Supplemental Digital Content (SDC)

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Supplemental Digital Content 1. Appendix. Serum-based assays and histology

Serum-based assays. Research blood samples were collected at each assessment, processed and stored at -70C at each site, and shipped in batches to a central repository for subsequent transfer to central testing laboratories: University of Washington, Seattle, WA, for quantitative HBV DNA and quantitative HBeAg (qHBeAg) (tested every 24 weeks) and quantitative HBsAg (qHBsAg) (tested every 48 weeks), and Abbott Diagnostics, Abbott Park, IL, for quantitative HBV RNA and HBcrAg (tested every 48 weeks).

HBV DNA levels were determined using a real-time PCR assay (COBAS Ampliprep/COBAS TaqMan HBV Test, v2.0; Roche Molecular Diagnostics, Branchburg, NJ) with a lower limit of detection (LLOD) of 10 IU/mL and lower limit of quantification (LLOQ) of 20 IU/mL. Quantitative HBsAg and HBeAg were tested using the Roche Diagnostics Elecsys platform with LLOD of 0.05 IU/mL for HBsAg and LLOD of 0.3 IU/mL for HBeAg[1,2]. Participants with an HBeAg result below the limit of detection were considered to be HBeAg negative. When central laboratory results were missing, local results for HBV DNA and qualitative HBsAg and HBeAg, employing commercially available enzyme immunoassays, were used. When local labs did not dilute HBV DNA samples above upper limit of quantification, values were randomly imputed using the pool of HBV DNA values that exceeded $1.7x10^8$ IU/mL. HBV DNA below the lower limit of quantification or detection were imputed by random numbers from uniform distributions with ranges of 10 to 19 IU/mL and 0 and 9 IU/mL, respectively. Likewise, quantitative HBeAg <0.3 IU/mL was imputed by random numbers from a uniform distribution with a range of 0.00 to 0.29 IU/mL. No participants had quantitative HBsAg values below LLOD throughout follow-up. HBV DNA, HBsAg and HBeAg were log-transformed (log10) to improve the distributions.

HBV RNA was isolated from plasma and amplified as described by Butler et al.[3] using the m2000 system (Abbott Molecular; Department of Infectious Diseases, Abbott Diagnostics, Abbott Park, USA), with a LLOQ of 1.65 log10 U/ml. Levels below LLOQ were randomly imputed using a

uniform distribution with a number between 0.01 and 1.64 log10 U/mL. Non-detected HBV RNA levels were set to 0 log10 U/mL.

HBcrAg serum concentrations were analyzed by chemiluminescence enzyme immunoassay (Lumipulse G® HBcrAg assay by Fujirebio Europe, Gent, Belgium). This measures the antigenic reactivity of 3 proteins: HBeAg, HBV core antigen (HBcAg) and a core-related protein p22cr, all products of the HBV precore/core gene[4]. The assay has a LLOD of 3.0 log10 U/ml and linear measurement range of 3.0-<6.8 log10 U/ml. As recommended by manufacturer, dilution was not performed for samples with concentration >6.8 log10 U/ml. Levels below and above quantification were randomly imputed using a uniform distribution with a number between 0-2.9, and 6.8-10.3 log10 U/mL, respectively. The upper limit for imputation was selected based on a maximum HBcrAg value of 10.34 log U/mL among untreated patients[5]. Neither HBV RNA nor HBcrAg have an international standard unit.

Histology. Liver biopsy was performed in standard percutaneous fashion. Hematoxylin and Eosin (H&E) and Masson trichrome staining was done centrally by University of Pittsburgh Medical Center. The HBRN Pathology Committee centrally scored histological findings blinded to clinical data. Total length of biopsy was recorded. A minimum of three portal tracts was required. Biopsies were evaluated for inflammation (histology activity index; HAI) and fibrosis using Ishak scoring system.

HBcAg and HBsAg immunohistology (IH) was performed with the Roche Ventana BenchMark ULTRA System without antigen retrieval. Simultaneous positive and negative control samples were run in parallel. Biopsies were graded according to the percent of immunoreactive hepatocytes for both antigens: Grade A: no positive hepatocytes, Grade B: <10% positive hepatocytes, and Grade C: ≥10% positive hepatocytes. Grade C included a wide range of values due to the low frequency of values ≥10% (e.g., only 2 participants had ≥50% HBcAg hepatocytes and only 4 had ≥50% HBsAg at either time point). Biopsies with both nuclear and cytoplasmic

HBcAg staining were grouped by predominant pattern (only/predominately nuclear, only/predominately cytoplasmic, neither). For HBsAg, IH staining patterns were also assessed: granular cytoplasmic with continuous regions, granular cytoplasmic with scattered hepatocytes, inclusion-like, and membranous staining (i.e., yes/no to each).

References

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4. Kimura T, Rokuhara A, Sakamoto Y, et al. Sensitive enzyme immunoassay for hepatitis B virus core-related antigens and their correlation to virus load. *J Clin Microbiol.* 2002;40(2):439-445.
5. Maasoumy B, Wiegand SB, Jaroszewicz J, et al. Hepatitis B core-related antigen (HBcrAg) levels in the natural history of hepatitis B virus infection in a large European cohort predominantly infected with genotypes A and D. *Clin Microbiol Infect.* 2015;21(6):606.e601-610.

Supplemental Digital Content 2, Table 1. Categories of serum markers of HBV by time point, stratified by HBeAg status throughout follow-up.

	Time points				
	Entry	**Week 48**	**Week 96**	**Week 144**	**Week 192[a]**
			n (%)		
HBeAg positive	n=46	n=39	n=32	n=30	n=29
HBV DNA					
BLD (<10 IU/mL)	8 (17.4)	11 (28.2)	6 (18.8)	12 (40.0)	10 (34.5)
10-<1000 IU/mL	26 (56.5)	18 (46.2)	20 (62.5)	15 (50.0)	15 (51.7)
≥1000 IU/mL	12 (26.1)	10 (25.6)	6 (18.8)	3 (10.0)	4 (13.8)
HBV RNA					
Quantifiable	46 (100.0)	39 (100.0)	32 (100.0)	30 (100.0)	29 (100.0)
HBcrAg					
Quantifiable	24 (52.2)	23 (59.0)	21 (65.6)	23 (76.7)	22 (75.9)
>ULQ (≥6.8 log10 U/mL)	22 (47.8)	16 (41.0)	11 (34.4)	7 (23.3)	7 (24.1)
HBeAg positive to negative	n=12	n=9	n=11	n=6	n=10
HBV DNA					
BLD (<10 IU/mL)	5 (41.7)	3 (33.3)	6 (54.6)	2 (33.3)	6 (60.0)
10-<1000 IU/mL	4 (33.3)	5 (55.6)	4 (36.4)	4 (66.7)	4 (40.0)
≥1000 IU/mL	3 (25.0)	1 (11.1)	1 (9.1)	0 (0.0)	0 (0.0)
HBV RNA					
Non-detected	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (20.0)
<LLQ (<1.65 log10 U/mL)	1 (8.3)	1 (11.1)	1 (9.1)	1 (16.7)	0 (0.0)
Quantifiable	11 (91.7)	8 (88.9)	9 (81.8)	5 (83.3)	8 (80.0)
HBcrAg					
Quantifiable	10 (83.3)	9 (100.0)	10 (90.9)	5 (83.3)	10 (100.0)
>ULQ (≥6.8 log10 U/mL)	2 (16.7)	0 (0.0)	1 (9.1)	1 (16.7)	0 (0.0)
HBeAg negative	n=37	n=33	n=30	n=27	n=20
HBV DNA					
BLD (<10 IU/mL)	21 (56.8)	20 (60.6)	22 (73.3)	17 (63.0)	17 (85.0)
10-<1000 IU/mL	16 (43.2)	13 (39.4)	8 (26.7)	10 (37.0)	3 (15.0)
≥1000 IU/mL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HBV RNA					
Non-detected	9 (24.3)	5 (15.2)	8 (26.7)	7 (25.9)	3 (15.0)
<LLQ (<1.65 log10 U/mL)	10 (27.0)	9 (27.3)	8 (26.7)	7 (25.9)	6 (30.0)
Quantifiable	18 (48.7)	19 (57.6)	14 (46.7)	13 (48.2)	11 (55.0)
HBcrAg					
<LLQ (<3.0 log10 U/mL)	15 (40.5)	13 (39.4)	13 (43.3)	9 (33.3)	8 (40.0)
Quantifiable	22 (59.5)	20 (60.6)	17 (56.7)	18 (66.7)	12 (60.0)

Acronyms: DNA, Deoxyribonucleic acid; HBcrAg, Hepatitis B core-related antigen; HBeAg, Hepatitis B e-antigen; RNA, Ribonucleic acid.

[a]If laboratory data at week 192 was missing, lab markers from week 168 was at that time point.

Supplemental Digital Content 3, Table 2. Observed serum markers of HBV by time point, stratified by HBeAg status throughout follow-up

	Time Points				
	Entry	**Week 48**	**Week 96**	**Week 144**	**Week 192**
	Median (25th%, 75th%)				
HBeAg positive	n=46	n=39	n=32	n=30	n=29[b]
HBV DNA (log10 IU/mL)	1.42 (1.11, 3.44)	1.36 (0.78, 3.14)	1.28 (1.10, 2.15)	1.18 (0.85, 1.53)	1.11 (0.78, 1.71)
HBV RNA (log10 U/mL)	5.46 (4.28, 6.78)	5.46 (4.20, 6.72)	5.36 (4.15, 6.64)	4.63 (3.81, 5.67)	4.45 (3.35, 5.53)
HBcrAg (log10 U/mL)	6.65 (5.80, 8.60)	6.60 (5.80, 8.10)	6.25 (5.80, 8.40)	5.95 (5.40, 6.70)	6.00 (5.40, 6.40)
HBsAg (log10 IU/mL)	3.47 (3.11, 4.35)	3.43 (3.08, 4.38)	3.27 (2.97, 4.32)	3.21 (2.98, 3.57)	3.30 (2.97, 3.55)
HBeAg (log10 IU/mL)	1.35 (0.30, 2.44)	1.20 (0.23, 2.54)	1.12 (0.26, 2.12)	0.75 (0.08, 1.42)	0.63 (0.11, 1.29)
HBeAg positive to negative	n=12	n=9	n=11	n=6	n=10[b]
HBV DNA (log10 IU/mL)	1.22 (0.78, 2.60)	1.08 (0.78, 2.21)	0.95 (0.60, 1.62)	1.11 (0.70, 1.20)	0.87 (0.30, 1.11)
HBV RNA (log10 U/mL)	3.79 (3.04, 5.29)	3.31 (2.62, 4.76)	2.96 (2.01, 5.33)	2.73 (1.94, 4.27)	2.68 (1.73, 3.78)
HBcrAg (log10 U/mL)	5.65 (5.20, 6.25)	5.40 (5.10, 5.70)	5.20 (5.10, 5.80)	4.90 (4.50, 5.90)	4.65 (4.40, 5.20)
HBsAg (log10 IU/mL)	3.15 (2.89, 3.40)	2.94 (2.91, 3.38)	2.83 (2.63, 3.29)	2.86 (2.71, 3.76)	2.69 (2.60, 3.29)
HBeAg (log10 IU/mL)[a]	0.20 (-0.19, 0.73)	-0.22 (-0.30, 0.15)	-0.30 (-0.60, 0.20)	-0.77 (-0.92, -0.40)	-0.75 (-1.00, -0.62)
HBeAg negative	n=37	n=33	n=30	n=27	n=20[b]
HBV DNA (log10 IU/mL)	0.95 (0.85, 1.18)	0.95 (0.70, 1.08)	0.77 (0.70, 1.08)	0.90 (0.48, 1.15)	0.65 (0.30, 0.93)
HBV RNA (log10 U/mL)	1.62 (0.29, 2.20)	1.84 (0.25, 2.38)	1.40 (0.00, 2.47)	1.25 (0.00, 2.31)	1.84 (0.82, 2.50)
HBcrAg (log10 U/mL)	3.30 (1.90, 4.00)	3.30 (2.10, 4.10)	3.30 (1.90, 4.10)	3.40 (2.30, 4.20)	3.20 (1.95, 4.10)
HBsAg (log10 IU/mL)	2.59 (1.90, 3.29)	2.53 (1.80, 3.26)	2.37 (1.66, 2.95)	2.31 (1.59, 3.03)	2.07 (1.64, 2.39)

Acronyms: DNA, Deoxyribonucleic acid; HBcrAg, Hepatitis B core-related antigen; HBeAg, Hepatitis B e-antigen; HBsAg, Hepatitis B surface antigen; RNA, Ribonucleic acid.

[a]Quantitative HBeAg <0.3 IU/mL was imputed by random numbers from a uniform distribution with a range of 0.00 to 0.29 IU/mL

[b]HBsAg was available in 26 HBeAg positive, 7 HBeAg positive to negative and 15 HBeAg negative participants at week 192.

Supplemental Digital Content 4, Table 3. Modeled serum markers of HBV by time point, stratified by HBeAg status throughout follow-up

	Time point					
	Entry	Week 48	Week 96	Week 144	Week 192[b]	*P*[c]
	Mean (95% CI)					
HBeAg positive (n=46)						
HBV DNA (log10 IU/mL)	2.64 (2.25, 3.04)	2.39 (2.12, 2.68)	2.15 (1.93, 2.38)	1.90 (1.64, 2.18)	1.66 (1.28, 2.06)	0.002
HBV RNA (log10 U/mL)	5.59 (5.34, 5.78)	5.44 (5.27, 5.57)	5.29 (5.14, 5.39)	5.14 (4.94, 5.29)	4.99 (4.73, 5.24)	<.001
HBcrAg (log10 U/mL)	7.19 (6.91, 7.49)	7.01 (6.82, 7.22)	6.83 (6.66, 6.97)	6.65 (6.43, 6.85)	6.47 (6.15, 6.78)	<.001
HBsAg (log10 IU/mL)	3.77 (3.64, 3.88)	3.67 (3.58, 3.75)	3.57 (3.49, 3.64)	3.48 (3.36, 3.56)	3.38 (3.23, 3.51)	<.001
HBeAg (log10 IU/mL)	1.43 (1.26, 1.54)	1.31 (1.18, 1.39)	1.19 (1.08, 1.27)	1.07 (0.94, 1.17)	0.95 (0.79, 1.09)	<.001
HBeAg positive to negative (n=12)						
HBV DNA (log10 IU/mL)	1.78 (1.27, 2.33)	1.51 (1.18, 1.87)	1.24 (1.01, 1.48)	0.97 (0.70, 1.21)	0.70 (0.27, 1.06)	0.004
HBV RNA (log10 U/mL)	3.99 (3.31, 4.77)	3.67 (3.24, 4.20)	3.36 (3.02, 3.71)	3.04 (2.53, 3.39)	2.72 (1.95, 3.31)	0.01
HBcrAg (log10 U/mL)	5.94 (5.41, 6.60)	5.70 (5.37, 6.17)	5.47 (5.18, 5.77)	5.24 (4.84, 5.60)	5.01 (4.43, 5.59)	0.04
HBsAg (log10 IU/mL)	3.17 (3.02, 3.35)	3.07 (2.96, 3.18)	2.97 (2.86, 3.09)	2.87 (2.71, 3.04)	2.78 (2.55, 3.01)	0.01
HBeAg (log10 IU/mL)[a]	0.38 (0.07, 0.68)	0.11 (-0.10, 0.34)	-0.16 (-0.34, 0.01)	-0.43 (-0.66, -0.21)	-0.69 (-1.01, -0.35)	<.001
HBeAg negative (n=37)						
HBV DNA (log10 IU/mL)	0.93 (0.81, 1.04)	0.87 (0.79, 0.94)	0.81 (0.74, 0.89)	0.75 (0.66, 0.88)	0.69 (0.57, 0.88)	0.03
HBV RNA (log10 U/mL)	1.60 (1.45, 1.78)	1.58 (1.46, 1.71)	1.55 (1.45, 1.67)	1.53 (1.40, 1.67)	1.51 (1.33, 1.71)	0.49
HBcrAg (log10 U/mL)	3.04 (2.86, 3.26)	3.02 (2.90, 3.19)	3.00 (2.87, 3.15)	2.98 (2.82, 3.17)	2.96 (2.75, 3.22)	0.63
HBsAg (log10 IU/mL)	2.49 (2.40, 2.58)	2.45 (2.36, 2.53)	2.40 (2.32, 2.49)	2.36 (2.27, 2.45)	2.32 (2.22, 2.41)	<.001

Acronyms: DNA, Deoxyribonucleic acid; HBcrAg, Hepatitis B core-related antigen; HBeAg, Hepatitis B e-antigen; HBsAg, Hepatitis B surface antigen; RNA, Ribonucleic acid.

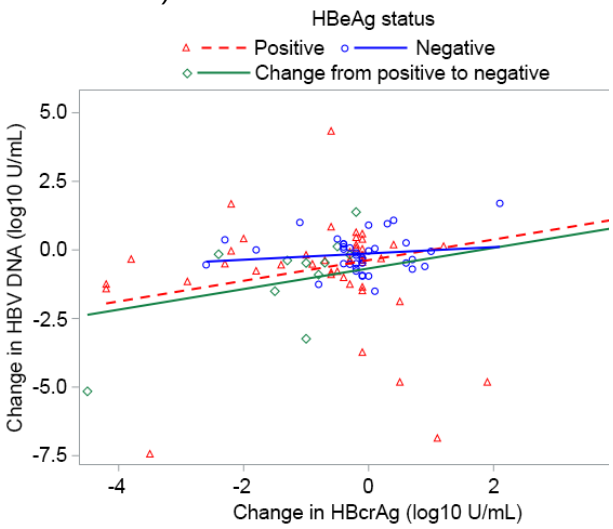
[a]Quantitative HBeAg <0.3 IU/mL was imputed by random numbers from a uniform distribution with a range of 0.00 to 0.29 IU/mL

[b]If laboratory data at week 192 was missing, HBV markers from week 168 was at that time point.

[c]Changes in serum-based markers over time were tested with generalized linear mixed-effects models with each outcome as a repeated measure, time (i.e., days since baseline) as a continuous fixed effect, and random intercept.

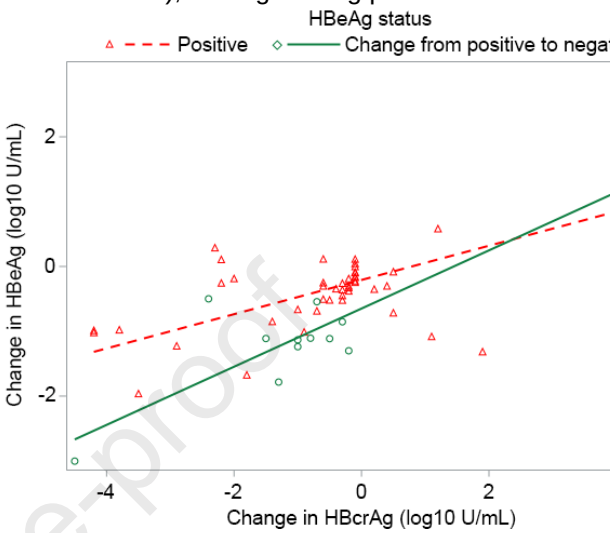
Supplemental Digital Content 5, Figure 1. Correlations between change *(last follow-up minus baseline value*) in HBcrAg with change in HBV DNA, qHBeAg and qHBsAg, respectively, across follow-up, stratified by HBeAg status throughout follow-up

A. HBcrAg (log10 U/mL) and DNA (log10 U/mL)



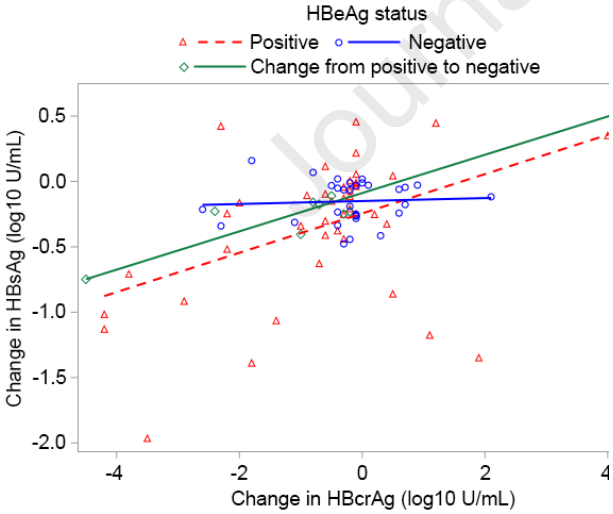
HBeAg positive: n=46, ρ=.09, p=.55
HBeAg positive to negative: n=12, ρ=.45, p=.14
HBeAg negative: n=37, ρ=-.05, p=.79

B. HBcrAg (log10 U/mL) and qHBeAg (log10 IU/mL), among HBeAg positive



HBeAg positive: n=46, ρ=0.43, p=.003
HBeAg positive to negative: n=12, ρ=.36, p=.25

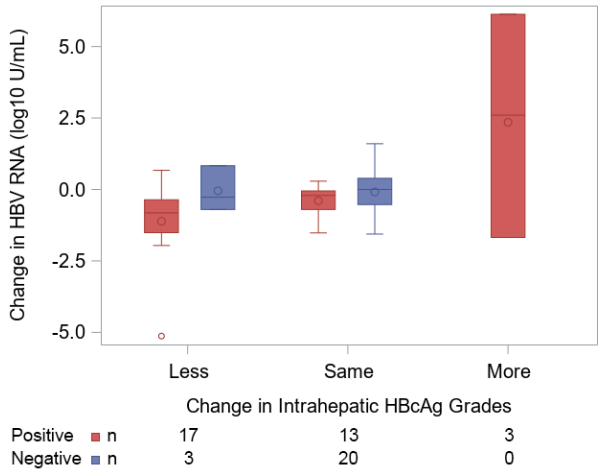
C. HBcrAg (log10 U/mL) and qHBsAg (log10 IU/mL)



HBeAg positive: n=43, ρ=.41, p=.007
HBeAg positive to negative: n=9, ρ=.53, p=.14
HBeAg negative: n=31, ρ=.06, p=0.77

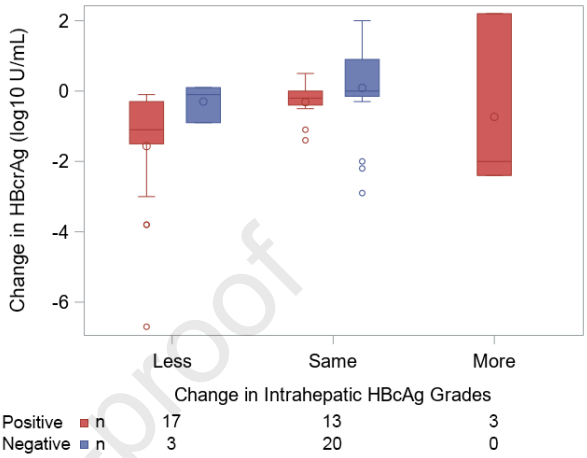
Supplemental Digital Content 6, Figure 2. Change in serum-based HBV RNA and HBcrAg, respectively, by change in HBcAg and HBsAg intrahepatic staining grades, stratified by baseline HBeAg status.

A. HBV RNA by intrahepatic HBcAg staining grade



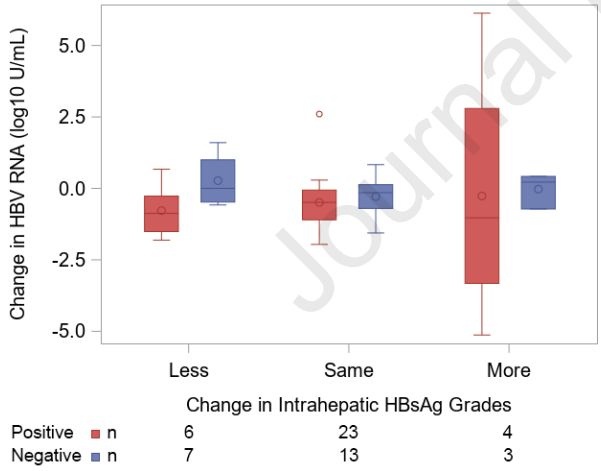
HBeAg positive: p=0.047; HBeAg negative: p=0.93

B. HBcrAg by intrahepatic HBcAg staining grade



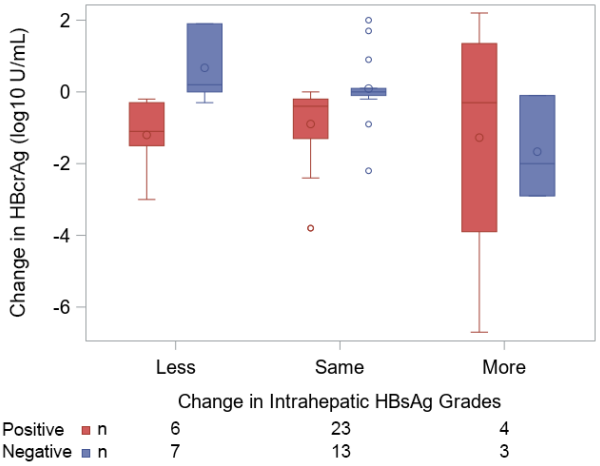
HBeAg positive: p=0.04; HBeAg negative: p=0.49

C. RNA by intrahepatic HBsAg staining grade



HBeAg positive: p=0.66; HBeAg negative: p=0.55

D. HBcrAg by intrahepatic HBsAg staining grade



HBeAg positive: p=0.53; HBeAg negative: p=0.045

Supplemental Digital Content 7, Table 4. Associations between serum markers of HBV and change in intrahepatic staining (yes to no positive for HBcAg hepatocytes), histological activity index (HAI) and change in fibrosis score, respectively, between biopsies.

	No longer positive for HBcAg hepatocytes[a] (N=35)		Change in HAI (N=56)		Change in fibrosis score (N=55)	
	OR (95%CI)	**P-value**	***Beta* (95% CI)**	**P-value**	***Beta* (95% CI)**	**P-value**
Baseline status						
HBV RNA	[a]			0.87		0.64
Non-detected	-		ref		Ref	
<LLQ (<1.65 log10 U/mL)	-		0.60 (-1.80, 2.99)		-0.30 (-1.82, 1.21)	
Quantifiable	-		0.19 (-1.61, 1.98)		0.21 (-0.93, 1.35)	
HBV RNA (log10 U/mL)	0.74 (0.49, 1.12)	0.15	-0.01 (-0.25, 0.23)	0.94	0.02 (-0.13, 0.18)	0.77
HBcrAg		0.56		0.98		0.76
<LLQ (<3.0 log10 U/mL)	[b]		Ref		Ref	
Quantifiable	Ref		-0.11 (-1.72, 1.50)		-0.50 (-1.52, 0.51)	
>ULQ (≥6.8 log10 U/mL)	0.65 (0.15, 2.79)		0.01 (-1.88, 1.89)		-0.14 (-1.32, 1.05)	
HBcrAg (log10 U/mL)	0.88 (0.60, 1.29)	0.51	-0.04 (-0.27, 0.19)	0.72	-0.03 (-0.17, 0.12)	0.69
HBV DNA (log10 IU/mL)	0.81 (0.54, 1.19)	0.28	[c]		[c]	
HBsAg (log10 IU/mL)	0.40 (0.15, 1.08)	0.07	[c]		[c]	
HBeAg (log10 IU/mL)	0.50 (0.25, 1.01)	0.056	[c]		[c]	
HBeAg status (ref=positive)		0.16				
Negative	5.45 (0.51, 58.88)		[c]		[c]	
Change from baseline						
HBV RNA (log10 U/mL)	0.71 (0.40, 1.26)	0.24	0.14 (-0.23, 0.51)	0.46	0.05 (-0.19, 0.29)	0.67
HBcrAg (log10 U/mL)	0.76 (0.46, 1.23)	0.26	0.16 (-0.23, 0.55)	0.41	0.03 (-0.21, 0.28)	0.79
HBV DNA (log10 IU/mL)	0.95 (0.70, 1.29)	0.74	0.10 (-0.19, 0.40)	0.48	0.17 (-0.01, 0.36)	0.07
HBsAg (log10 IU/mL)	0.64 (0.23, 1.81)	0.40	-0.14 (-0.94, 0.66)	0.73	-0.01 (-0.52, 0.5)	0.96
HBeAg (log10 IU/mL)	0.33 (0.10, 1.11)	0.07	0.09 (-0.56, 0.74)	0.77	0.15 (-0.26, 0.57)	0.46
HBeAg status (ref=always positive)		0.004		0.32		0.78
Positive to negative	33.25 (3.15, 350.90)		-0.79 (-2.36, 0.77)		-0.19 (-1.21, 0.82)	
Always negative	14.25 (1.16, 174.80)		-0.84 (-2.00, 0.33)		0.16 (-0.60, 0.92)	

[a]34 of 35 people who was positive for HBcAg hepatocytes at baseline had quantifiable HBV RNA. See next variable.
[b]No one who was positive for HBcAg hepatocytes at baseline had HBcrAg <LLQ (3.0 log10 U/mL).

[c]Associations between baseline HBV DNA, HBsAg, HBeAg and HBeAg status with change in HAI and change in fibrosis score, respectively, were previously reported in Sterling RK, King WC, Khalili M, et al., A Prospective Study Evaluating Changes in Histology, Clinical and Virologic Outcomes in HBV-HIV Co-infected Adults in North America. *Hepatology*. 2021 Mar 20. doi: 10.1002/hep.31823. Online ahead of print. PMID: 33743541