Transaminase flares during HBsAg reduction to < 1 IU/mL are correlated with the establishment of functional cure of HBV following NAP-based combination therapy

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Disclosures

AV and MB are employees and shareholders in Replicor Inc.

The NAP genus

All single stranded phosphorothioate oligonucleotides with sequence independent activity

Novel SAR driven by interaction with hydrophobic surfaces of amphipathic α-helices

Unique pharmacology validated *in vitro*, *in vivo* and in humans:

length (> antisense) and phosphorothioation dependent

independent of nucleotide sequence or base and sugar modifications

Broad spectrum anti-infective activity (all targets contain structurally conserved amphipathic α-helices)

Infectious agent targets (all identified)
HDV, HIV, all *herpesviridae*, RSV, PIV-3, influenza A and B, Ebola, Marburg, LCMV, malaria, prion disease

Host target (not yet identified!)
HCV – post entry fusion inhibitor

HBV – selective inhibition of SVP assembly and secretion (no effects on HBV DNA and HBeAg)

A retrospective analysis of transaminase elevations during combination therapy with NAPs and pegIFN

REP 301: REP 2139-Ca + peg IFN in chronic HBeAg- HBV / HDV co-infection

n=12

Treatment naïve
HDV RNA > 10000 copies / mL, HDAg+
HBeAg negative, anti-HBe positive
HBsAg > 1000 IU/mL
Negative for HCV, HIV or active CMV infection
3.5 years follow-up completed

REP 401: REP 2139-Mg or REP 2165-Mg + pegIFN + TDF in HBeAg- chronic HBV infection

n=40

Treatment naïve
HBV DNA > 2000 IU/mL
HBeAg negative, anti-HBe positive
HBsAg > 1000 IU/mL
Negative for HDV, HCV, HIV or active CMV infection
48 weeks follow-up completed

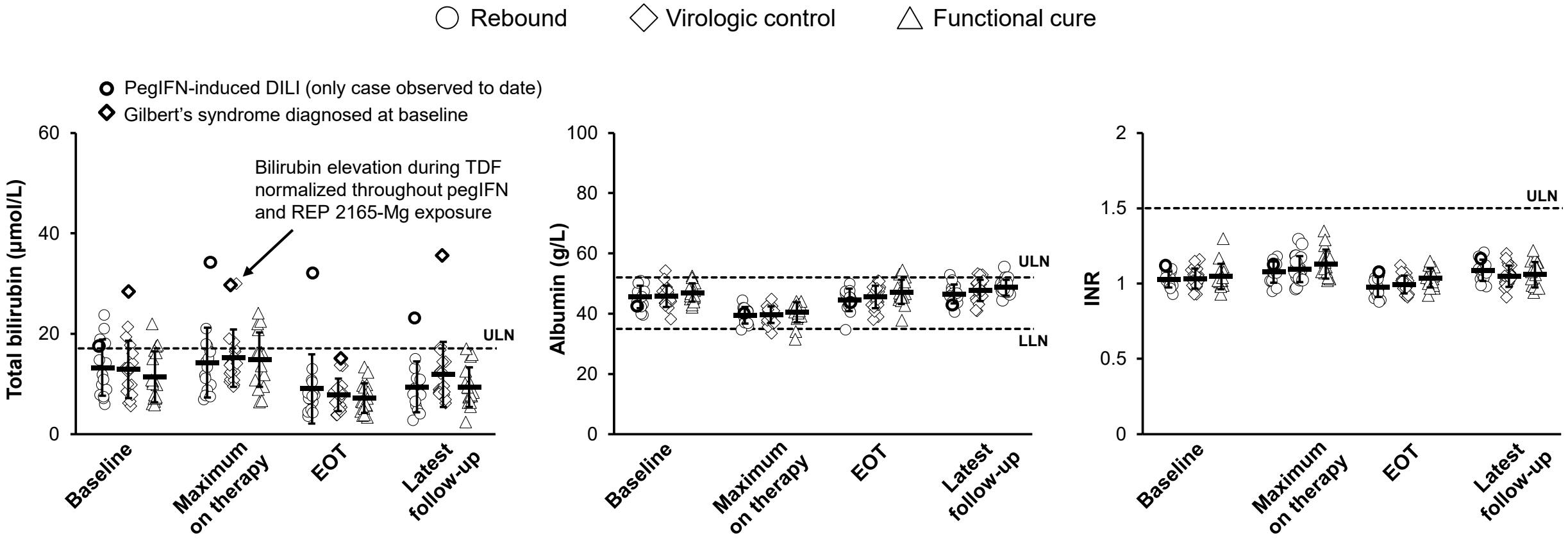
A retrospective analysis of transaminase elevations during combination therapy with NAPs and pegIFN

96% of participants experienced transaminase elevations during therapy

		Outcome during treatment free follow-up			p-value
		Rebound (HBV DNA > 2000 IU/mL) (n=15)	**Virologic control** (HBV DNA ≤ 2000 IU/mL, normal ALT) (n=20)	**Functional cure** (HBV DNA TND, HBsAg < LLOQ, normal ALT) (n=17)	
Age ($\bar{x}$ / median)		39.5 / 44	37.2 / 37	37.7 / 39	0.750
Sex	**Male**	12	16	14	0.979
	Female	3	4	3	
HBV genotype	**A**	1	1	0	0.922
	D	10	14	14	
	ND (HDV dominant)	4	5	3	
Baseline HBsAg (IU/mL, $\bar{x} \pm SD$)		$1.67x10^4 \pm 8.23x10^3$	$1.12x10^4 \pm 7.03x10^3$	$1.13x10^4 \pm 1.38x10^3$	0.274
Baseline HBV DNA (IU/mL, $\bar{x} \pm SD$)		$9.66x10^6 \pm 2.28x10^7$	$3.73x10^6 \pm 1.57x10^7$	$3.46x10^7 \pm 1.40x10^8$	0.494
Baseline transaminases (U/L, $\bar{x} \pm SD$)	**ALT**	76.1 ± 69.2	96.4 ± 72.4	88.4 ± 66.0	0.695
	AST	46.5 ± 30.8	57.0 ± 38.0	51.9 ± 25.6	0.635
	GGT	31.4 ± 24.6	33.1 ± 16.4	39.6 ± 25.6	0.531
Baseline LMS (kPa)	**≤ 7**	6	10	7	0.942
	7 - 9	5	5	5	
	9 - 11	1	3	0	
	11 - 18	2	2	3	
	>18	0	0	2	
Transaminase flare during therapy (> 3x ULN)	**ALT**	11	16	14	0.733
	AST	6	9	13	
	GGT	4	10	11	
	Any	11	17	17	0.248

Therapeutic outcomes independent of baseline characteristics or overall flare activity

Transaminase flares are not accompanied by altered liver function

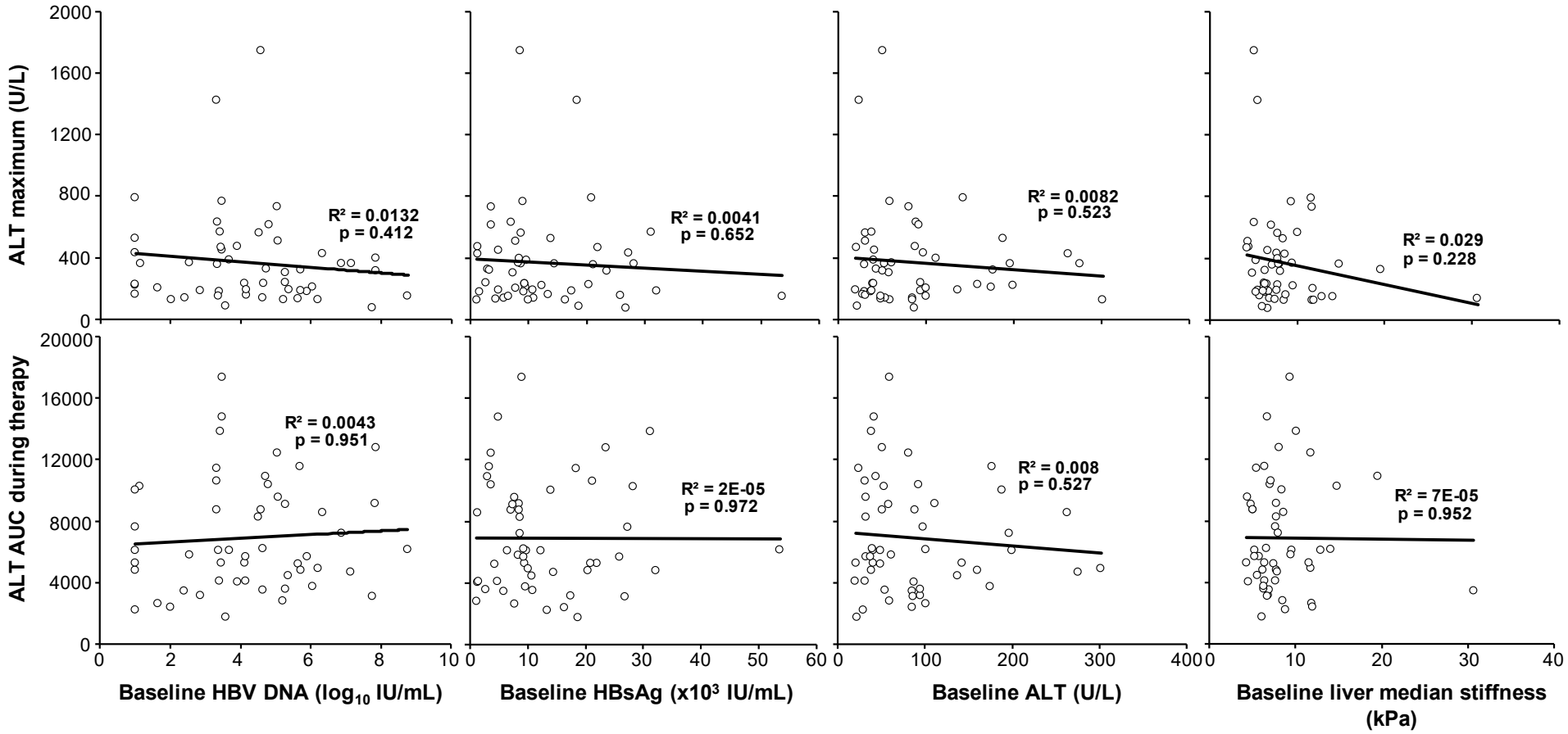


All transaminase elevations otherwise asymptomatic

No evidence of autoimmune hepatitis throughout therapy

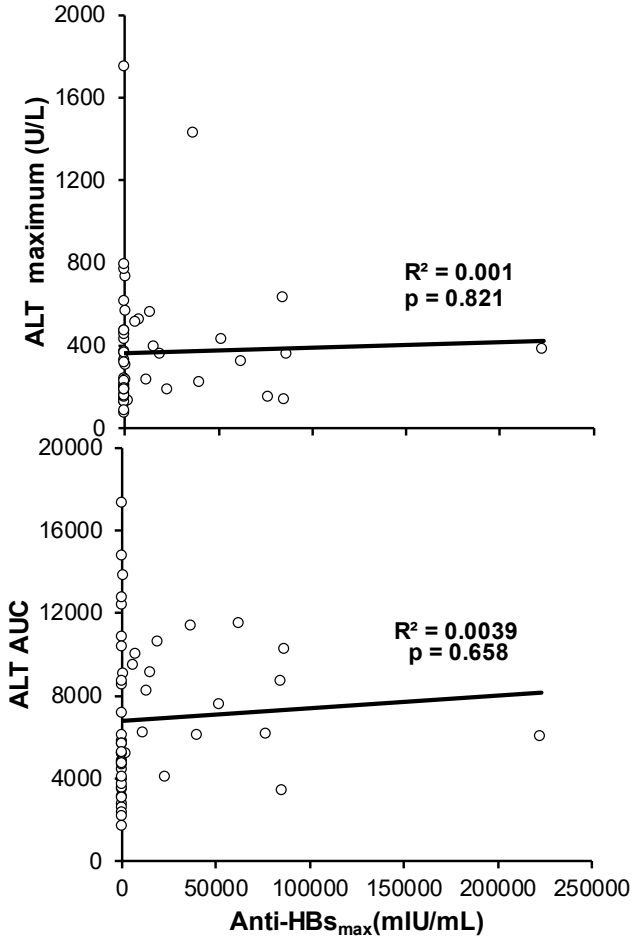
(anti-ANA negative, anti-LKM1 negative)

Factors influencing transaminase elevations

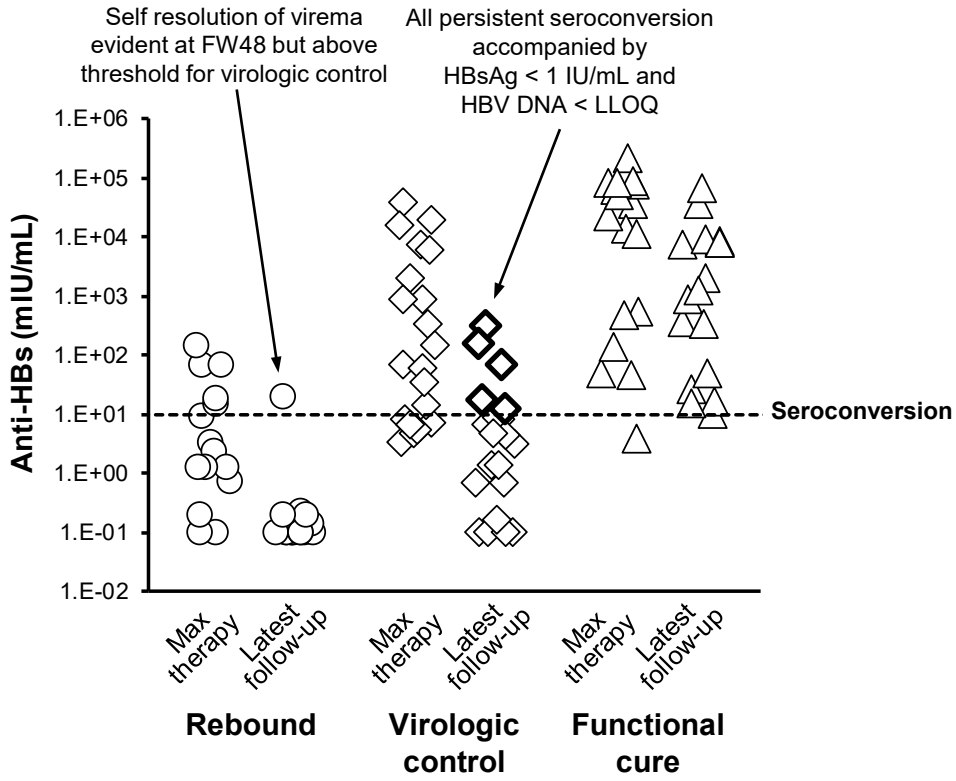


Transaminase elevations are independent of baseline characteristics

Factors influencing transaminase elevations



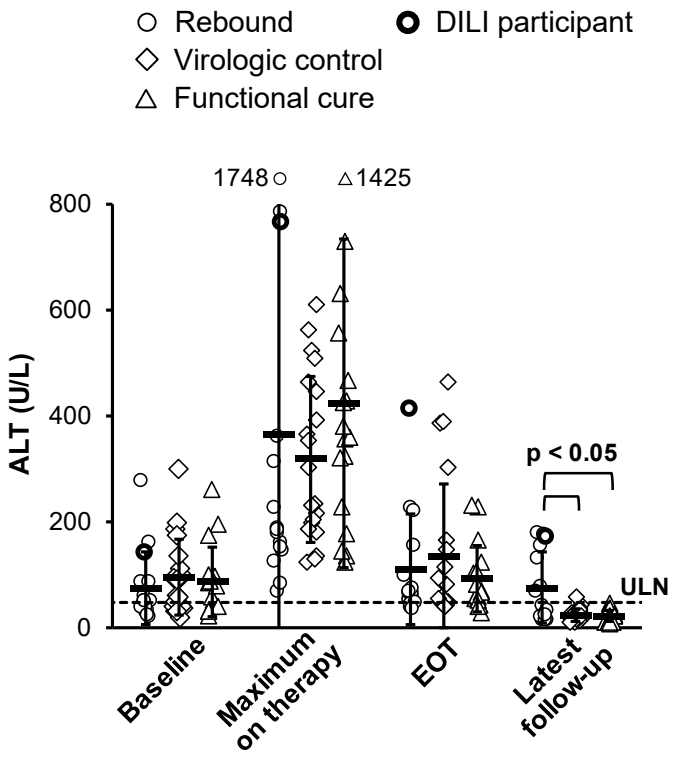
Transaminase elevations are independent of anti-HBs evolution during therapy



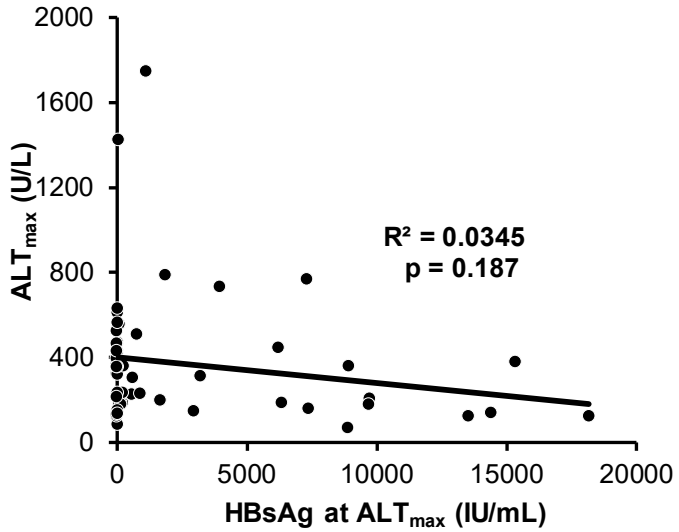
HBsAg seroconversion during therapy is correlated with clinical benefit

Only persists during follow-up with functional cure or "strong" virologic control

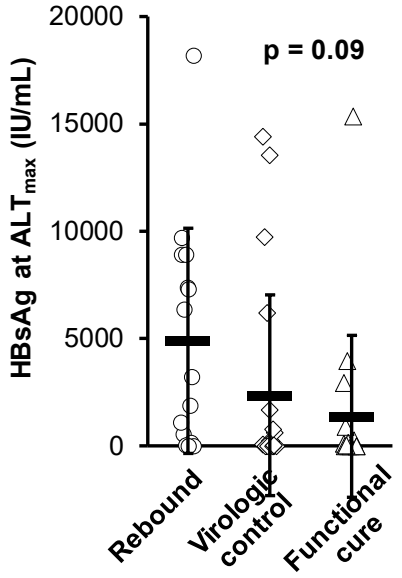
Effect of HBsAg response on transaminase flare activity



No significant difference in transaminase elevations during therapy between different therapeutic outcome groups

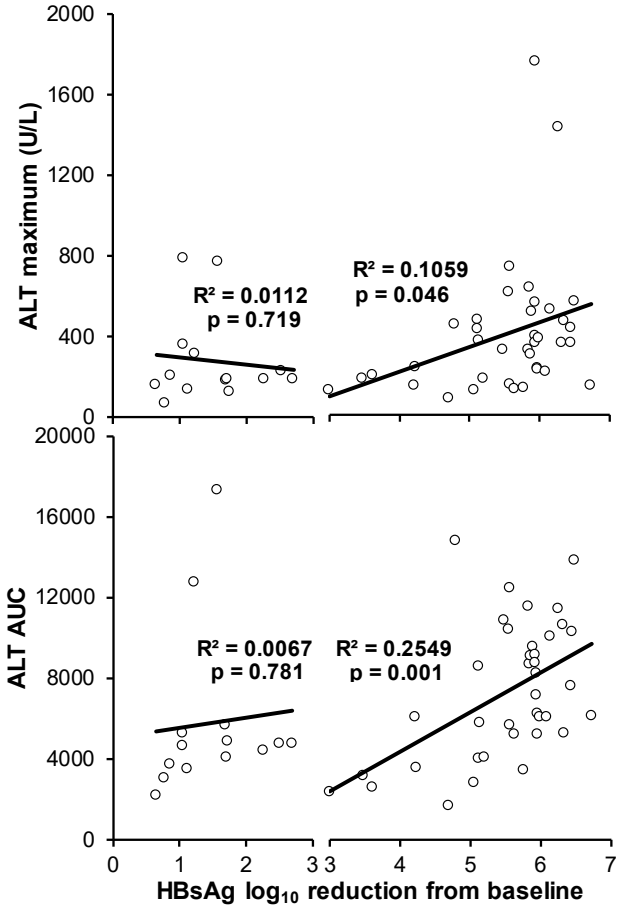


Maximum transaminase elevation not correlated with HBsAg clearance overall



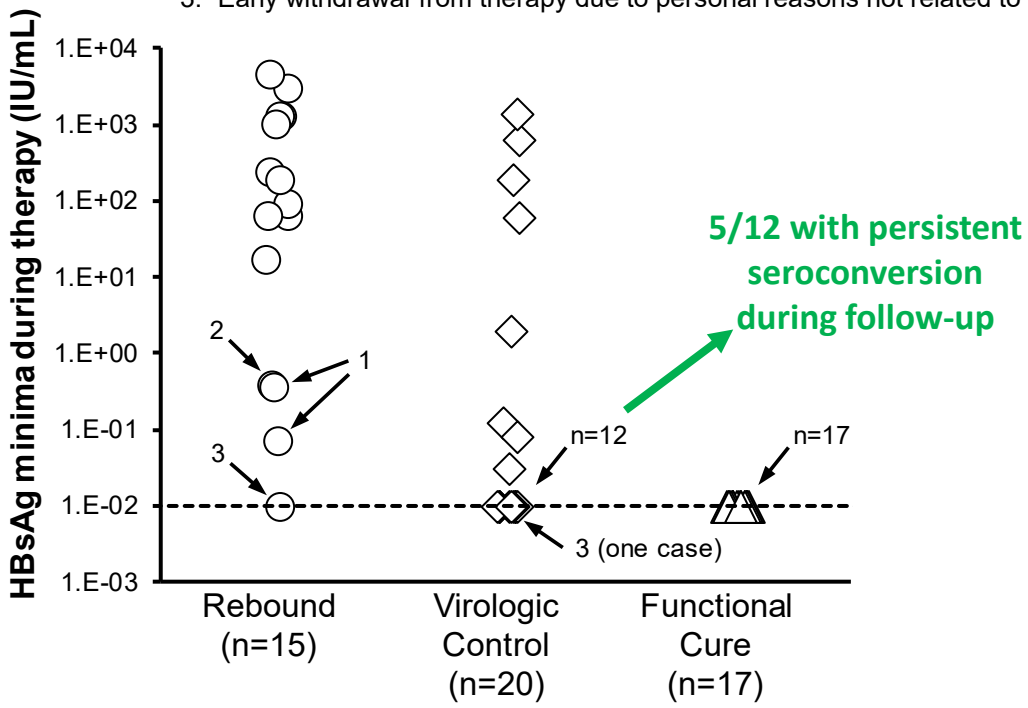
HBsAg clearance better at transaminase maxima in virologic control and functional cure groups

Effect of HBsAg response on transaminase flare activity



Intensity and duration of transaminase elevation is correlated with HBsAg decline > 3 log_{10} from baseline

1. Late decline in HBsAg.
2. Early withdrawal from therapy due to pegIFN related depression.
3. Early withdrawal from therapy due to personal reasons not related to tolerability.



All functional cure participants achieved HBsAg 0.00 IU/mL during therapy

Predicting virologic outcomes

Analysis of HBeAg negative patients completing therapy in the REP 301 and REP 401 studies

Transaminase elevation during HBsAg reduction	Incidence (%) in different therapeutic outcome groups			p-value
	Rebound (n=15)	Virologic control (n=20)	Functional cure (n=17)	
< 1000 IU/mL	73	95	100	0.194
< 100 IU/mL	47	85	100	0.066
< 10 IU/mL	27	80	100	0.001
< 1 IU/mL	20*	70	100	< 0.001

*all withdrew early from therapy or had late HBsAg decline during therapy

All functional cure participants experienced transaminase elevation while HBsAg was < 1IU/mL

Predicting therapeutic outcomes

Milestone during therapy		PPV	NPV	Sensitivity	Specificity
Transaminase elevation during HBsAg clearance	No functional cure (R + VC) vs functional cure				
	< 1 IU/mL	50	100	100	51
	< 10 IU/mL	46	100	100	43
	< 100 IU/mL	41	100	100	31
	< 1000 IU/mL	36	100	100	14
	No clinical benefit (R) vs clinical benefit (VC + FC)				
	< 1 IU/mL	**84**	**80**	**91**	**66**
	< 10 IU/mL	**89**	**73**	**89**	**73**
	< 100 IU/mL	92	53	83	72
	< 1000 IU/mL	97	27	77	80
HBsAg < LLOQ	No functional cure (R + VC) vs functional cure				
		59	100	100	66
	No clinical benefit (R) vs clinical benefit (VC + FC)				
		100	65	78	100
HBsAg seroconversion (> 10 mIU/mL)	No functional cure (R + VC) vs functional cure				
		44	94	94	43
	No clinical benefit (R) vs clinical benefit (VC + FC)				
		86	62	84	67

Summary

Transaminase flares are common during combination therapy with NAPs and pegIFN:

- Independent of baseline characteristics or therapeutic outcome
- Not accompanied by alteration in liver function and are otherwise asymptomatic
- **Cumulative flare activity during therapy is correlated with HBsAg reduction > 3 log_{10} from baseline**

All participants with HBV functional cure experience HBsAg 0.00 IU/mL and transaminase elevation while HBsAg is < 1 IU/mL during therapy – also associated with functional cure of HDV.

Both these milestones appear to be required to achieve functional cure.

The presence of transaminase flares while HBsAg is < 1 or < 10 IU/mL predict clinical benefit after therapy (virologic control or functional cure).

Flare activity during higher HBsAg thresholds (> 10 IU/mL) has relatively poor predictive value

HBsAg specific immune function likely plays an important role in establishing virologic control and functional cure.

A collaborative effort !

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