Hepatic flares after nucleos(t)ide analogue cessation in HBeAg-negative hepatitis B: results from the Nuc-Stop Study

M. Holmberg[1, 2], O. Dalgard[2, 3], S. Aleman[4], N. Berhe[1, 5, 6], H. Desalegn[5, 7], N. Weis[8, 9], L. Heggelund[10, 11], L. N. Karlsen[12], P. Brugger-Synnes[13], H. E. Simonsen[14], D. H. Reikvam[2, 6], A. Johannessen[1, 2, 6]

[1]Vestfold Hospital, Tønsberg, Norway, [2]University of Oslo, Oslo, Norway, [3]Akershus University Hospital, Lørenskog, Norway, [4]Karolinska University Hospital, Stockholm, Sweden, [5]Addis Ababa University, Addis Ababa, Ethiopia, [6]Oslo University Hospital, Oslo, Norway, [7]St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia, [8]Copenhagen University Hospital, Hvidovre, Denmark, [9]University of Copenhagen, Copenhagen, Denmark, [10]Vestre Viken Hospital, Drammen, Norway, [11]University of Bergen, Bergen, Norway, [12]Stavanger University Hospital, Stavanger, Norway, [13]Ålesund Hospital, Ålesund, Norway, [14]Nordland Hospital, Bodø, Norway.

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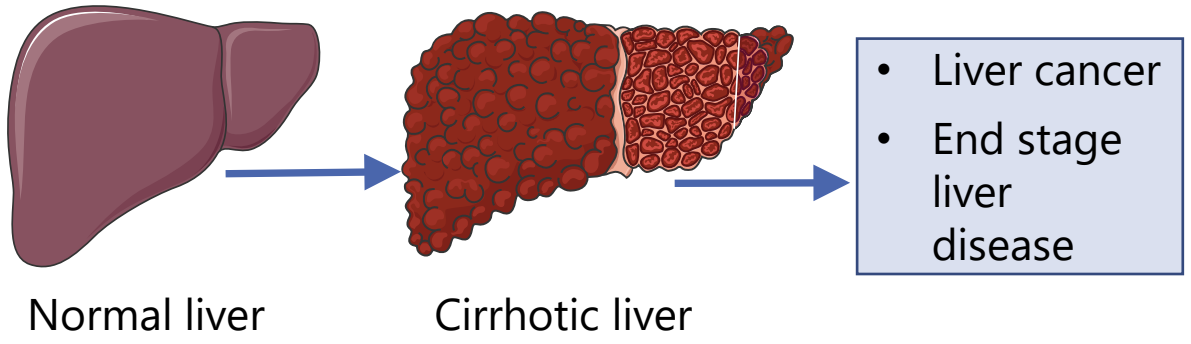
The Nuc-Stop Study

Chronic hepatitis B infection (CHB)

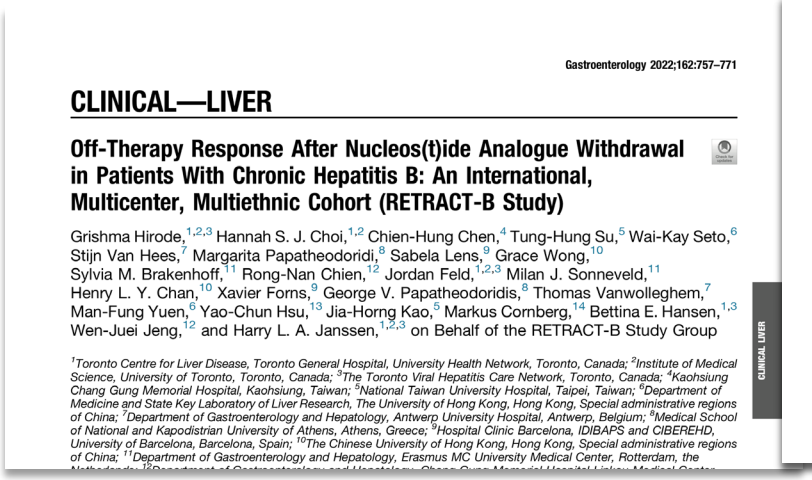
~254 million living with CHB



~1.1 million deaths/year

World Health Organization 2024

Stopping nucleos(t)ide analogue (NA) treatment to achieve functional cure (HBsAg loss)



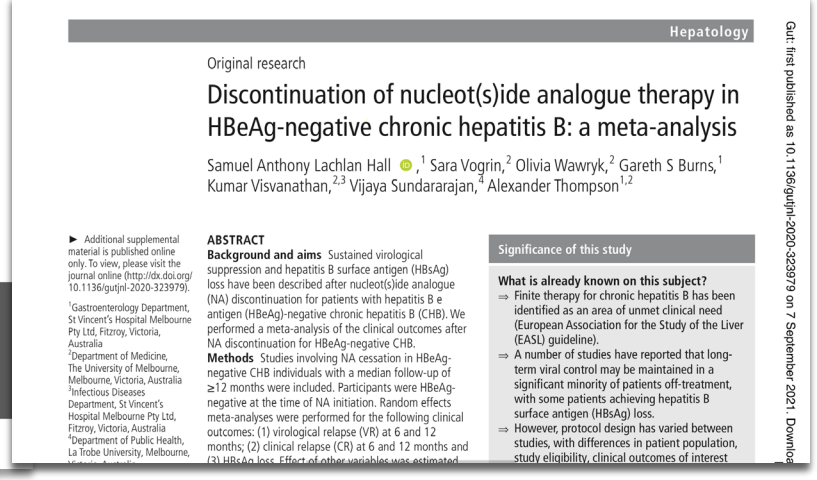
Gastroenterology 2022;162:757–771

CLINICAL—LIVER

Off-Therapy Response After Nucleos(t)ide Analogue Withdrawal in Patients With Chronic Hepatitis B: An International, Multicenter, Multiethnic Cohort (RETRACT-B Study)

Grishma Hirode,[1,2,3] Hannah S. J. Choi,[1,2] Chien-Hung Chen,[4] Tung-Hung Su,[5] Wai-Kay Seto,[6] Stijn Van Hees,[7] Margarita Papatheodoridi,[8] Sabela Lens,[9] Grace Wong,[10] Sylvia M. Brakenhoff,[11] Rong-Nan Chien,[12] Jordan Feld,[1,2,3] Milan J. Sonneveld,[11] Henry L. Y. Chan,[10] Xavier Forns,[9] George V. Papatheodoridis,[8] Thomas Vanwolleghem,[7] Man-Fung Yuen,[6] Yao-Chun Hsu,[13] Jia-Horng Kao,[5] Markus Cornberg,[14] Bettina E. Hansen,[1,3] Wen-Juei Jeng,[12] and Harry L. A. Janssen,[1,2,3] on Behalf of the RETRACT-B Study Group

[1]Toronto Centre for Liver Disease, Toronto General Hospital, University Health Network, Toronto, Canada; [2]Institute of Medical Science, University of Toronto, Toronto, Canada; [3]The Toronto Viral Hepatitis Care Network, Toronto, Canada; [4]Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; [5]National Taiwan University Hospital, Taipei, Taiwan; [6]Department of Medicine and State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong, Special administrative regions of China; [7]Department of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium; [8]Medical School of National and Kapodistrian University of Athens, Athens, Greece; [9]Hospital Clinic Barcelona, IDIBAPS and CIBEREHD, University of Barcelona, Barcelona, Spain; [10]The Chinese University of Hong Kong, Hong Kong, Special administrative regions of China; [11]Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, the Netherlands; [12]Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital-Linkou Medical Center



Original research

Discontinuation of nucleot(s)ide analogue therapy in HBeAg-negative chronic hepatitis B: a meta-analysis

Samuel Anthony Lachlan Hall ,[1] Sara Vogrin,[2] Olivia Wawryk,[2] Gareth S Burns,[1] Kumar Visvanathan,[2,3] Vijaya Sundararajan,[4] Alexander Thompson[1,2]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/gutjnl-2020-323979).

[1]Gastroenterology Department, St Vincent's Hospital Melbourne Pty Ltd, Fitzroy, Victoria, Australia
[2]Department of Medicine, The University of Melbourne, Melbourne, Victoria, Australia
[3]Infectious Diseases Department, St Vincent's Hospital Melbourne Pty Ltd, Fitzroy, Victoria, Australia
[4]Department of Public Health, La Trobe University, Melbourne,

ABSTRACT

Background and aims Sustained virological suppression and hepatitis B surface antigen (HBsAg) loss have been described after nucleot(s)ide analogue (NA) discontinuation for patients with hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB). We performed a meta-analysis of the clinical outcomes after NA discontinuation for HBeAg-negative CHB.

Methods Studies involving NA cessation in HBeAg-negative CHB individuals with a median follow-up of ≥12 months were included. Participants were HBeAg-negative at the time of NA initiation. Random effects meta-analyses were performed for the following clinical outcomes: (1) virological relapse (VR) at 6 and 12 months; (2) clinical relapse (CR) at 6 and 12 months and (3) HBsAg loss. Effect of other variables was estimated

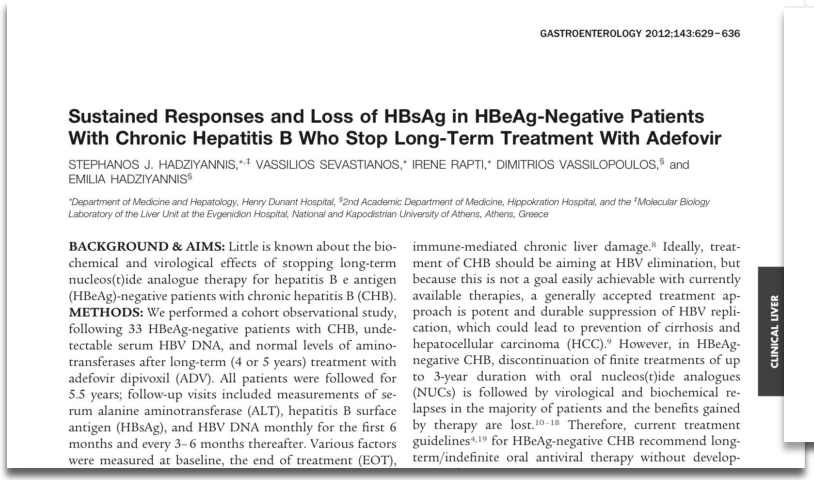
Significance of this study

What is already known on this subject?

⇒ Finite therapy for chronic hepatitis B has been identified as an area of unmet clinical need (European Association for the Study of the Liver (EASL) guideline).

⇒ A number of studies have reported that long-term viral control may be maintained in a significant minority of patients off-treatment, with some patients achieving hepatitis B surface antigen (HBsAg) loss.

⇒ However, protocol design has varied between studies, with differences in patient population, study eligibility, clinical outcomes of interest



GASTROENTEROLOGY 2012;143:629–636

CLINICAL LIVER

Sustained Responses and Loss of HBsAg in HBeAg-Negative Patients With Chronic Hepatitis B Who Stop Long-Term Treatment With Adefovir

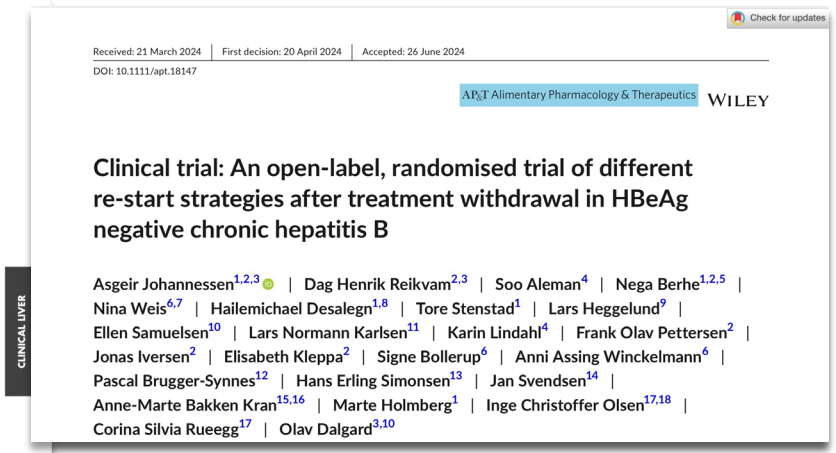
STEPHANOS J. HADZIYANNIS,*,‡ VASSILIOS SEVASTIANOS,* IRENE RAPTI,* DIMITRIOS VASSILOPOULOS,§ and EMILIA HADZIYANNIS§

*Department of Medicine and Hepatology, Henry Dunant Hospital, §2nd Academic Department of Medicine, Hippokration Hospital, and the ‡Molecular Biology Laboratory of the Liver Unit at the Evgenidion Hospital, National and Kapodistrian University of Athens, Athens, Greece

BACKGROUND & AIMS: Little is known about the biochemical and virological effects of stopping long-term nucleos(t)ide analogue therapy for hepatitis B e antigen (HBeAg)-negative patients with chronic hepatitis B (CHB).

METHODS: We performed a cohort observational study, following 33 HBeAg-negative patients with CHB, undetectable serum HBV DNA, and normal levels of aminotransferases after long-term (4 or 5 years) treatment with adefovir dipivoxil (ADV). All patients were followed for 5.5 years; follow-up visits included measurements of serum alanine aminotransferase (ALT), hepatitis B surface antigen (HBsAg), and HBV DNA monthly for the first 6 months and every 3–6 months thereafter. Various factors were measured at baseline, the end of treatment (EOT),

immune-mediated chronic liver damage.[8] Ideally, treatment of CHB should be aiming at HBV elimination, but because this is not a goal easily achievable with currently available therapies, a generally accepted treatment approach is potent and durable suppression of HBV replication, which could lead to prevention of cirrhosis and hepatocellular carcinoma (HCC).[9] However, in HBeAg-negative CHB, discontinuation of finite treatments of up to 3-year duration with oral nucleos(t)ide analogues (NUCs) is followed by virological and biochemical relapses in the majority of patients and the benefits gained by therapy are lost.[10–18] Therefore, current treatment guidelines[4,19] for HBeAg-negative CHB recommend long-term/indefinite oral antiviral therapy without develop-



Check for updates

Received: 21 March 2024 | First decision: 20 April 2024 | Accepted: 26 June 2024

DOI: 10.1111/apt.18147

Alimentary Pharmacology & Therapeutics WILEY

Clinical trial: An open-label, randomised trial of different re-start strategies after treatment withdrawal in HBeAg negative chronic hepatitis B

Asgeir Johannessen[1,2,3] | Dag Henrik Reikvam[2,3] | Soo Aleman[4] | Nega Berhe[1,2,5] | Nina Weis[6,7] | Hailemichael Desalegn[1,8] | Tore Stenstad[1] | Lars Heggelund[9] | Ellen Samuelsen[10] | Lars Normann Karlsen[11] | Karin Lindahl[4] | Frank Olav Pettersen[2] | Jonas Iversen[2] | Elisabeth Kleppa[2] | Signe Bollerup[6] | Anni Assing Winckelmann[6] | Pascal Brugger-Synnes[12] | Hans Erling Simonsen[13] | Jan Svendsen[14] | Anne-Marte Bakken Kran[15,16] | Marte Holmberg[1] | Inge Christoffer Olsen[17,18] | Corina Silvia Rueegg[17] | Olav Dalgard[3,10]

Stopping treatment can be harmful

- Hepatic flares
- Hepatic decompensation
- Death

Aim

- To describe the flares and identify predictive factors for flares after nucleos(t)ide analogue (NA) cessation in a prospective, multicenter trial

This knowledge may contribute to a better tailored treatment strategy for future patients with chronic hepatitis B

The Nuc-Stop Study

The Nuc-Stop Study

- 127 patients enrolled
- All HBeAg-negative and non-cirrhotic

From 11 centres in Norway, Sweden, Denmark, and Ethiopia

- Prospective study
- Originally designed to investigate if it is beneficial to let patients undergo a prolonged flare to achieve functional cure
- Stopped NA-treatment and were followed up for 36 months

REK (2018/988) og SLV (EudraCT 2018-000724-34)
Initiert av Asgeir Johannessen, Olav Dalgard og Dag Henrik Reikvam

The Nuc-Stop Study

Flares - definitions

ALT increase above 2x upper limit of normal (ULN) or above 2x baseline

GROUP	ALT
Mild	2 – 5 x ULN or 2 – 5x baseline
Moderate	5 – 20x ULN or 5 – 20x baseline
Severe	>20x ULN or > 20x baseline

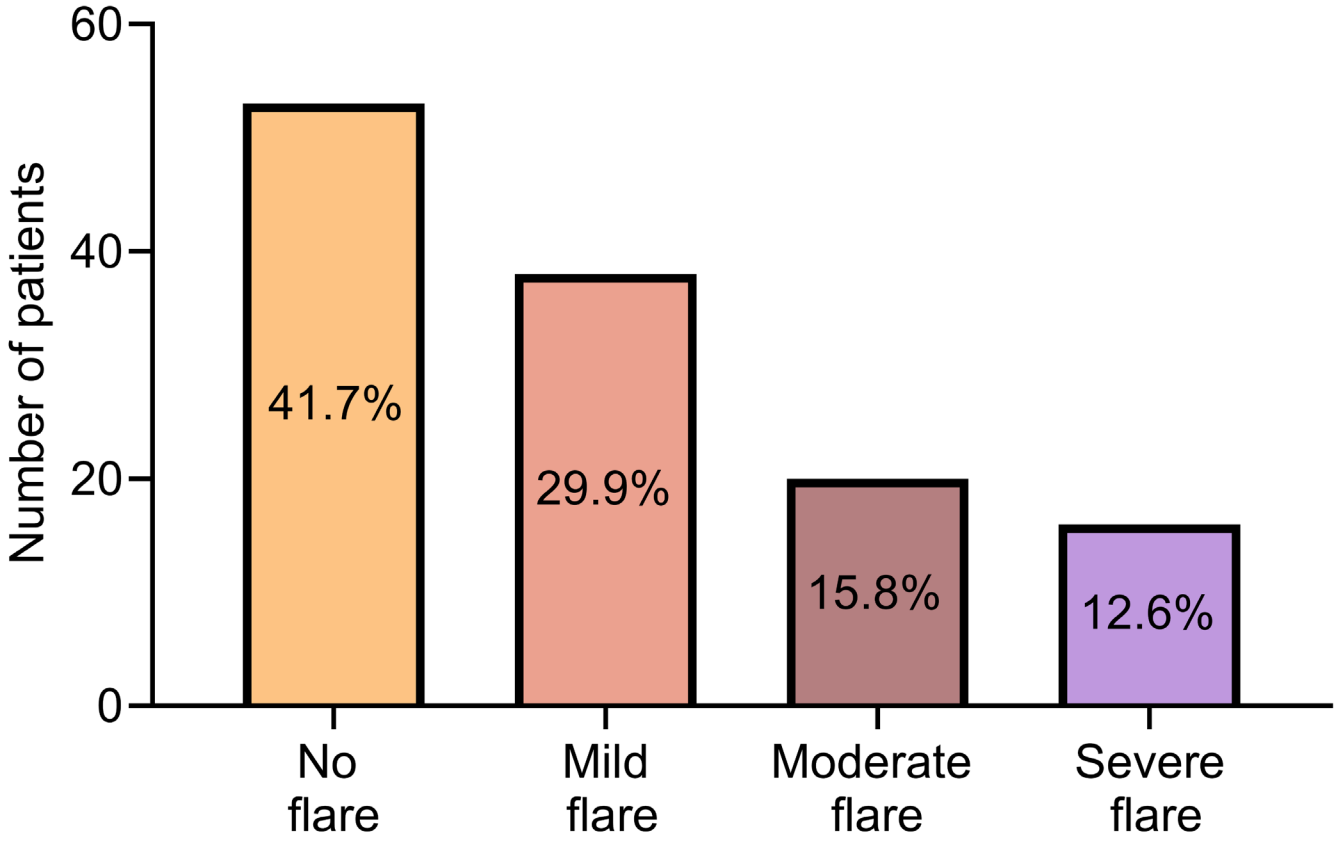
The Nuc-Stop Study

Baseline characteristics

Number of patients	127	BMI (kg/m^2)	24.6 (21.8-26.7)
Age (years)	43 (38-51)	Tenofovir/Entecavir (%)	76.4 / 23.6
Male (%)	67.7	Months on NA	45.0 (32.4-75.5)
African/Asian/European (%)	40.9 / 43.3 / 15.8	ALT (U/L)	29 (23-40)
Genotype A/B/C/D/E/unknown (%)	22.8 / 13.4 / 14.2 / 32.3 / 7.9 / 9.5	qHBsAg (IU/mL)	2213 (762-6105)

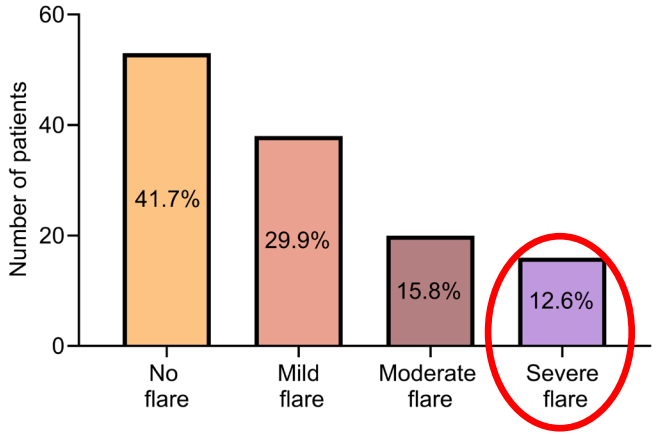
The Nuc-Stop Study

More than half of the patients experienced a flare



The Nuc-Stop Study

Severe flares

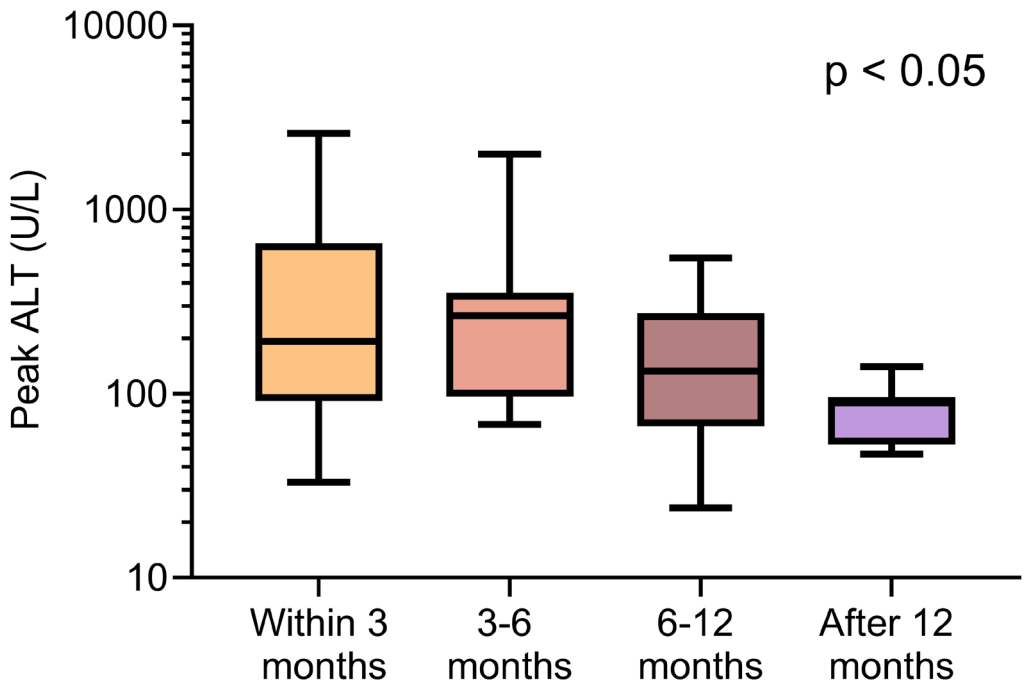


1. All tenofovir
2. Occurred early
   - Median time to severe flares was 2.0 (IQR 1.8 – 3.0) months
   - All within 6 months
3. Restart of NA therapy → ALT normalized & HBV DNA suppressed

No patients developed decompensated liver disease

The Nuc-Stop Study

Most flares occurred early, and early flares were more severe



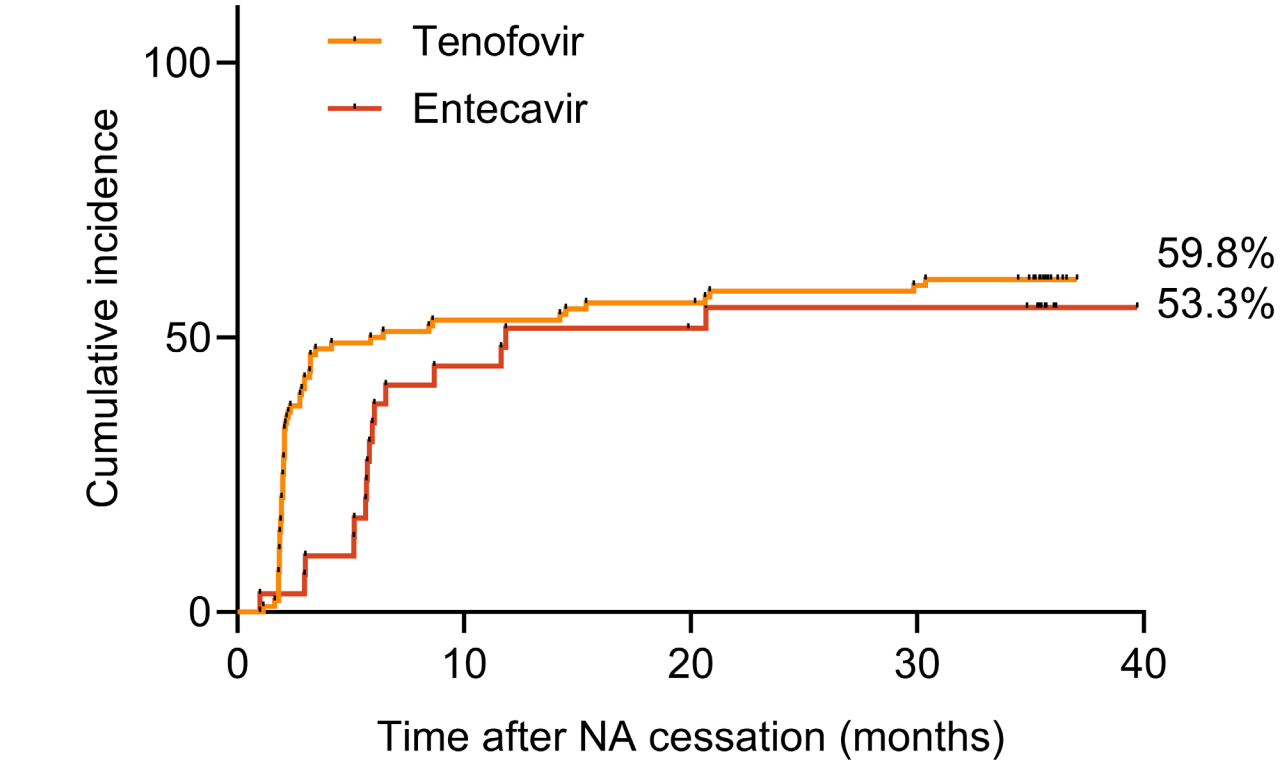
Timing	N (%)	Peak ALT (U/L) Median (range)
≤ 3months	44 (59.5)	192 (33-2600)
3-6 months	14 (18.9)	265 (68-2000)
6-12 months	8 (10.8)	133 (24-546)
> 12 months	8 (10.8)	89 (47-140)

Total n=74

The Nuc-Stop Study

Median time from treatment stop to first flare was significantly shorter for patients who stopped tenofovir ($p<0.01$)

NA	Months (IQR)
Tenofovir	2.1 (1.9-3.2)
Entecavir	5.8 (5.1-7.6)



The Nuc-Stop Study

Flares had no impact on qHBsAg decline

Flare	**qHBsAg loss or >1log$_{10}$ decline**	
	Yes N (%)	No N (%)
No flare	9 (17.0)	44 (83.0)
Mild/moderate	5 (8.6)	53 (91.4)
Severe	3 (18.8)	13 (81.3)

The Nuc-Stop Study

Predictors of hepatic flares

Variable	Unadjusted			Adjusted		
	OR	95% CI	p-value	OR	95% CI	p-value
Age (years)	1.05	1.01-1.09	0.02	1.07	1.02-1.12	0.01
Sex (male vs. female)	0.98	0.46-2.09	0.97			
Ethnicity (Asian vs. Non-Asian)	1.40	0.68-2.88	0.36			
Genotype (B/C vs. other)	2.36	0.98-5.68	0.05	2.29	0.87-6.02	0.09
BMI (kg/m^2)	0.97	0.89-1.06	0.47			
Tenofovir vs. entecavir	0.77	0.34-1.75	0.53			
Treatment duration (months)	1.00	0.99-1.01	0.70			
qHBsAg (log_{10} IU/mL)	1.61	1.07-2.42	0.02	2.09	1.20-3.62	0.01

The Nuc-Stop Study

qHBsAg and flares

Baseline qHBsAg (IU/ml)	Total number of patients	Flare ALT>2xULN or 2xBA	Flare ALT>5xULN or 5xBA	Flare ALT>20xULN or 20xBA	qHBsAg loss	qHBsAg decline (1 log_{10}) or loss
≤ 100	12	4 (33.3%)	2 (16.7%)	1 (8.3%)	8 (66.7%)	11 (91.7%)
100-1000	29	17 (58.6%)	13 (44.8%)	6 (20.7%)	3 (10.3%)	4 (13.8%)
>1000	86	53 (61.6%)	21 (24.4%)	9 (10.5%)	0	2 (2.3%)

Patients with qHBsAg ≤ 100 have the highest chance of qHBsAg decline and the lowest risk of flares

The Nuc-Stop Study

Conclusions

- Flares occurred in more than half of the patients and were associated with age and baseline qHBsAg level
- Severe flares occurred in 12.6%, all within 6 months, and normalized quickly after restart of NA therapy

The Nuc-Stop Study

Acknowledgments

- **Participating centres**
  - Akershus University Hospital
  - Copenhagen University Hospital, Denmark
  - Karolinska University Hospital, Sweden
  - Nordland Hospital
  - Oslo University Hospital
  - Stavanger University Hospital
  - St. Paul's Hospital, Ethiopia
  - Vestfold Hospital
  - Vestre Viken Hospital (Bærum)
  - Vestre Viken Hospital (Drammen)
  - Ålesund Hospital
- **Supervisors**
  - Asgeir Johannessen
  - Dag Henrik Reikvam
- **Funding**
  - South-Eastern Norway Regional Health Authority (Helse Sør-Øst)

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The Nuc-Stop Study

Thank you!