Press.

Factors Associated With Spontaneous HBsAg Seroclearance



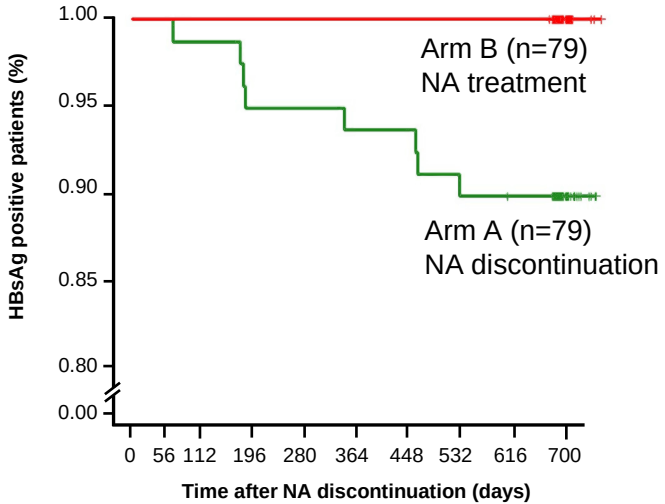


- HBsAg clearance mostly w/less active disease
- HBsAg clearance not associated with
  - HBV genotype
  - Treatment history

Yeo HY et al. *Gastroenterology*. 2018, doi: https://doi.org/10.1053/j.gastro.2018.10.027.

Pros and Cons of Finite NA Therapy

May facilitate HBsAg loss



Risk of clinical flares

- NA treatment cessation frequently leads to HBV DNA and ALT flares[1]
- ALT flares >5-10 x ULN rare in non-cirrhotic patients[1]
- ALT flares during HBV DNA reactivation phase usually transient; most likely an indicator of restoration of immune control[1]
- Hepatic decompensation and death following HBV reactivation reported only in patients with pre-existing cirrhosis1 ~1% of patients over 5 years' follow-up in largest study to date[2]
- Potentially harmful ALT flares require early identification and reintroduction of NA treatment[1]

HBsAg, hepatitis B surface antigen; NA, nucelos(t)ide analogue; HBV, hepatitis B virus; ALT, alanine aminotransferase; ULN, upper limit of normal.
Reprinted from J Hepatol, S118, van Bömmel F, et al, Response to discontinuation of long-term nucleos(t)ide analogue treatment in HBeAg negative patients: Results of the Stop-NUC trial, © 2020, with permission from Elsevier.
1. Van Bömmel F, Berg T. *Hepatology Communications*. 2021;5:1632-1648; 2. Jeng WJ, et al. *Hepatology*. 2018;68:425-434.

Nucleos(t)ide Analogue Withdrawal in Patients With Chronic Hepatitis B Leads to Limited Sustained Remission in the Absence of HBsAg Loss: Results From the RETRACT-B Study

Background and aims

- NUC withdrawal may result in HBsAg loss and durable off-treatment responses but may result in severe reactivation, with risk of severe flares, liver failure, and death
- This is a retrospective study to look at long-term virologic and clinical outcomes ≥1 year after stopping NUCs

Methods

- RETRACT-B global study of 1557 patients with CHB
- All patients virally suppressed and HBeAg(−) at NUC cessation
- Patients were excluded if within 1st year after stopping they experienced:
  - sAg loss (n=42); retreatment (n=440); LTFU (n=120); other (n=10)

Primary endpoint: Sustained remission after 1 year, irrespective of HBV DNA and ALT within the 1st year after NUC cessation, with/without HBsAg loss

Endpoint definitions

- Sustained remission: DNA ≤2000 IU/mL and ALT ≤1.5x ULN
- Virologic relapse: DNA >2000 IU/mL
- Biochemical relapse: ALT >1.5x ULN
- Clinical relapse: DNA >2000 IU/mL and ALT >1.5x ULN

Hirode G et al. *AASLD*. 2021. #O22.

Study Population

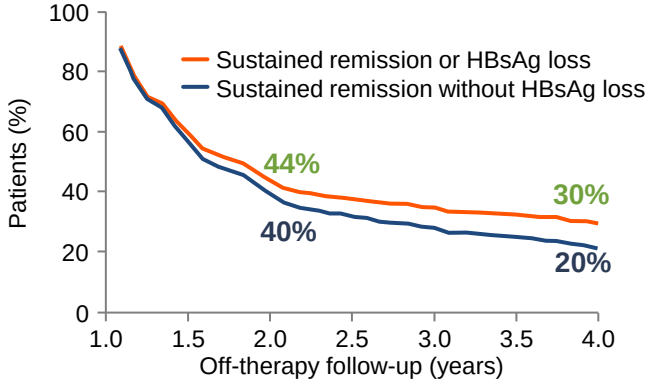
	N=945
Age at NUC cessation, years	53 ±12
Asian	91%
Cirrhotic prior to NUC cessation	11%
NUC duration, years	3.0 (3.0–3.6)
HBsAg at NUC cessation, Log_{10} IU/mL	2.6 ±0.8
Duration between visits, months	4.0 (2.7–6.6)
Data are mean ±SD or median (IQR) unless otherwise stated	

Events during 1st year post-NUC cessation

n (%) or median (IQR)	N=945
Virologic Relapse Max HBV DNA (Log_{10} IU/mL)	542 (57) 4.4 (3.9–5.2)
Biochemical relapse Max ALT xULN	340 (36) 2.8 (1.9–5.4)
Clinical relapse	222 (24)
At least 1 relapse	621 (66)

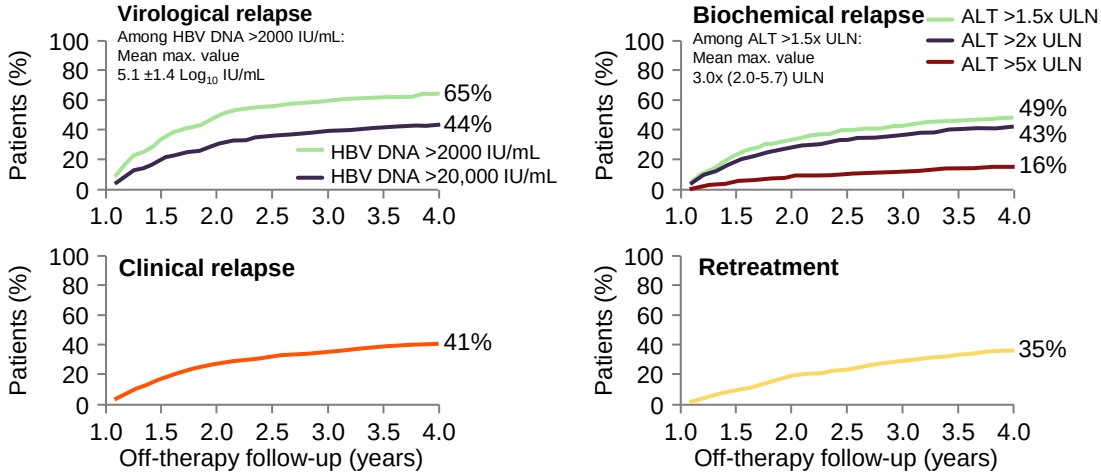
Nucleos(t)ide Analogue Withdrawal in Patients With Chronic Hepatitis B Leads to Limited Sustained Remission in the Absence of HBsAg Loss: Results From the RETRACT-B Study

1. Sustained remission beyond 1 year



Factor	Sustained remission without HBsAg loss		
	Yes	No	P-value
Age <50 years	24%	19%	NS
Male gender	21%	21%	NS
Tenofovir	21%	21%	NS
Non-Asian ethnicity	**30%**	**20%**	**<0.05**
HBeAg(+) at baseline	**31%**	**19%**	**<0.05**
HBsAg <100 IU/mL at baseline	**24%**	**20%**	**<0.05**
No relapse in 1st year	**37%**	**13%**	**<0.05**

2. Relapse and retreatment beyond 1 year



- At 4 years after NUC cessation, only 30% of patients remain in sustained remission
- Success is lower in Asians
- Need better guidelines for when to restart treatment
- Need continuous monitoring and compliant patients

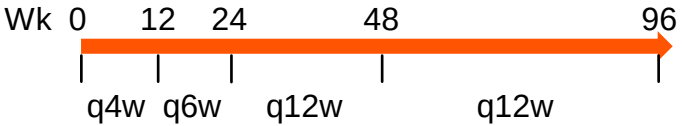
Final Results of HBV-Stop: Low Baseline HBsAg Levels Predict Disease Remission and HBsAg Loss After Stopping NUCs in HBeAg− Patients With CHB

Objective: 96-week, prospective trial from 8 Australian centers to evaluate clinical outcomes after stopping NUC therapy

Patient population

- Chronic hepatitis B
- HBeAg(−)
- Non-cirrhotic
- Suppressed on NUC for ≥18 months
- Treatment duration of >2 years

Monitoring frequency after stopping NUC therapy



- Additional study visits for biochemical or virologic flare
- NUCs restarted if persistent moderate/large ALT flares occurred or any evidence of hepatic decompensation (per investigator discretion)

Baseline characteristics

	NUC-Stop (N=110)
Age, years	56 [50–63]
Male	64 (58)
Race Asian White Other	 94 (85) 10 (9) 7 (6)
NUC-ceased at baseline Entecavir Tenofovir Other	 68 (61) 32 (29) 10 (9)
ALT (IU/mL)	24 [17–32]
HBsAg level (IU/mL) <10 10–100 100–500 500–1000 >1000	705 [214–2325] 8 (7) 14 (13) 29 (26) 15 (14) 45 (41)
No cirrhosis	100 (100)

Data are n (%) or median [IQR]
LSM <9.5kPa, non-cirrhotic prior to starting NUC therapy

Safety through Week 96

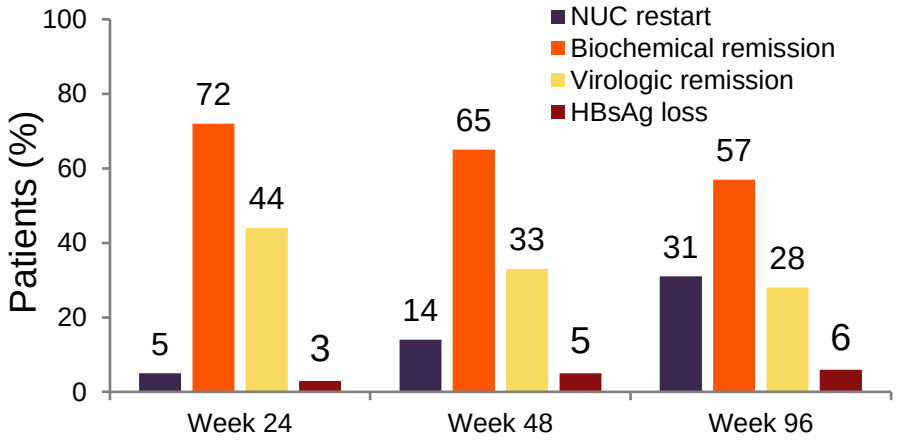
	NUC-Stop (N=110)
Bilirubin >2x ULN	5 (5)[a]
INR >1.5	0 (0)
Ascites	0 (0)
Hepatic encephalopathy	0 (0)
HCC	0 (0)

Data are n (%)
[a]3 events led to NUC restart

Hall S et al. *AASLD*. 2021. #P787.

Final Results of HBV-Stop: Low Baseline HBsAg Levels Predict Disease Remission and HBsAg Loss After Stopping NUCs in HBeAg− Patients With CHB

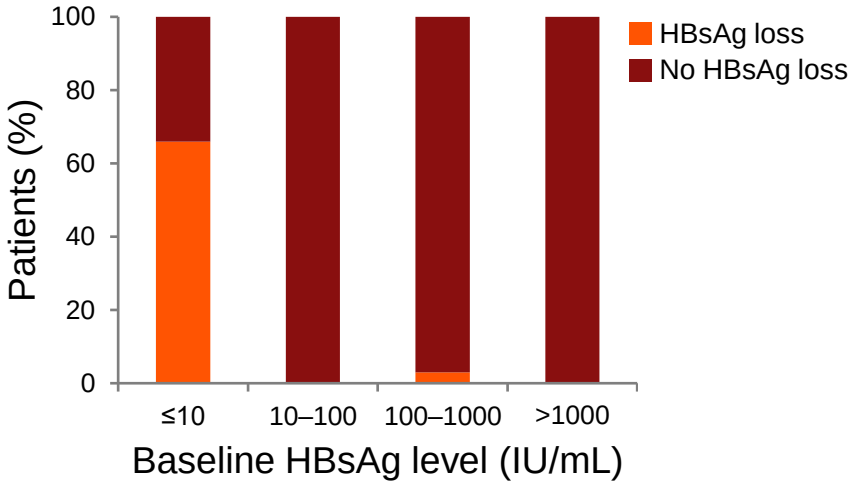
Clinical outcomes



At 96 weeks

- 6% HBsAg loss
- 31% NUC restart
- 28% virologic remission (HBV DNA <2000 IU/mL)
- 57% biochemical remission (ALT <2x ULN)

HBsAg loss

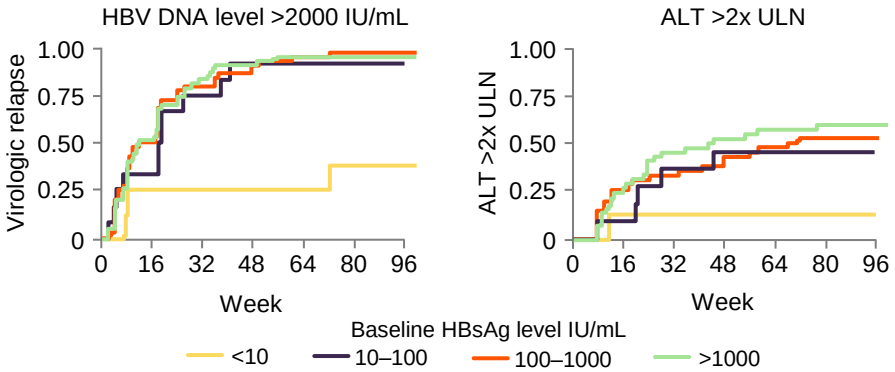


Baseline HBsAg	chemical loss	
• HBsAg ≤10 IU/mL (n=8)	6/8 (75%)	
• HBsAg >10 IU/mL (n=99)	1/99 (1%)	P<0.001

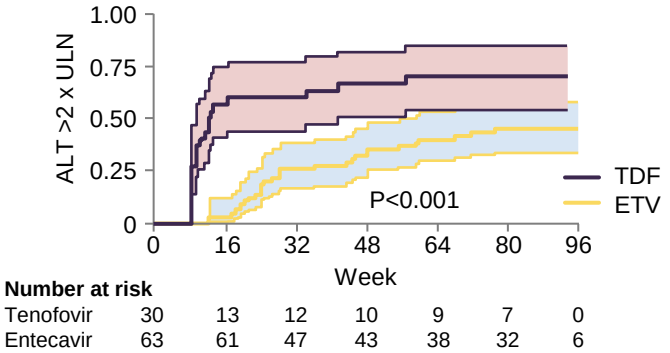
Hall S et al. *AASLD*. 2021. #P787.

Final Results of HBV-Stop: Low Baseline HBsAg Levels Predict Disease Remission and HBsAg Loss After Stopping NUCs in HBeAg− Patients With CHB

Baseline HBsAg level ≤10 IU/mL associated with lower risk of virologic relapse and ALT flare up to Week 96



Biochemical relapse occurred earlier with TDF vs ETV



- Authors conclude the data ‘support treatment withdrawal in selected patients’
- HBsAg <10 IU/mL is uncommon but these remain optimal patients for stop NUC
- Does longer time to relapse with entecavir than tenofovir suggest greater viral suppression below LLD?
- Decision to stop should be as much patient-driven than clinician-driven

Hall S et al. *AASLD*. 2021. #P787.

Severe Hepatitis Flare and Related Mortality After Discontinuation of Oral Antiviral Treatment in Patients With Chronic Hepatitis B: A Population-Based Study

Background: Fear of severe flares is a leading barrier to stopping NUC therapy in clinical practice

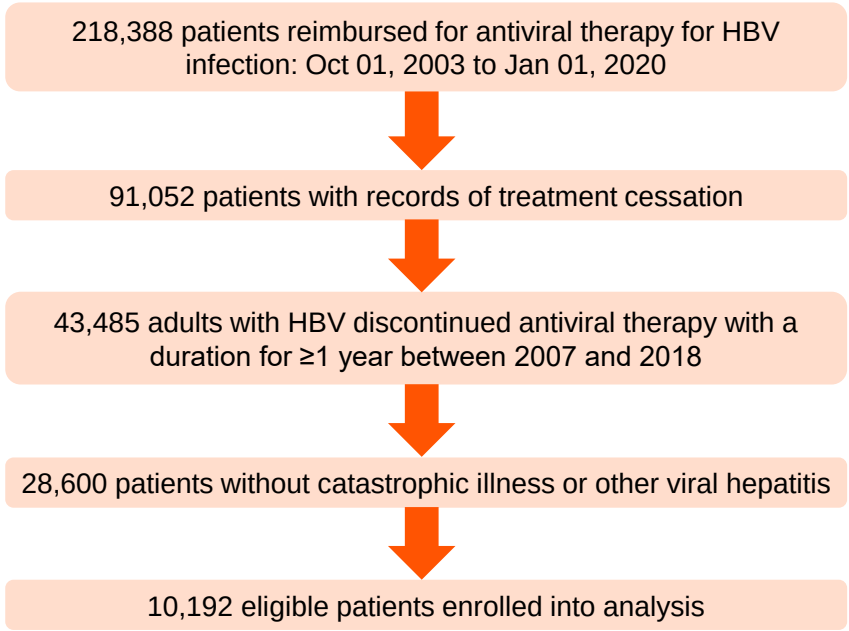
Methods

- This issue was studied in a very large database from the Taiwan National Health Insurance Lab Database
- Included adults with CHB treated with TDF or ETV ≥1 year who then stopped therapy
- Patients with comorbid liver conditions or malignancy were excluded
- Patients followed for 4 years

Outcomes and definitions

- Severe flare: ALT >5x ULN (200 U/L) + bilirubin >2 mg/dL
- Mortality or liver transplant within 6 months of severe flare
- HBsAg data were not reported

Study population



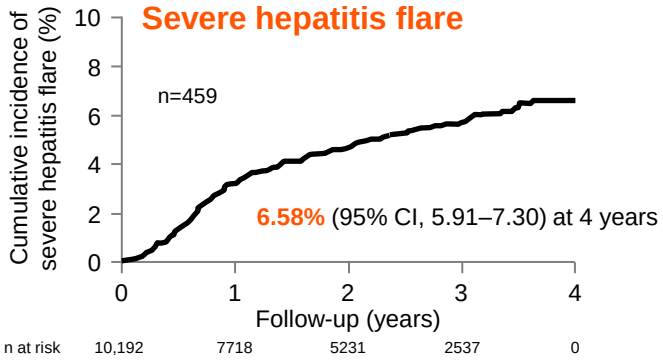
Hsu Y-C, et al. *AASLD*. 2021. #O23.

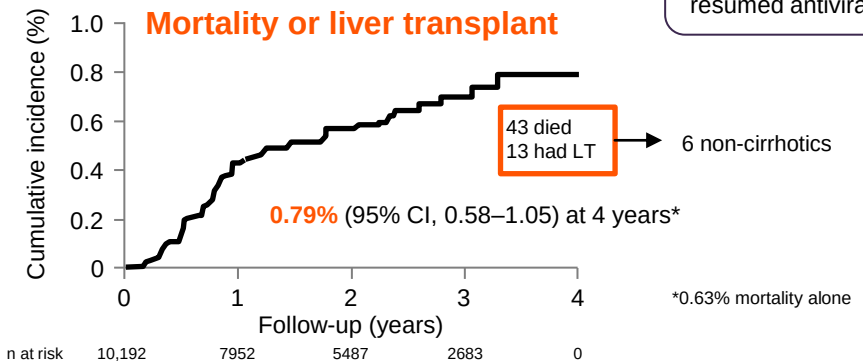
Severe Hepatitis Flare and Related Mortality After Discontinuation of Oral Antiviral Treatment in Patients With Chronic Hepatitis B: A Population-Based Study

Patient characteristics at treatment cessation

	N=10,192
Age, years	51 (42–59)
Male	7308 (72)
Cirrhosis	1092 (11)
History of hepatic decompensation	465 (5)
Diabetes mellitus	2752 (27)
Hypertension	3528 (35)
Dyslipidemia	4575 (45)
Antiviral regimen Entecavir Tenofovir	 6921 (68) 3271 (32)
Treatment duration, years	3.0 (3.0–3.0)
Serum ALT, U/L[a]	24.0 (17.3–36.0)
Data are n (%) or median (IQR); [a]Available for 7413 patients	

Off-therapy follow-up and event occurrences





During a median 2.2 years of follow-up: 3360 patients resumed antiviral therapy

*0.63% mortality alone

Hsu Y-C, et al. *AASLD*. 2021. #O23.

Severe Hepatitis Flare and Related Mortality After Discontinuation of Oral Antiviral Treatment in Patients With Chronic Hepatitis B: A Population-Based Study

Associated risk factors for severe flare off NUC

Variables	Sub-distributional hazard ratio (95% CI)	P
Age, per 10 years	1.19 (1.09–1.29)	<0.0001
Male vs female sex	1.76 (1.41–2.22)	<0.0001
TDF vs ETV	1.17 (0.96–1.42)	0.12
Diagnosis of cirrhosis	1.84 (1.45–2.33)	<0.0001
History of hepatic decompensation	1.45 (1.01–2.09)	0.044
Dyslipidemia	0.99 (0.81–1.20)	0.89
Diabetes mellitus	1.13 (0.92–1.39)	0.25
Hypertension	1.07 (0.87–1.31)	0.55

Associated risk factors for subsequent mortality

Variables	Sub-distributional hazard ratio (95% CI)	P
Age, per 10 years	1.70 (1.32–2.19)	<0.0001
Male vs Female sex	1.85 (0.89–3.85)	0.098
TDF vs ETV	1.28 (0.73–2.25)	0.39
Diagnosis of cirrhosis	6.12 (3.17–11.8)	<0.0001
History of hepatic decompensation	1.29 (0.55–3.02)	0.56
Dyslipidemia	0.64 (0.35–1.19)	0.16
Diabetes mellitus	1.38 (0.75–2.25)	0.30
Hypertension	2.29 (1.09–4.82)	0.029

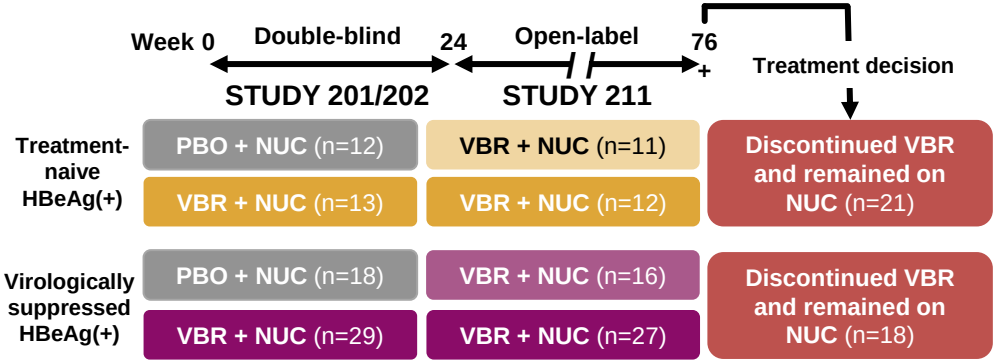
- This huge database provides valuable information on the frequency of severe flares, mortality, and the need for liver transplantation after stopping NUC therapy; most mortality/LT occurs in cirrhotics
- Data stated to be an outgrowth of 3-year cap on coverage in Taiwan
- Reassuring data on rarity of mortality from flares in non-cirrhotics that can be shared with patients who are thinking of stopping (but severe flares can still occur!)
- Results are unlikely to change practice in cirrhotics in most areas, because guidelines recommend not to stop NUCs in those patients (Terrault N et al, AASLD Guidelines, Hepatology 2018): No caps!

How Does This Translate to Novel Therapies and Combinations?

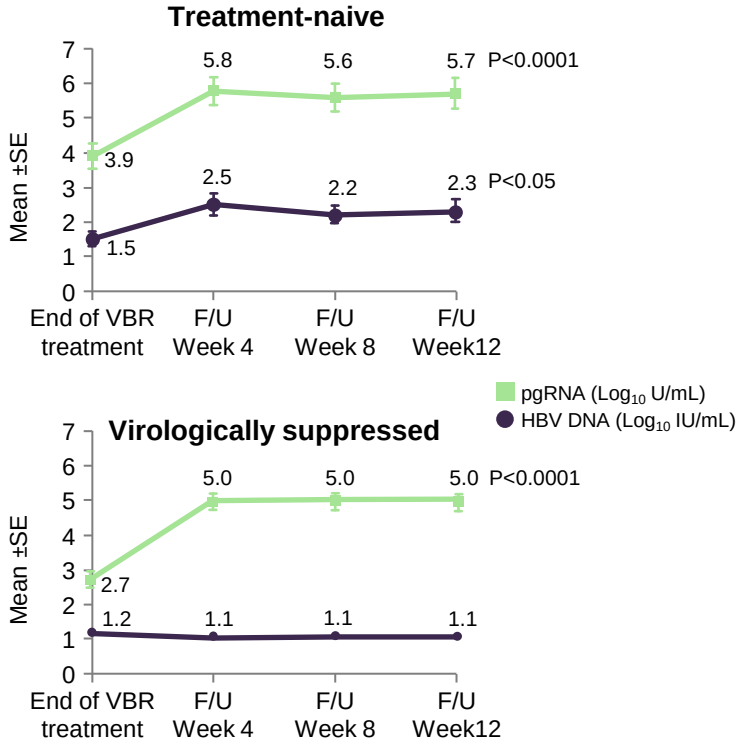
Each Mechanism and Combination Needs to Define an Individualized Strategy

- Mechanism
  - Viral suppression, viral production, targeting cccDNA and immune strategies
  - ALL have different rationales on when to stop NUC
  - Some commonalities mostly relating to HBsAg levels
- SAFETY
  - Reassuring data from real world and clinical trials on flares

Profound Suppression >1yr With Vebicorvir + NUC Unable to Maintain Viral Suppression After Stopping



- No HBsAg suppression or clearance on treatment – mean HBsAg 3 log
- No sustained HBV DNA or pgRNA suppression after stopping
- Rapid virological relapse even with continuation of NUC



X = treatment discontinued

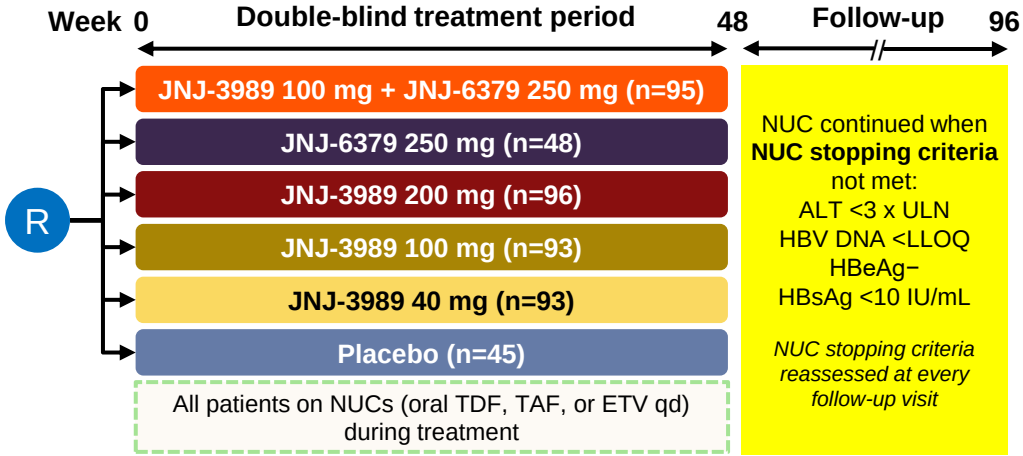
Suppression Alone???

- Cannot use this approach even with most sensitive HBV DNA and pgRNA measurements when HBsAg at 3 $\log^{10}$
- Although >1 year of treatment with vebicorvir, the issue of duration is critical
- Loss of HbsAg in HBeAg negative patients suppressed on NUC and remaining on NUC increases with time
- Use of quantitative HbsAg in clinical practice demonstrates steady decline with longer duration
- Suppressive strategies will need combination approach if goal is to shorten duration to functional cure

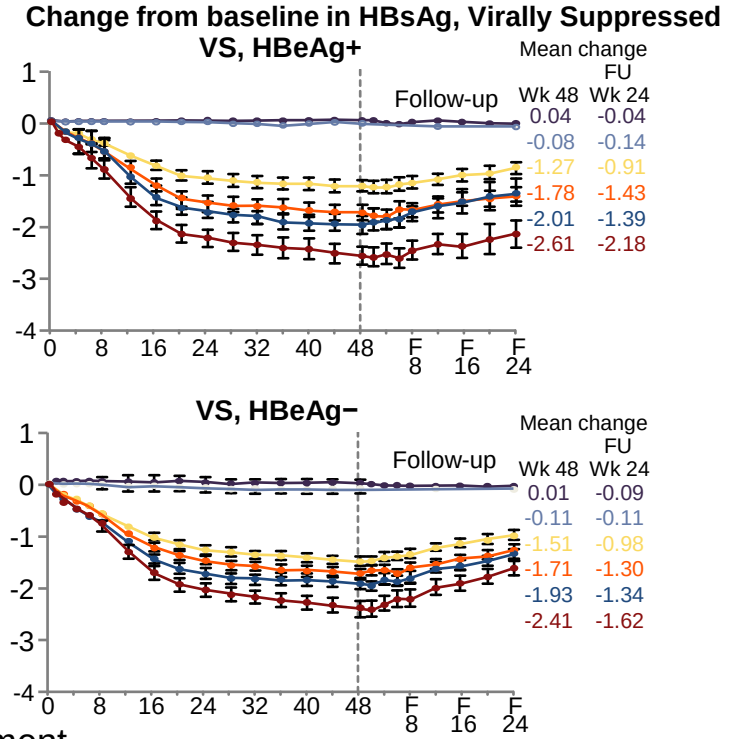
siRNA and Anti-Sense Therapies

- Stopping rules harder to define due to direct effect on HBsAg
- In clinical trials variations on HBV DNA <LLOQ, HBsAg undetectable versus <10 IU, ALT normal
- Trials have used variable fixed duration of therapy rather than waiting until pre-specified stopping rules achieved
- Inclusive of HBeAg +ve and -ve, NUC suppressed and naïve – while this strategy is acceptable for Phase 2 exploratory complexity in Phase 3 will be confounding
- Immunological evaluations in some trials during and at time of stopping therapy

REEF 1 Trial

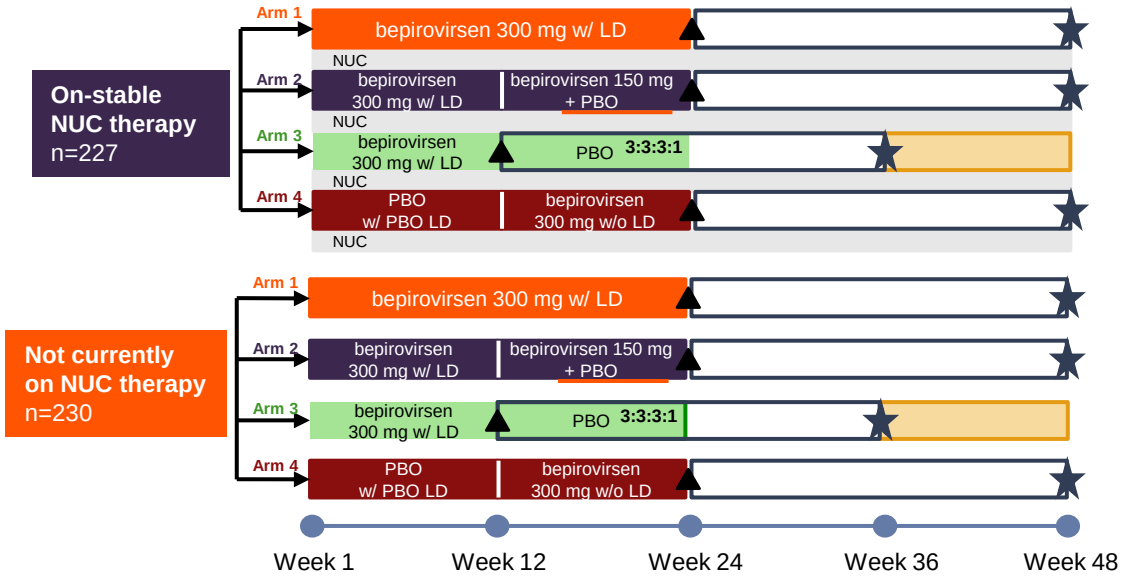


This analysis: 24-weeks follow-up



- Dose-response relationship between JNJ-3989 (siRNA)
- Dose and reduction in all viral markers studied
- Greatest reductions in naïve HBeAg+ patients
- Notable stability or further decline in viral markers after treatment discontinued: in contrast to slow increase in HBsAg

B-CLEAR: Bepirovirsen



NO PREDEFINED STOP RULE

- Bepirovirsen 300 mg qw for 24 weeks suppressed HBsAg/HBV DNA to <LLOQ in 29% of patients not on NUCs and 28% on NUCs
- Patients with a low HBsAg titer at baseline (naïve and NUC treated) had highest rates of HBsAg loss
- Off-treatment follow-up will be needed to determine whether Functional Cure (loss of HBsAg) can be achieved
- ALT flares seen

Conclusions

- Long term NUC and spontaneous HBsAg loss different to that induced by novel short term drug treatment
- Different stop rules for different MOA
- Role of duration unclear
- Role of consolidation period unclear
- Different stop rules for NUC naïve versus suppressed
- Different stop rules for baseline low HBsAg versus high >3log HBsAg at baseline

- ALL WE REALLY KNOW IS THAT FUNCTIONAL CURE IS DIFFICULT