

Improvement in Liver Histology Is Observed in Most Patients With Chronic Hepatitis Delta After 48 Weeks of Bulevirtide Monotherapy

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Conclusions

- In a subanalysis of patients with paired BL and W48 liver biopsies, an improvement in liver histology was observed in most patients with CHD after 48 weeks of BLV monotherapy, including those who did not achieve VR
- Decreases in ALT levels and/or HAI were observed in most patients treated with BLV
 - The degrees of improvement in HAI and ALT levels did not necessarily correlate
- Histologic improvement and improvement in HAI or HAI category occurred more frequently in patients with VR or PR
- An improvement in fibrosis occurred most frequently in patients with VR
- No consistent pattern of HAI, ALT level, or fibrosis change was observed in the control group

Plain Language Summary

- An improvement in liver histology, or how liver cells look under a microscope, was observed in most patients with chronic hepatitis delta after 48 weeks of bulevirtide treatment
- This improvement in liver histology was observed even in patients who did not have a large decrease in the amount of hepatitis delta virus from bulevirtide treatment

References: 1. Stockdale AJ, et al. *J Hepatol*. 2020;73:523-32. 2. Hepcludex. European Medicines Agency SmPC. Gilead Sciences, Inc.; 2023. 3. Wedemeyer H, et al. *EASL*. 2023. Oral #OS-068. 4. Dietz-Fricke C, et al. *JHEP Rep*. 2023;5:100696.

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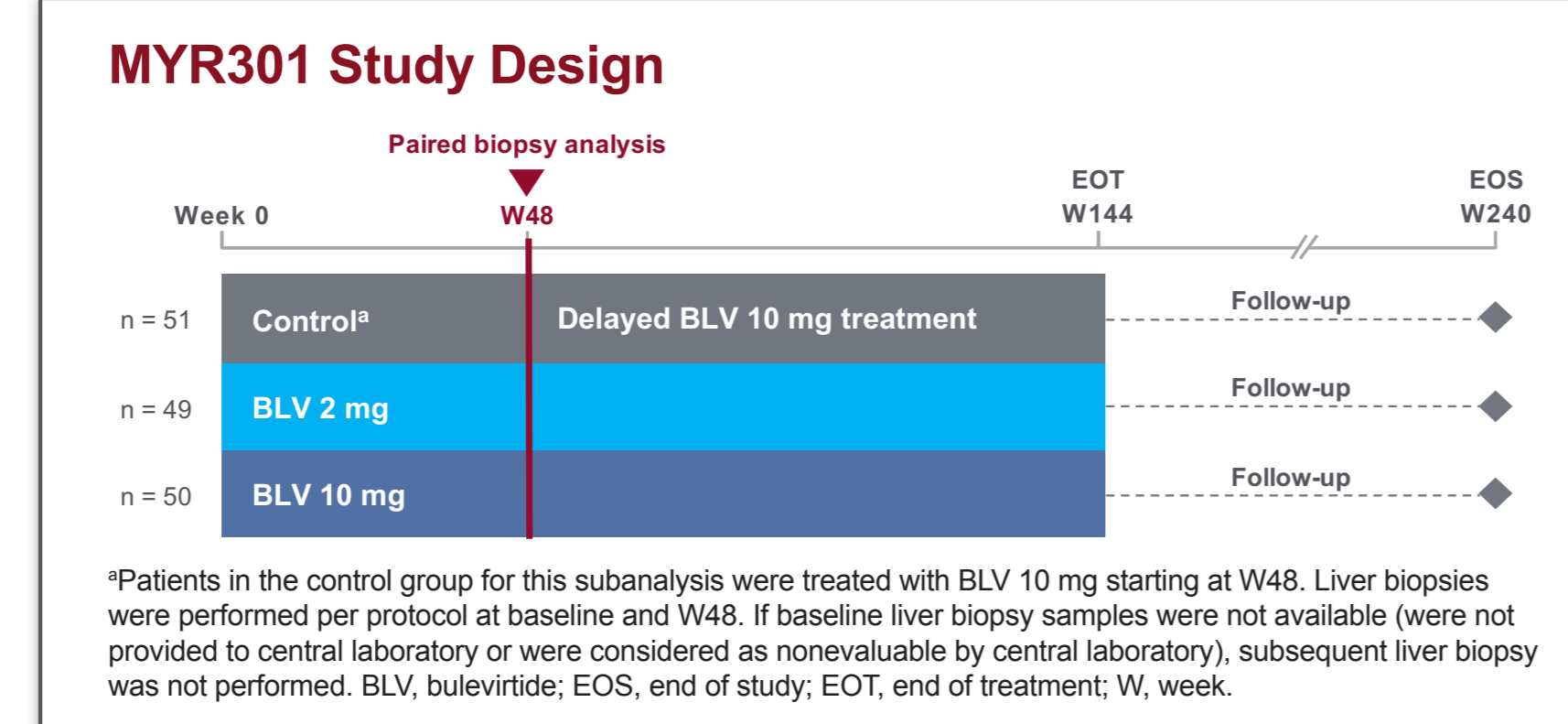
Introduction

- Hepatitis delta virus (HDV) represents the most severe form of chronic viral hepatitis and is estimated to affect between 10 and 20 million individuals worldwide¹
- Bulevirtide (BLV), a novel entry inhibitor of HDV, is fully approved in the European Union, Great Britain, Switzerland, and the Russian Federation at the dose of 2 mg/day for the treatment of chronic hepatitis delta (CHD) with compensated liver disease²
- In the MYR301 study, BLV monotherapy (2 or 10 mg) resulted in a virologic response in 76% to 82%, normalisation of alanine aminotransferase (ALT) in 63% to 64%, and a combined response (ALT normalisation + virologic response) in 55% to 56% of patients after 96 weeks³
- A recent subanalysis showed that ALT improvement may occur discordantly of virologic response with BLV treatment⁴
- It remains unclear whether histologic improvement correlates with ALT and/or virologic response in patients treated with BLV monotherapy

Objective

- This study aims to evaluate the evolution and correlation of biochemical, virologic, and histologic parameters in patients with CHD treated with BLV monotherapy for 48 weeks

Methods



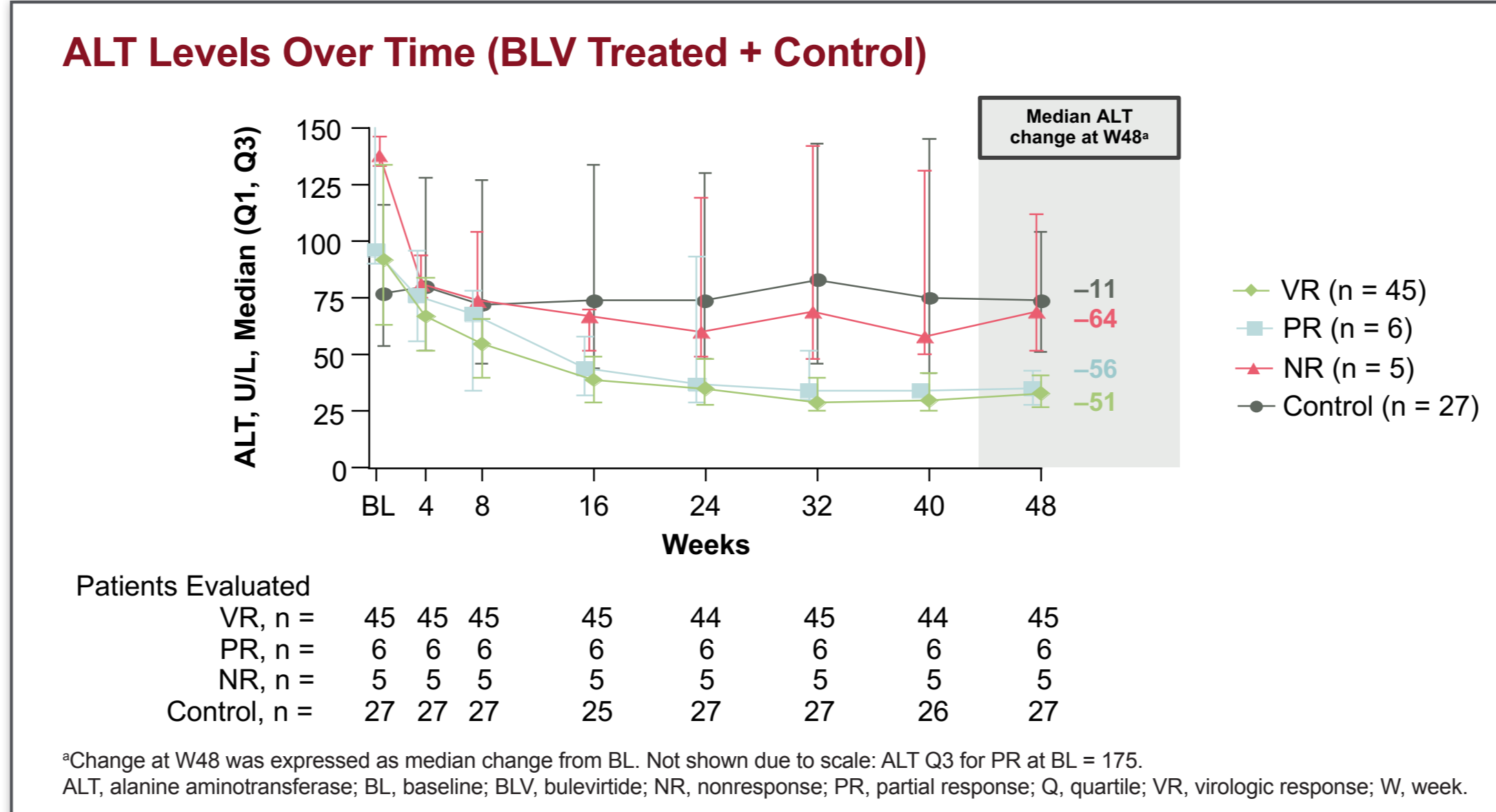
- This analysis included data up to week (W) 48 from patients in the ongoing randomised Phase 3 Study MYR301 (NCT03852719) who had paired (baseline [BL] and W48) liver biopsies
- At W48, there were 3 study arms: BLV 2 mg, BLV 10 mg, and a delayed-treatment arm that received no anti-HDV therapy to this point (control)
- Virologic response groups at W48 were defined as follows:
 - Virologic response (VR) = HDV RNA decline of $\geq 2 \log_{10}$ IU/mL from BL or undetectable HDV RNA
 - Partial response (PR) = HDV RNA decline of ≥ 1 but $< 2 \log_{10}$ IU/mL from BL
 - Nonresponse (NR) = HDV RNA decline of $< 1 \log_{10}$ IU/mL from BL
- Histologic analysis included:
 - Histologic parameters: histologic activity index (HAI; 0–18), HAI category (0–4), and Ishak fibrosis score (0–6)
 - Improvement at W48 was defined as ≥ 1 -point improvement from BL for HAI and Ishak fibrosis score and ≥ 1 HAI category improvement from BL
 - Histologic improvement was defined as ≥ 2 -point improvement in HAI with no worsening of fibrosis score
- ALT normalisation was defined at Russian sites as ≤ 31 U/L for females and ≤ 41 U/L for males, and at all other sites as ≤ 34 U/L for females and ≤ 49 U/L for males
- HDV RNA levels were determined by RT-qPCR using RoboGene[®] HDV RNA Quantification Kit 2.0 (lower limit of quantification 50 IU/mL, lower limit of detection 6 IU/mL)

Results

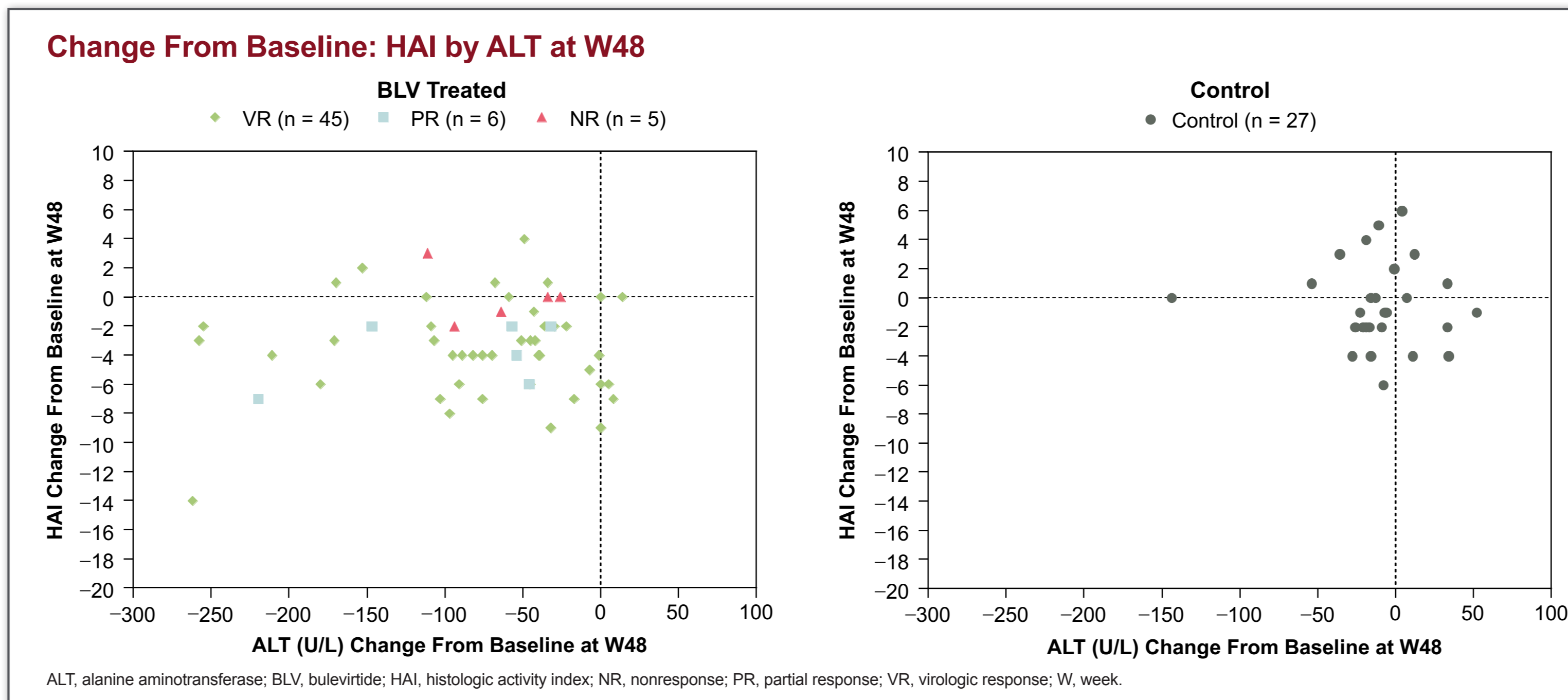
	BLV (2 or 10 mg)					Total (N = 83)
	VR at W48 (n = 45)	PR at W48 (n = 6)	NR at W48 (n = 5)	Control (n = 27)		
Age, years, mean (SD)	44 (8.6)	38 (9.2)	46 (10.7)	40 (7.4)	42 (8.6)	
Male sex, n (%)	22 (48.9)	4 (66.7)	3 (60.0)	14 (51.9)	43 (51.8)	
Race, n (%)						
White	41 (91.1)	6 (100.0)	3 (60.0)	20 (74.1)	70 (84.3)	
Asian	3 (6.7)	0	2 (40.0)	7 (25.9)	12 (14.5)	
Black or African American	1 (2.2)	0	0	0	1 (1.2)	
Cirrhosis present, n (%)	16 (35.6)	1 (16.7)	1 (20.0)	9 (33.3)	27 (32.5)	
HBeAg positive, n (%)	6 (13.3)	1 (16.7)	0	3 (11.1)	10 (12.0)	
Concomitant NA therapy, n (%)	28 (62.2)	2 (33.3)	3 (60.0)	18 (66.7)	51 (61.4)	
Prior IFN therapy, n (%)	33 (73.3)	2 (33.3)	2 (40.0)	16 (59.3)	53 (63.9)	
Genotype HDV-1, n (%) ^a	43 (95.6)	6 (100.0)	5 (100.0)	27 (100.0)	81 (97.6)	
HDV RNA, log ₁₀ IU/mL, mean (SD)	5.1 (1.4)	5.2 (1.1)	5.1 (1.8)	5.2 (1.2)	5.1 (1.3)	
ALT, U/L, median (Q1, Q3)	92 (63, 134)	96 (90, 175)	138 (133, 146)	77 (54, 116)	92 (63, 136)	
LSM, kPa, mean (SD)	12.8 (7.0)	8.1 (2.2)	8.2 (3.9)	12.4 (8.1)	12.1 (7.1)	
HAI, mean (SD)	9 (3.4)	8 (3.1)	8 (2.8)	8 (3.3)	8 (3.3)	
Ishak fibrosis score, mean (SD)	3 (1.5)	2 (1.6)	2 (0.4)	2 (1.4)	2 (1.4)	

^aIn the BLV 10 mg group, 1 patient was HDV genotype 5 and 1 patient was missing HDV genotype data; both patients had VR at W48. ALT, alanine aminotransferase; BLV, bulevirtide; HAI, histologic activity index; HBeAg, hepatitis B e antigen; HDV, hepatitis delta virus; IFN, interferon; LSM, liver stiffness measurement; NA, nucleos(t)ide analogue; NR, nonresponse; PR, partial response; Q, quartile; VR, virologic response; W, week.

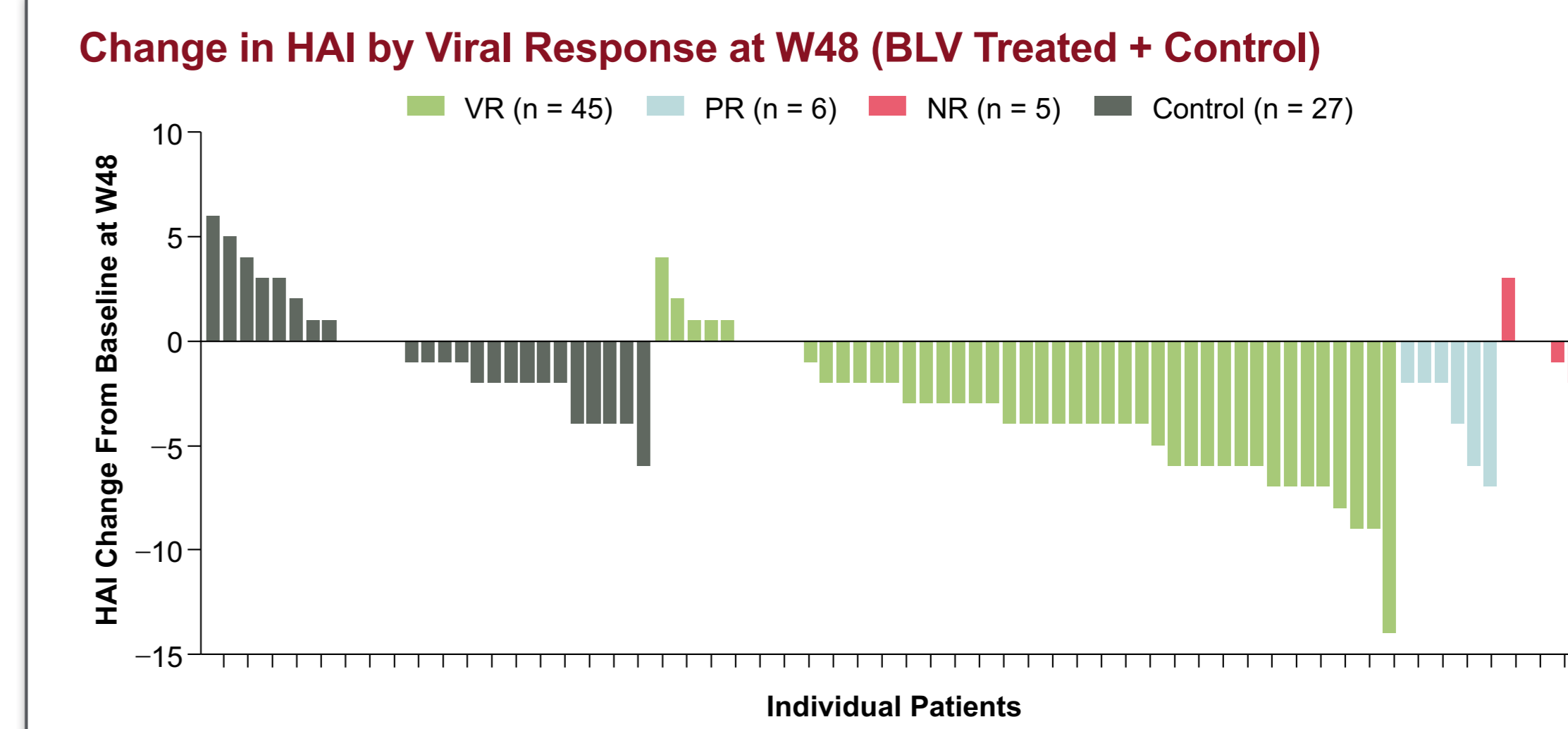
- Overall, 83 patients with paired BL and W48 liver biopsies were included in this subanalysis
 - BLV treated (n = 56): VR at W48 (n = 45), PR at W48 (n = 6), and NR at W48 (n = 5)
 - Control (n = 27)



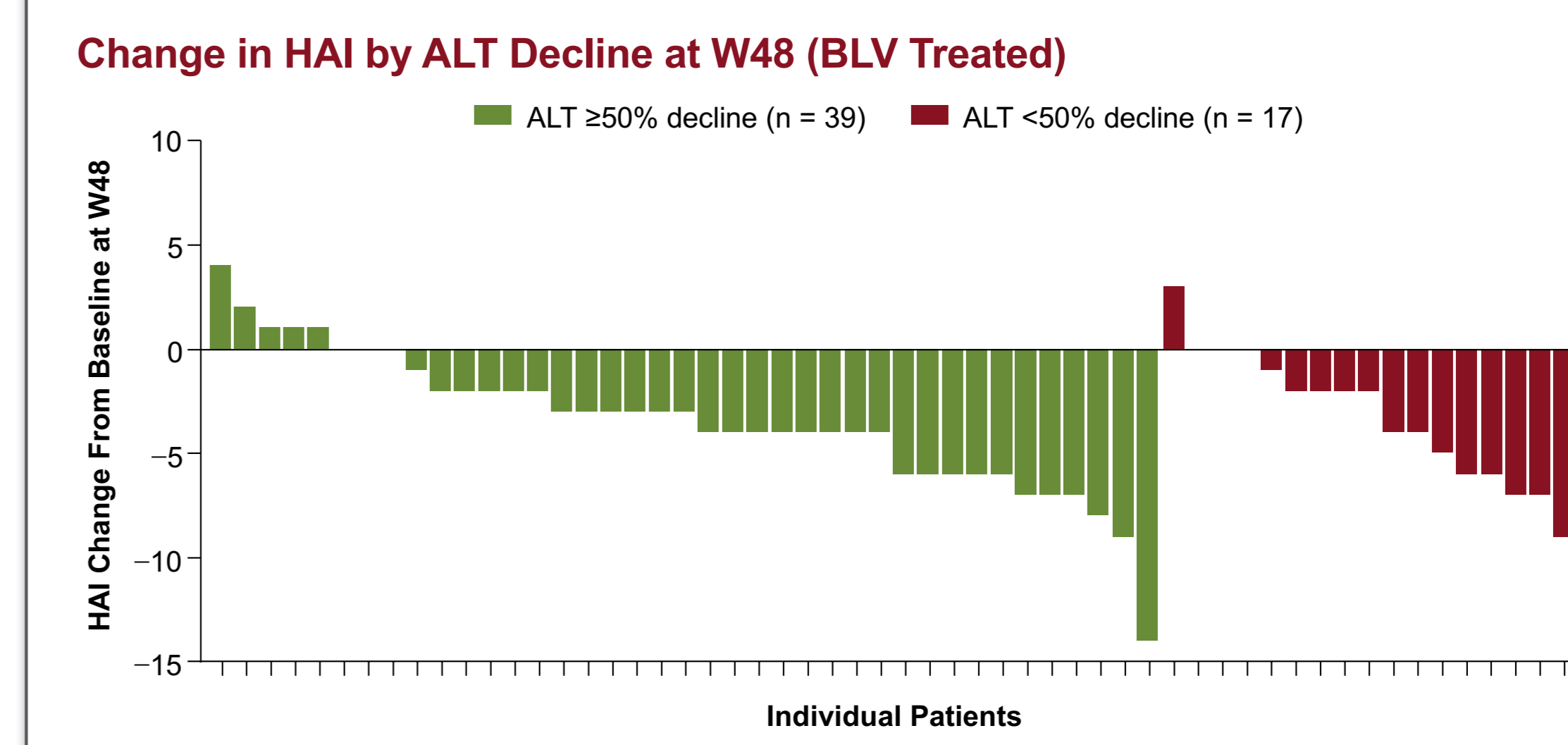
- Greater median changes in ALT levels from BL were observed in BLV-treated patients compared with the control group at W48, regardless of viral response
 - Similar median changes in ALT levels were observed across viral response groups in patients treated with BLV



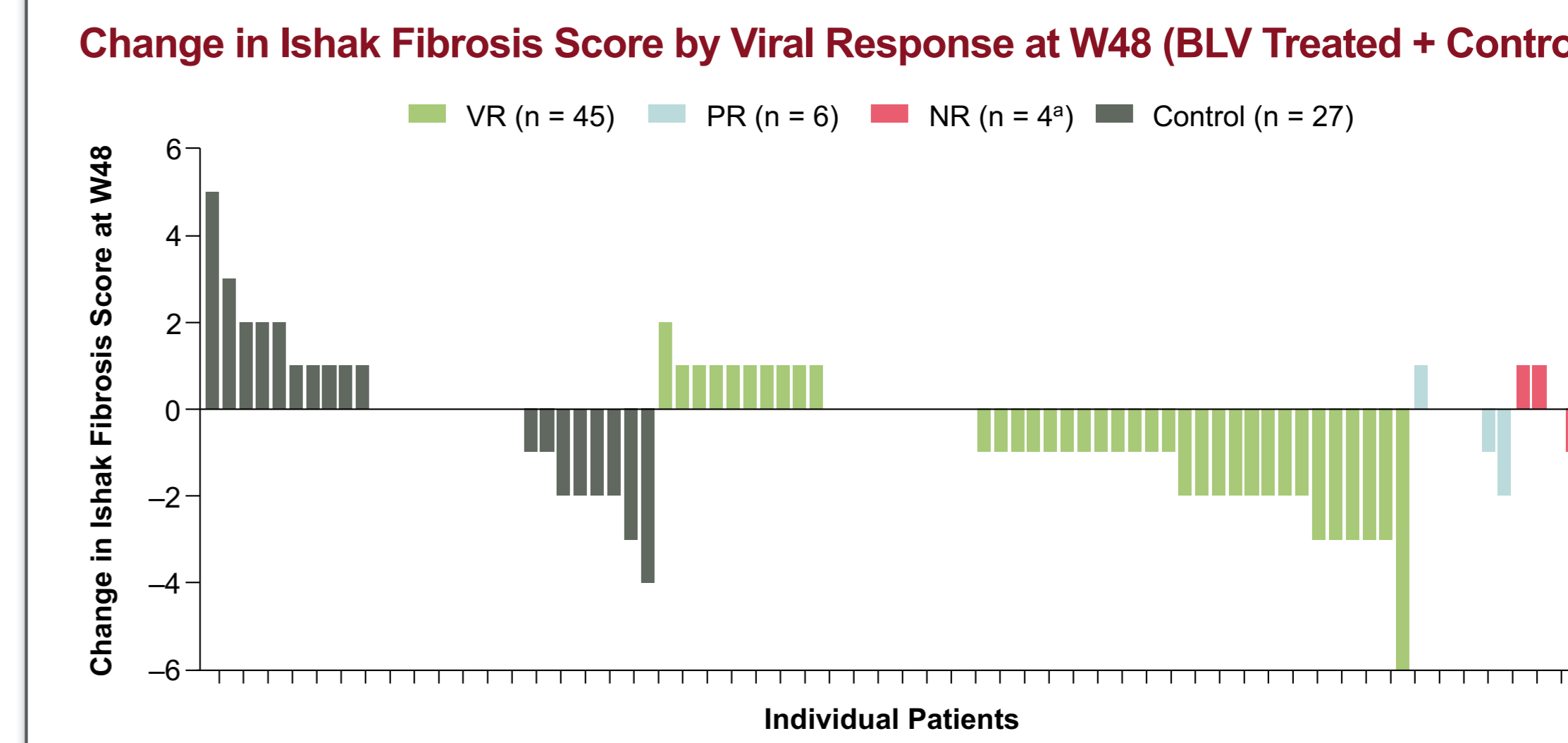
- Decreases in ALT levels and HAI were observed in most patients treated with BLV, irrespective of viral response group
- The degree of improvement in HAI and ALT levels did not necessarily correlate
- No consistent pattern of HAI or ALT level change was observed in the control group



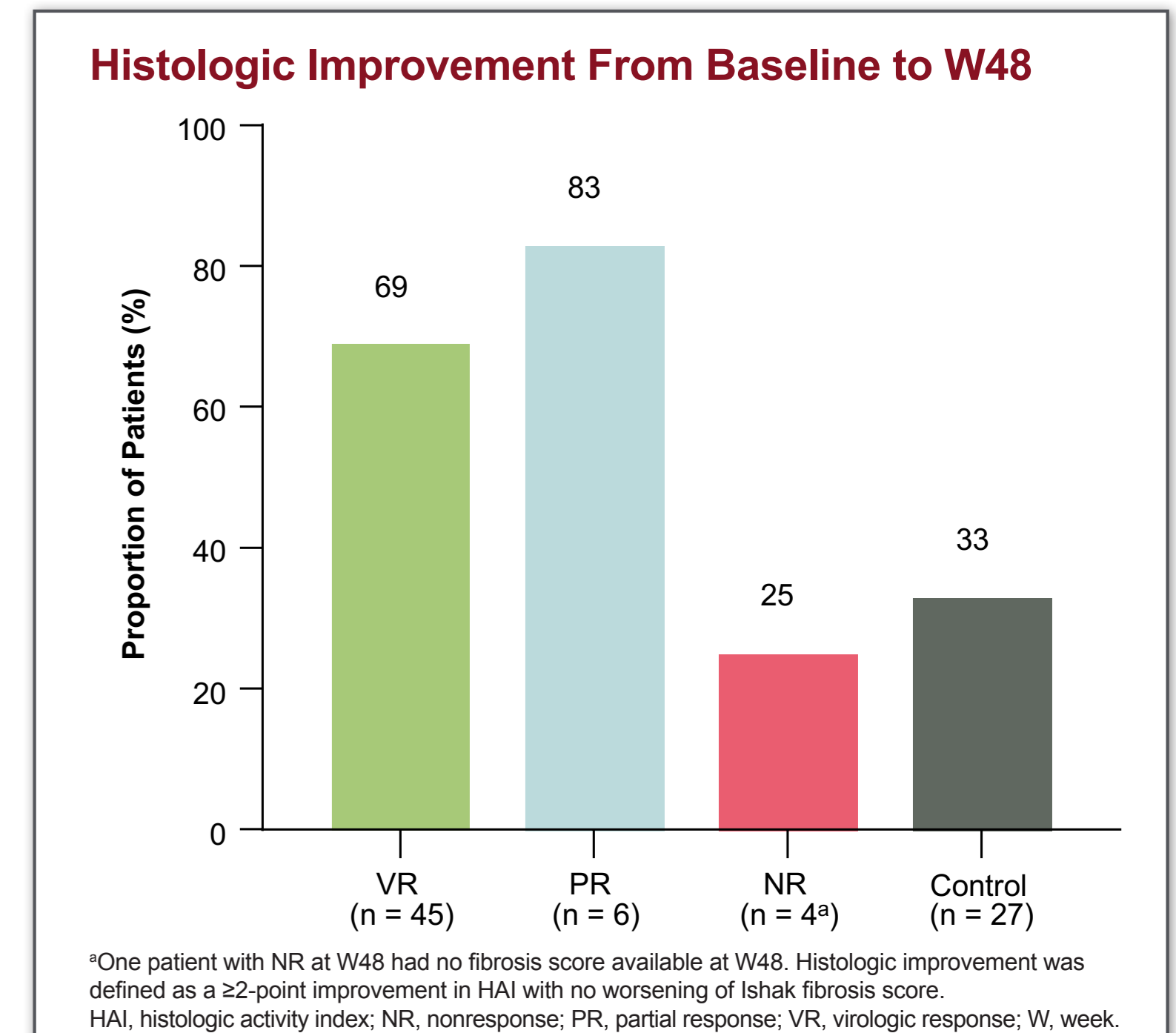
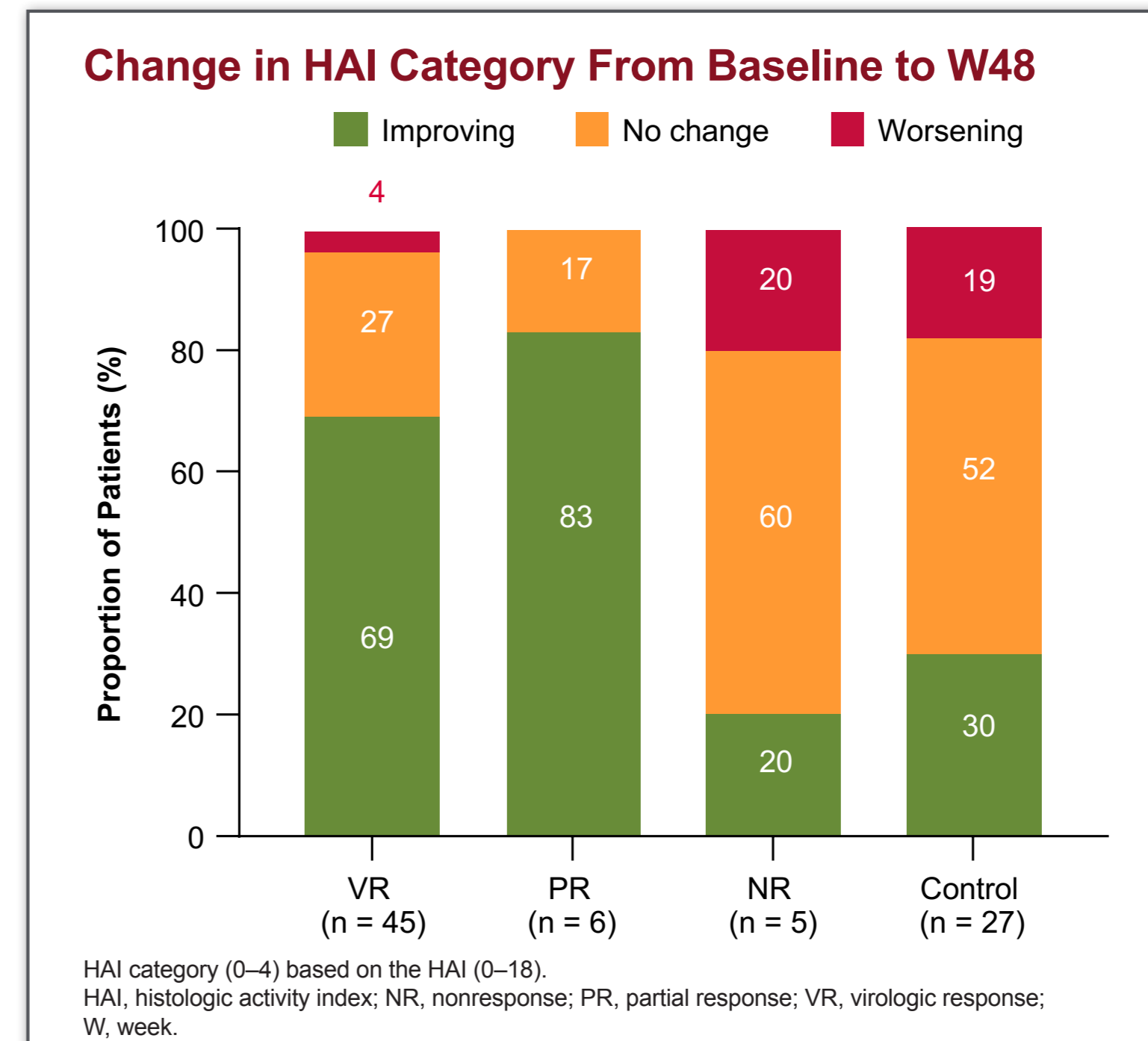
- Improvement in HAI occurred as follows:
 - VR: 80% (36/45)
 - PR: 100% (6/6)
 - NR: 40% (2/5)
 - Control: 56% (15/27)



- HAI improvement was seen even in patients who had <50% decline in ALT
 - ALT $\geq 50\%$ decline: 79% (31/39)
 - ALT <50% decline: 76% (13/17)



- Improvement in Ishak fibrosis score occurred as follows:
 - VR: 58% (26/45)
 - PR: 33% (2/6)
 - NR: 25% (1/4)
 - Control: 30% (8/27)



- Improvement in HAI category occurred more frequently in patients with VR and PR
- Histologic improvement occurred more frequently in patients with VR and PR