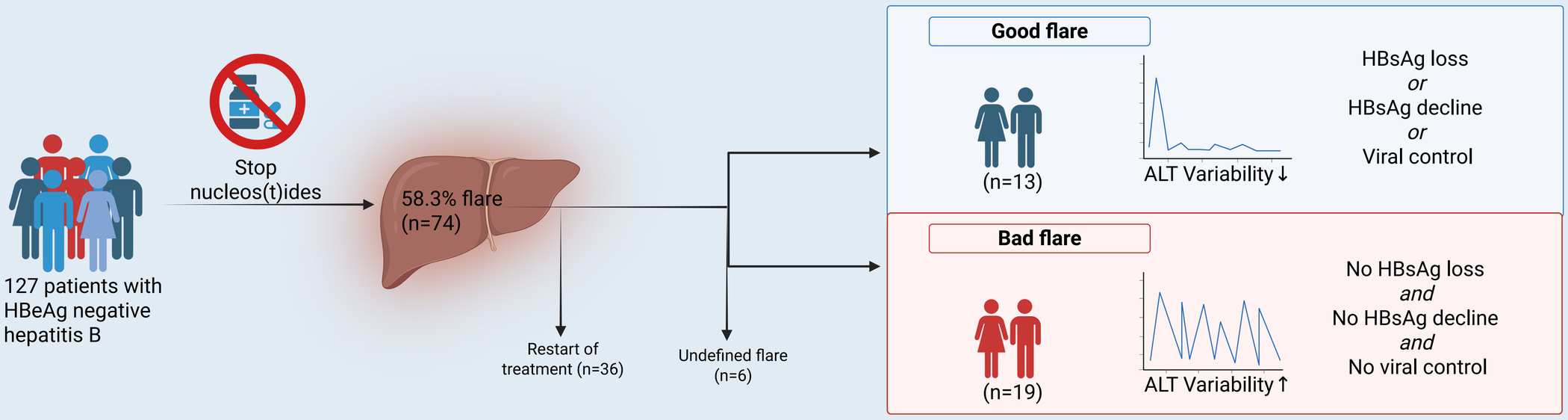
Good flare or bad flare? ALT variability predicts outcome after stopping nucleos(t)ide analogue therapy in HBeAg-negative chronic hepatitis B

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

Contact information: Marte Holmberg, MD. E-mail: marte.holmberg@online.no



INTRO / BACKGROUND

Flares are common after nucleos(t)ide analogue (NA) cessation in patients with HBeAg-negative chronic hepatitis B (CHB). Whether these flares represent a beneficial immune response leading to HBsAg decline ("good flare") or are detrimental, leading to hepatic necroinflammation and fibrosis progression ("bad flare"), is difficult to discern. We aimed to investigate whether differences in ALT variability following a flare can predict outcomes in patients enrolled in an NA stop trial (the Nuc-Stop study).

METHODS

This study was nested in the prospective Nuc-Stop study, in which 127 HBeAg-negative CHB patients discontinued NA treatment with a 36-month follow-up. Of these, 38 patients who experienced a flare without restarting treatment were included in the present analysis. ALT values following the initial flare were analysed, and Levene's test was used to assess ALT variability.

Definitions:

- Flare: an ALT increase >2× the upper limit of normal or >2× baseline.
- Good flare: flare leading to HBsAg loss, HBsAg decline >1 $\log_{10}$ IU/mL, or sustained off-therapy virological control (HBV DNA <2000 IU/mL at all study visits in year 3).
- Bad flare: flares without HBsAg decline (<0.5 $\log_{10}$ IU/mL) and without off-therapy virological control.

CONCLUSION

After discontinuing NA therapy in HBeAg-negative chronic hepatitis B patients, low ALT variability following the initial flare may serve as a favourable prognostic marker helping to distinguish good flares from bad flares.

RESULTS

	Good flare (N=13)	Bad flare (N=19)	P-value
Age (years)[a]	46 (43-56)	43 (32-50)	0.219[c]
Men[b]	9 (62.9)	10 (52.6)	0.471[d]
Ethnicity[b]			0.670[d]
African	6 (46.2)	9 (47.4)	
Asian	5 (38.5)	9 (47.4)	
European	2 (15.4)	1 (5.3)	
Genotype[b]			0.402[d]
A	2 (15.4)	5 (26.3)	
B	3 (21.1)	3 (15.8)	
C	0	3 (15.8)	
D	5 (38.5)	3 (15.8)	
E	3 (23.1)	3 (15.8)	
Unknown	0	2 (10.5)	
BMI (kg/m²)[a]	25.3 (21.6-27.4)	23.9 (20.8-26.6)	0.570[c]
NA[b]			1.000[d]
Tenofovir	11 (84.6)	16 (84.2)	
Entecavir	2 (15.4)	3 (15.8)	
Time on NA (months)[a]	44.9 (29.7-81.6)	44.2 (32.2-74.5)	0.970[c]
ALT (U/L)[a]	28 (24-40)	28 (22-40)	0.962[c]
qHBsAg (IU/mL)[a]	762 (220-3707)	4397 (1393-7707)	**0.025**[c]

Table1. Baseline characteristics.
[a]Median (IQR). [b]Count (percentage). [c]Mann-Whitney U test. [d]Fisher´s exact test. N, number of patients; BMI, Body Mass Index; NA, nucleos(t)ide analogue; qHBsAg, quantitative hepatitis B surface antigen.

- Of the 38 patients who experienced a flare and did not restart NA treatment, 13 had a good flare, 19 had a bad flare, and 6 did not fit into either category and were excluded from further analysis (Table 1).
- Among patients with good flares, 3 achieved HBsAg loss, 3 had an HBsAg decline >1 $\log_{10}$ IU/mL, and 7 had sustained off-therapy virological control.
- The median peak ALT was similar in patients with good flares and bad flares (89 (IQR 52-179) vs. 103 (IQR 74-154) U/L; p = 0.670).
- Good flares displayed less ALT variability after the initial spike than bad flares (standard deviation 9.7 vs. 22.7 U/L, p = 0.002 (Figure 1).

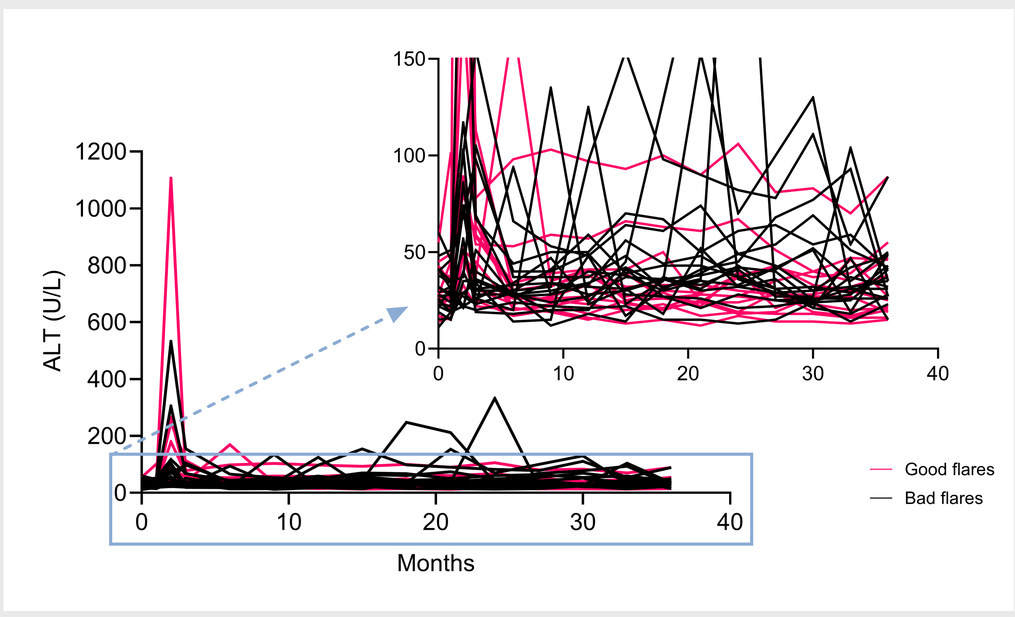


Figure 1. Longitudinal ALT levels from end-of-treatment to 36 months of follow-up in patients with good and bad flares. Each line represents an individual patient. The inset magnifies ALT fluctuations below 150 U/L.

ACKNOWLEDGEMENTS

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