How to treat HCV-HBV co-infection?

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Conflict od interest

Advisory and grants from:
AbbVie, Gilead, MSD, Roche

Categories of virus–virus interaction

I. Direct interactions
- a. Helper-dependent viruses
- b. Pseudotype viruses
- c. Superinfection exclusion
- d. Genomic recombination
- e. Embedded viruses
- f. Heterologous transactivation

II. Environmental interactions
- a. Indirect transactivation of genes
- b. Breakdown of physical barriers
- c. Altered receptor expression
- d. Heterologous activation of pro-drugs
- e. Modification of the interferon-induced antiviral state

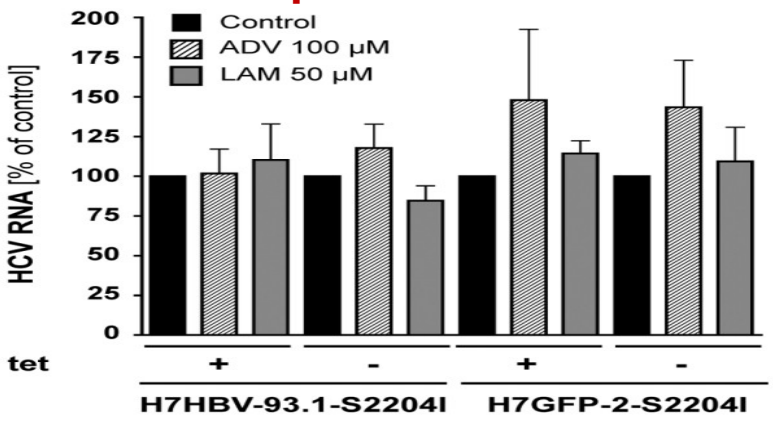
III. Immune effects
- a. Altered immune cell activation
- b. Induction of autoimmunity
- c. Antibody-dependent enhancement of infection
- d. Heterologous immunity

DaPalma T et al. Virus Res 2010;149:1-9

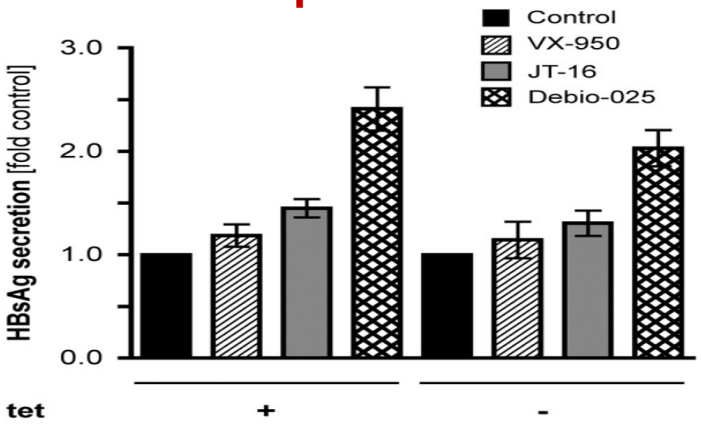
No direct viral interference in HBV/HCV coinfection

In vitro model of Huh-7 cell lines replicating HBV and HCV

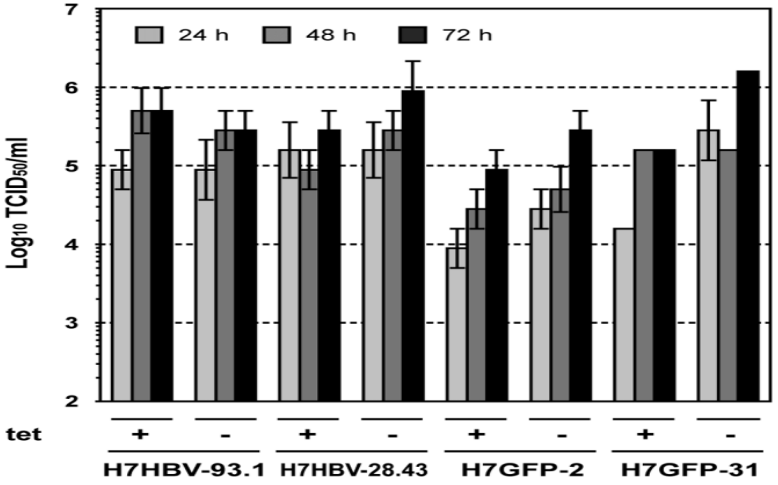
HBV inhibition does not affect HCV replication



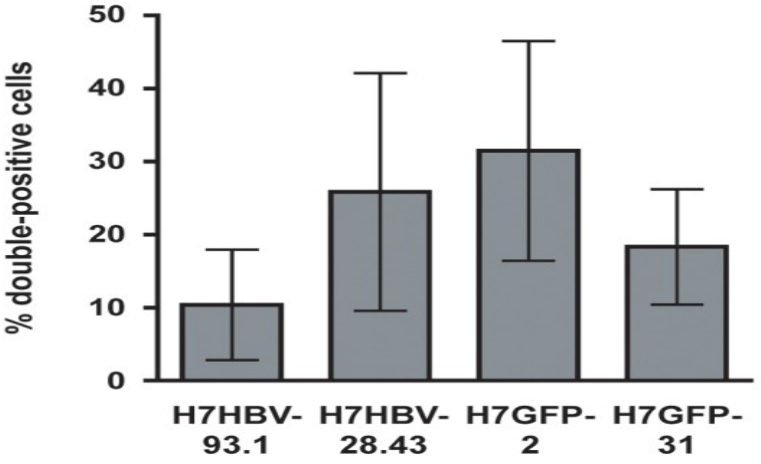
HCV inhibition does not affect HBV replication



HBV and HCV may replicate within the same cell



Possible superinfection of HBV-inducible cell lines with HCV



Bellecave P et al. Hepatology 2009; 50: 46-55

Practical issues related to treatment of HBV/HCV coinfected patients

1. Risk of drug to drug interactions between regimens provided to cure HCV and suppress HBV infection.
2. Possible reactivation of HBV during or shortly after therapy with direct acting antivirals (DAA) due to HCV infection.

DDI between HBV and HCV regimens

Tenofovir blood concentration can be increased when administered with sofosbuvir containing regimens, so patients on tenofovir disoproxil, particularly those with kidney diseases should be monitored and if possible an alternative DAA regimen should be selected.

https://www.hep-druginteractions.org/checker

HBV reactivation associated with DAA – FDA report

Case Number (Reference)	HCV Genotype	HBV Genotype	HBsAg	HBsAb	HBcAb	HBeAg	HBeAb	HBV DNA Level, *copies/mL**	DAA	Country of Report
1	1a	NR	NR	NR	NR	Negative	Positive	2700 (elevated)	Viekira Pak (AbbVie)/RBV	United States
2 (42)	1b	NR	Positive	NR	Positive	Negative	Positive	2.5 $\log_{10}$ (elevated)	DCV/ASV	Japan
3	NR	NR	NR	NR	NR	Negative	Positive	Undetectable	DCV/ASV	Japan
4	1b	NR	Positive	NR	NR	Negative	Positive	3.9 $\log_{10}$ (elevated)	DCV/ASV	Japan
5 (29)	1a	NR	NR	NR	NR	Negative	Positive	2300 (elevated)	SIM/SOF	United States
6 (29)	1a	NR	Negative	Negative	Positive	NR	NR	Undetectable	SIM/SOF	United States
7 (26)	1	NR	Negative	Negative	Positive	NR	NR	Undetectable	SIM/SOF/RBV	United States
8	3a	NR	Positive	NR	NR	NR	NR	244 (elevated)	SOF/RBV	Portugal
9 (38)	4	D	Negative	Negative	Positive	Negative	Positive	Undetectable	LDV/SOF	France
10 (28)	NR	NR	Positive	NR	NR	NR	NR	Undetectable	LDV/SOF	United States
11	NR	NR	NR	NR	Positive	NR	NR	Undetectable	LDV/SOF	Japan
12 (43)	1	B	Positive	NR	NR	Negative	Positive	Undetectable	SIM/PEG/RBV	Japan
13	1	A	Positive	NR	NR	Negative	Positive	Undetectable	SOF/RBV	Japan
14	NR	B	Positive	NR	NR	NR	NR	1.3 $\log_{10}$ (elevated)	LDV/SOF	Japan
15	1b	B	Positive	NR	NR	Negative	Positive	2.7 $\log_{10}$ (elevated)	DCV/ASV	Japan
16	NR	C	Positive	NR	NR	NR	NR	Undetectable	LDV/SOF	Japan
17	1a	NR	Positive	NR	Positive	Negative	Negative	Undetectable	DCV/SOF/RBV	Australia
18	NR	NR	NR	NR	NR	Negative	Positive	3.6 $\log_{10}$ (elevated)	LDV/SOF/RBV	Japan
19	1b	NR	Positive	NR	NR	Negative	Positive	<2.1 $\log_{10}$†	DCV/ASV	Japan
20	1b	NR	Positive	NR	NR	Negative	Positive	Undetectable	DCV/ASV	Japan
21	1	NR	NR	NR	NR	Negative	Negative	Undetectable	DCV/ASV	Japan
22	1	NR	NR	NR	NR	NR	NR	<2.1 $\log_{10}$†	DCV/ASV	Japan
23	NR	NR	NR	NR	NR	NR	NR	Undetectable	DCV/ASV	Japan
24	NR	C	NR	NR	NR	Negative	NR	3.3 $\log_{10}$ (elevated)	DCV/ASV	Japan
25	NR	NR	NR	NR	NR	NR	NR	Undetectable	DCV/ASV	Japan
26	NR	B	NR	NR	NR	NR	NR	<2.1 $\log_{10}$†	LDV/SOF	Japan
27	NR	NR	NR	NR	NR	NR	NR	Undetectable	LDV/SOF	Japan
28	NR	NR	Negative	NR	NR	NR	NR	NR	LDV/SOF/RBV	France
29 (44)	1b	NR	Positive	NR	NR	NR	Positive	Undetectable	LDV/SOF	China

ASV = asunaprevir; DAA = direct-acting antiviral agent; DCV = daclatasvir; HBcAb = hepatitis B core antibody; HBeAb = hepatitis B e antibody; HBeAg = hepatitis B e antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LDV = ledipasvir; NR = not reported; PEG = pegylated interferon; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir.

* Values interpreted as undetectable only if specifically stated as such in the U.S. Food and Drug Administration Adverse Event Reporting System report. Values expressed by a numeral, provided without units, and/or not specifically stated as undetectable were interpreted as elevated/detectable.

† Values preceded by "<" were regarded as uninterpretable if not specifically stated as undetectable.

Bersoff-Matcha S et al. Ann Intern Med. 2017;166:792-798

DAA and PegIFN cause similar risk of HBV reactivation

	N available and Rate per 1000 person-years	
	N available (Number of events/number available for analysis)	HBV reactivation rate
DAA	9/377 (2,4%)	30.04 (10.41, −49.67)
PEG/RBV	37/209 (18%)	25.42 (17.23, −33.62)
P-value. DAA vs PEG/RBV	—	0.8

Butt AA et al. Aliment Pharmacol Ther. 2018;47:412–420

HBV reactivation in 111 HCV coinfected, HBsAg-positive patients treated with LDV/SOF

HBV DNA reactivation through treatment and post-treatment week 12

Patients, n	Baseline HBV DNA <LLOQ n = 37			Baseline HBV DNA ≥LLOQ n = 74			Overall n = 111
	During treatment	After treatment[a]	Total	During treatment	After treatment[a]	Total	Total
≥LLOQ any time point	21 (57)	10 (27)	31 (84)	na	na	na	31 (28)
plus ALT >2 × ULN	0	0	0	na	na	na	0
HBV DNA increase >1 log_{10} to <2 log_{10} IU/mL	4 (11)	7 (19)	11 (30)	16 (22)	10 (14)	26 (35)	37 (33)
plus ALT >2 × ULN	0	0	0	1 (1)	0	1 (1)	1 (<1)
HBV DNA increase > 2 log_{10} IU/mL	5 (14)	6 (16)	11 (30)	7 (9)	6 (8)	13 (18)	24 (22)
plus ALT >2 × ULN	0	0	0	1 (1)	3 (4)	4 (5)	4 (4)

5 patients with concomitant HBV DNA elevation and ALT>2 ULN through post-treatment week 12

Visit	Patient 1 Female, 60 years old, with cirrhosis		Patient 2 Male, 61 years old, no cirrhosis		Patient 3 Male, 45 years old, no cirrhosis		Patient 4 Female, 60 years old, no cirrhosis		Patient 5 Male, 47 years old, no cirrhosis	
	ALT U/L	HBV DNA IU/mL	ALT U/L	HBV DNA IU/mL	ALT U/L	HBV DNA IU/mL	ALT U/L	HBV DNA IU/mL	ALT U/L	HBV DNA IU/mL
BL	200	35	228	191	112	453	40	824	167	286,000
Week 1	88	26	104	235	90	300	22	1060	76	310,000
Week 2	47	84	52	338	87	349	19	1540	75	309,000
Week 4	41	406	102	6400	111	808	19	15,900	83	217,000
Week 8 NUC	71	6290	74	54,900	124	6140	59	113,000	52	134,000
Week 12	91	<20	47	27,600	109	2240	22	1400	43	134,000
PT week 4	76	<20	NUC 115	882,000	118	3380	16	6120	47	61,000
PT week 12	45	<20	32	140	92	2780	87	1,300,000	61	2,150,000
Retest	-	-	-	-	-	-	-	-	212	99,200,000
Retest	-	-	-	-	-	-	-	-	677	38,200,000
PT Week 24	38	<20	23	<20	152	2790	47	1,130,000	576	9,350,000
Retest	-	-	-	-	-	-	-	-	300	7,160,000
Retest	-	-	26	-	-	-	-	-	131	11,700,000
PT week 36	26	<20	37	<20	162	207	44	1,510,000	NUC 164	53,700,000
PT week 48	29	<20	28	<20	132	4490	53	2,520,000	34	273

Liu CJ, et al.. Gastroenterology 2018;154:989–997.

EASL Recommendations on Treatment of Hepatitis C 2018

Journal of Hepatology 2018; 69: 461–511

There is a potential risk of HBV reactivation during or after HCV clearance, but the risk is unpredictable.

Patients commencing DAA-based treatment for hepatitis C should be tested for HBs antigen, anti-HBc antibodies and anti-HBs antibodies.

- Patients with HBV-HCV coinfection should be treated with the same anti-HCV regimens, following the same rules as HCV monoinfected patients (B1).
- Patients coinfected with HCV and HBV fulfilling the standard criteria for HBV treatment should receive nucleoside/ nucleotide analogue treatment according to the EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection (A1).
- Patients who are HBs antigen-positive should receive nucleoside/nucleotide analogue prophylaxis at least until week 12 post anti-HCV therapy and be monitored monthly if HBV treatment is stopped (B1).
- In patients who are HBs antigen-negative but anti-HBc antibody-positive, serum ALT levels should be monitored monthly, HBs antigen and HBV DNA should be tested if ALT levels do not normalise or rise during or after anti-HCV therapy, and nucleoside/nucleotide analogue therapy should be initiated if HBs antigen and/or HBV DNA are present (B1).

Do we really need to follow all HBsAg-negative but anti-HBc positive patients?

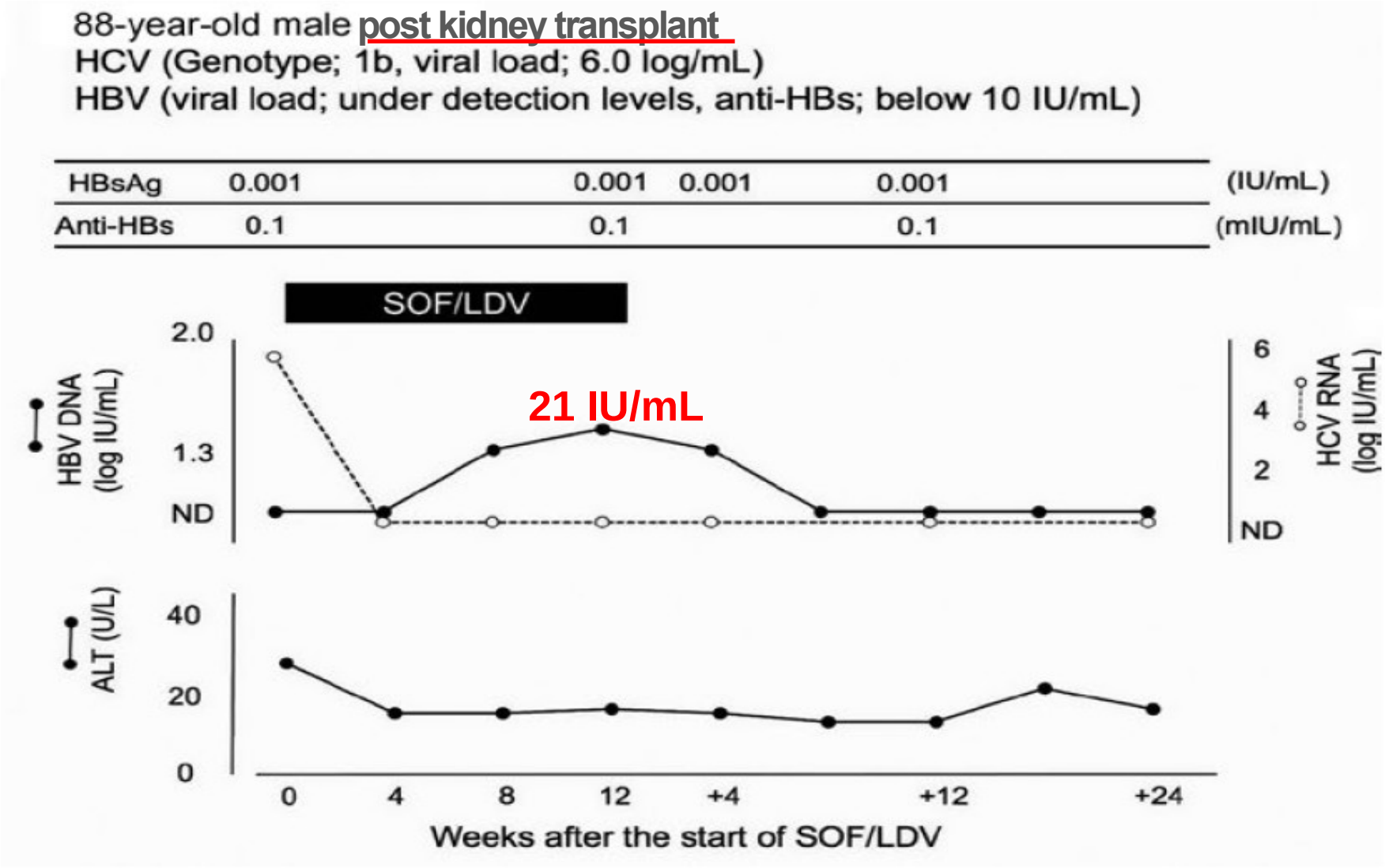
Risk of HBV reactivation on DAA in HBsAg-/anti-HBc+

Studies carried-out in immunocompetent, HCV infected with isolated anti-HBc positivity before start of DAA th

	anti-HBc positive
Yanny BT et al, 2018	127
Sulkowski MS et al, 2016	103
Wang C et al, 2017	124
Loggi E et al, 2017	42
Mucke VT et al, 2017	263
Liu et al, 2016	46
Yeh ML et al, 2017	57
Jaroszewicz J et al, 2019	742 **1504**

Case of HBV reactivation in HBsAg-/ant-HBc+

During DAA treatment in 88 years old patient after kidney transplantation

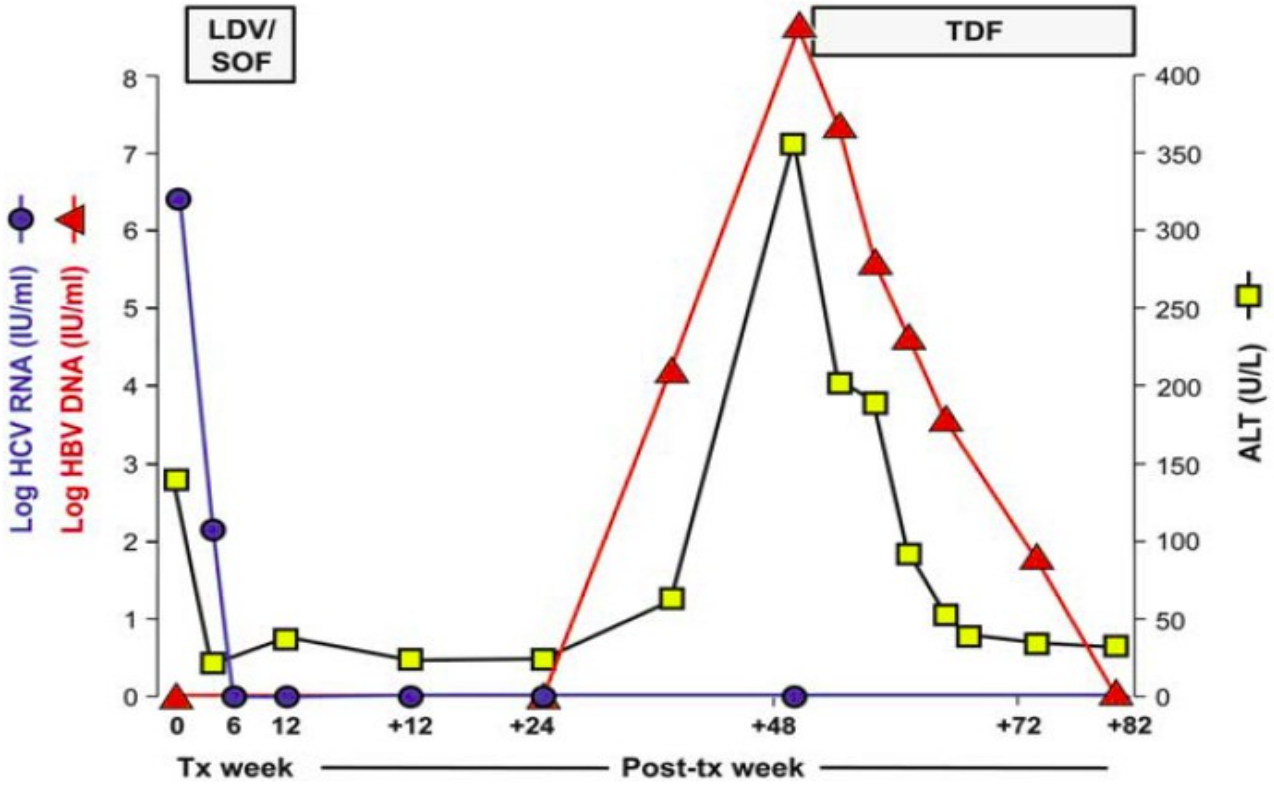


Tamari A et al. J Viral Hepatitis 2017

Case of HBV reactivation in HBsAg-/ant-HBc+

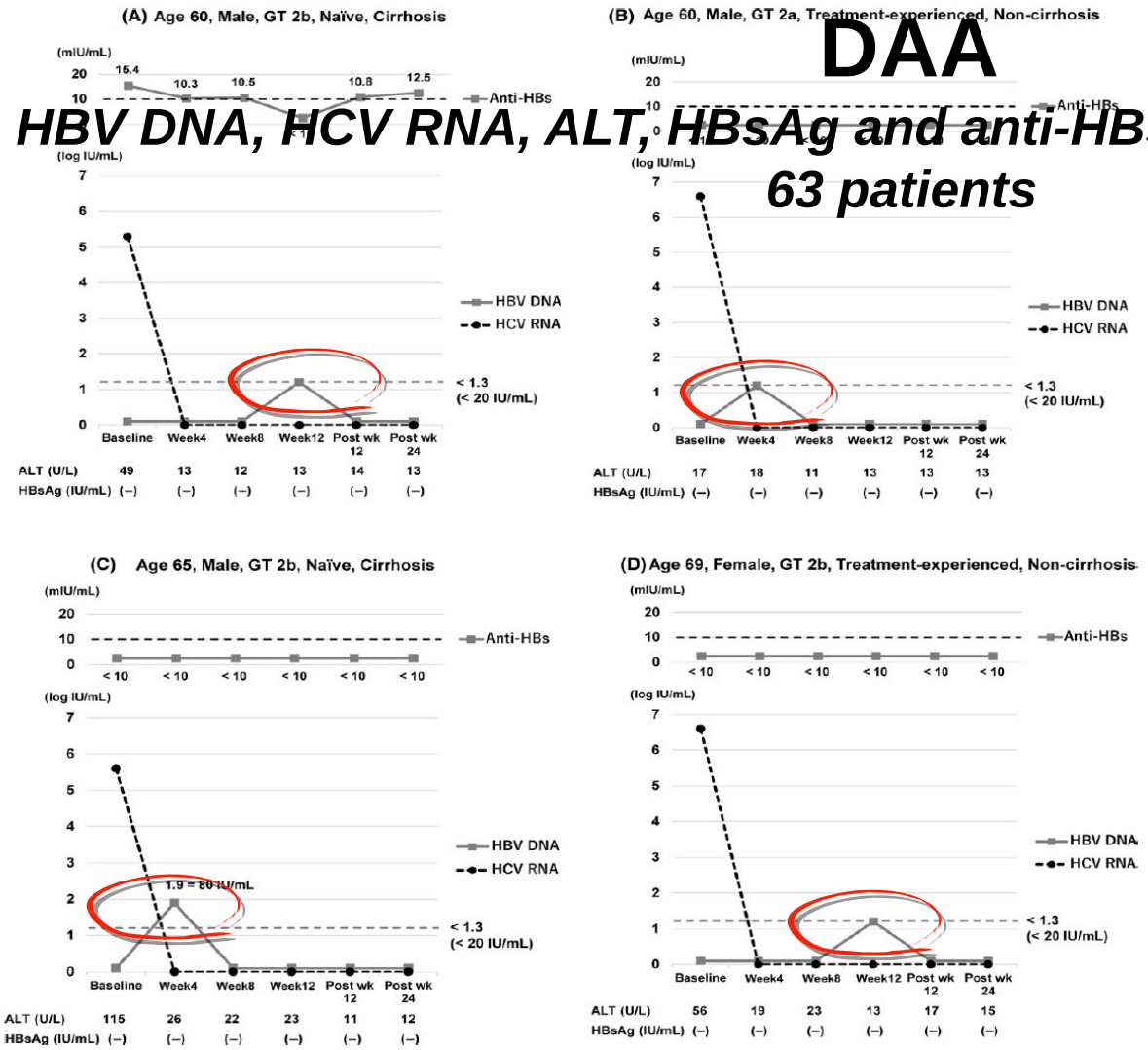
38 wks after DAA administered due to post OLTx recurrence of HCV

…a case of late HBV reactivation, 38wk after DAA-based treatment (2015) of recurrent hepatitis C in an antibody against hepatitis B core antigen (anti-HBc)-positive LT recipient (2011). Immunosuppressive treatment was unchanged over the last year and consisted of tacrolimus (trough levels 5-6 mg/L) and prednisone 5mg qd.



Transient increase of HBV DNA in patients HBsAg-/anti-HBc+ treated with DAA

HBV DNA, HCV RNA, ALT, HBsAg and anti-HBs measured every 4 wks in 63 patients



- About 6% patients with resolved HBV infection had HBV DNA become detectable during DAA treatment.
- Detectable HBV DNA was a transient phenomenon related to negative or very low-titre anti-HBs, which did not result in hepatic failure.

Ogawa E et al. Liver International. 2018;38:76–83.

Conclusions

- All patients scheduled for treatment of HCV infection should be tested for HBsAg.
- At least patients with confirmed or suspected immunodeficiency should be additionally tested for anti-HBc.
- Prophylaxis with potent nucleoside/nucleotide analogue should be administered at least 4 weeks before start of anti-HCV treatment in all HBsAg-positive and immunodeficient HBsAg-negative/anti-HBc-positive patients and continued at least untill 12 weeks after HCV treatment termination.
- Immunocompetent HBsAg-negative/anti-HBc-positive patients probably do not need specific monitoring for possible HBV reactivation.