

# Low Rate of Hepatitis B Reactivation Among Patients with Chronic Hepatitis C During Direct Acting Antiviral Therapy



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## BACKGROUND

- Hepatitis B Virus (HBV) reactivation occasionally occurs in patients with chronic hepatitis C (CHC) with prior HBV exposure during Direct Acting Antiviral (DAA) therapy
- The US FDA therefore issued black box warnings on all DAA drug labels to measure HBV DNA and monitor HBV reactivation during and after therapy
- As prior studies looked at single time points either during or after treatment, the true HBV reactivation incidence may be underestimated

## AIMS

- To comprehensively determine the incidence of HBV reactivation at multiple time points during and after DAA treatment for patients with CHC

## METHODS

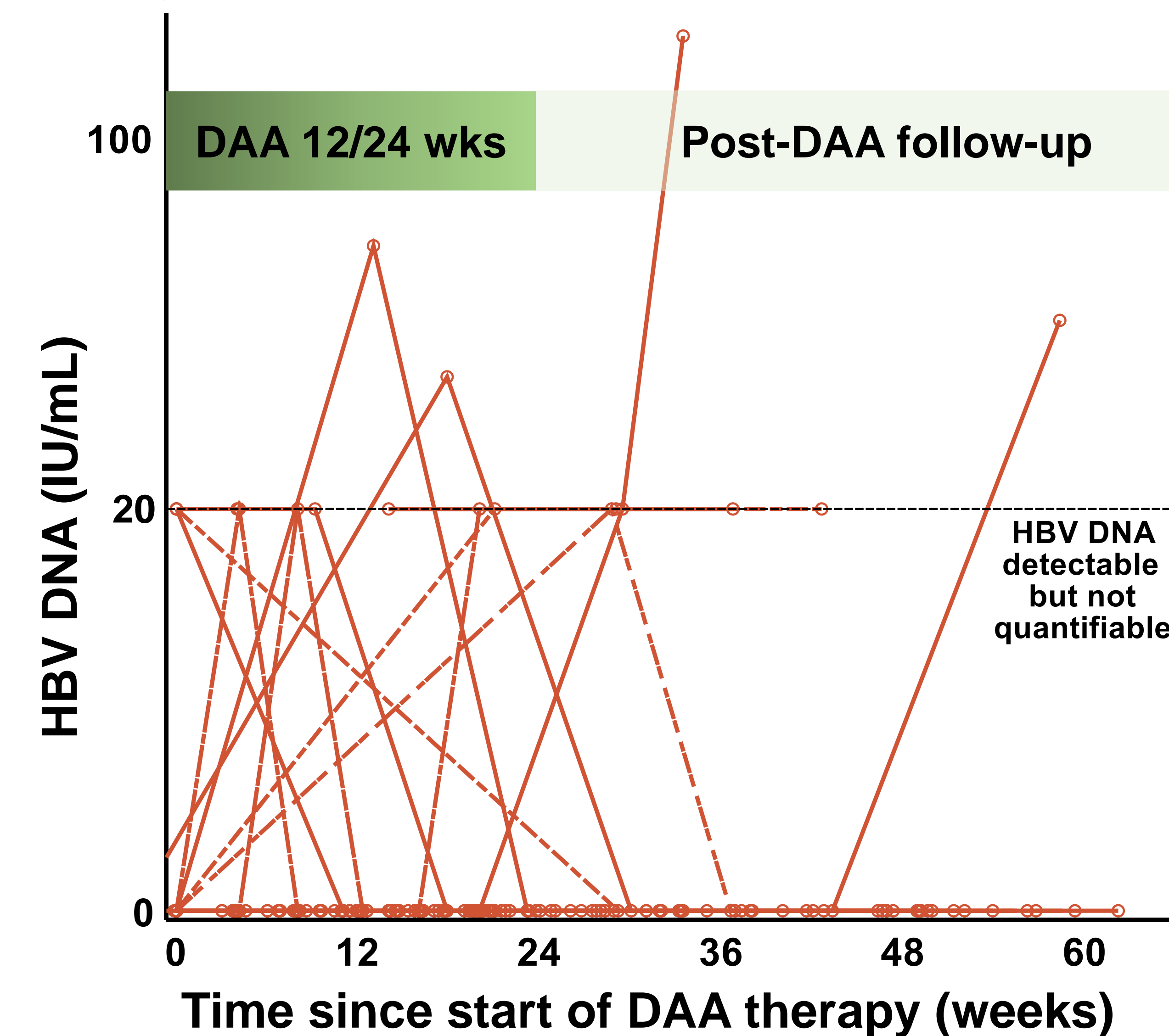
- Retrospective cohort study conducted at NIH (US) and Toronto Centre for Liver Disease (Canada)
- Major inclusion criteria:
  - CHC (anti-HCV and HCV RNA positive)
  - Treated with DAAs
  - Prior exposure to HBV (HBsAg negative and anti-HBc positive)
  - Available serum samples from clinic visits before, during and after DAA treatment
- Samples were tested for HBV DNA (Roche COBAS Assay) and HBsAg at each time point
- HBV reactivation was defined as:
  - Detectable HBV DNA, if initially negative, or
  - Quantifiable HBV DNA, if initially detectable (<20 IU/ml) ± HBsAg seroreversion
- ALT flare (≥2x ULN) incidence was examined

## RESULTS

**Table 1. Start of DAA therapy characteristics**

			N=79
Mean age (SD), years			62 (7)
Male sex, n (%)			52 (66)
Caucasian/Asian/Black/Other, %			66/11/15
HCV genotype 1/1a/1b/2/3/4/6, %			21/27/30/6/5/10/1
Previous (interferon) treatment, n (%)			46 (58)
Sustained Virologic Response achieved, n (%)			78 (99)
DAA regimen, n (%)			
	SOF-LED		53 (67)
	SOF-SIM		4 (5)
	SOF-RBV		2 (2)
	SOF-LED-RBV		4 (5)
	PAR-RTV-OMB-RBV		2 (2)
	PAR-RTV-OMB-DAS		9 (11)
	PAR-RTV-OMB-DAS-RBV		5 (7)
Mean ALT (SD), x ULN			2.2 (1.5)
HCV RNA positive, n (%)			5.9 (1.2)
Anti-HBs positive, n (%)			42 (53)
Metavir Fibrosis stage 0/1/2/3/4, %			5/14/14/23/46
Cirrhosis, n (%)			41 (52)
Decompensated cirrhosis prior to DAA, n (%)			59 (11)

**Figure 1. Serum HBV DNA before, during and after DAA therapy in patients with CHC (n=79)**



**Table 2. Characteristics of patients with HBV reactivation (n=8/79)**

ID	Geno type	DAA regimen (duration)	SVR	Pre-DAA cirrhosis	Pre-DAA HCV RNA (log IU/mL)	Pre-DAA HBV DNA (IU/mL)	On-DAA HBV DNA (IU/mL)	Off-DAA HBV DNA (IU/mL)	Peak ALT on/off-DAA (x ULN)
1	1b	SOF-LED (12 wks)	Yes	Yes	6.4	Neg	Wk 4 52	Wk 2 Neg Wk 17 Neg	0.9
2	1	SOF-LED (24 wks)	Yes	Yes	6.6	Neg	Wk 4 <20 Wk 8 184	-	1.4
3	1a	SOF-LED (24 wks)	Yes	Yes	6.5	Neg	Wk 4 Neg Wk 24 Neg	Wk 15 33	0.5
4	3a	SOF-RBV (12 wks)	Yes	No	6.8	Neg	Wk 4 <20 Wk 8 Neg	Wk 4 Neg Wk 8 <20 Wk 12 Neg	0.8
5	1a	SOF-LED (12 wks)	Yes	No	5.6	Neg	Wk 4 <20 Wk 12 <20	Wk 14 <20	0.4
6	1	SOF-LED (12 wks)	Yes	Yes	6.1	Neg	Wk 4 <20 Wk 12 Neg	Wk 13 Neg	0.4
7	2b	SOF-RBV (12 wks)	Yes	No	6.9	Neg	Wk 4 Neg Wk 8 <20	Wk 4 Neg Wk 12 Neg	0.6
8	1	SOF-LED (24 wks)	Yes	Yes	6.9	Neg	Wk 4 Neg	Wk 1 Neg Wk 14 <20	0.6

## CONCLUSIONS

- The risk of HBV reactivation was low in CHC patients with recovered HBV
- No ALT flares or HBsAg seroreversion was observed
- These data suggest that monitoring for HBV reactivation among CHC patients undergoing DAA therapy is probably not warranted
- We recommend only testing for HBV DNA in selected patients with ALT flares or failure of ALT normalization during DAA treatment

### HBV reactivation did not coincide with ALT flares

- ALT flares or HBsAg seroreversion was not observed in patients with HBV reactivation
- Detectable/quantifiable HBV DNA was transient in 4 patients
- The duration of detectable/quantifiable was unknown in 4 other patients due to lack of follow-up samples, but these did not have concurrent ALT flares

**Table 3. ALT elevations throughout DAA treatment**

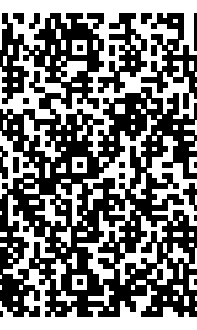
	n (%)	Before DAA	During DAA	After DAA	Peak ALT (x ULN)
ALT >1.5x ULN	32 (19)	26 (81)	4 (13)	2 (6.3)	5.5
ALT flare >1.5x ULN*	4 (2.3)	2 (1.2)	2 (1.2)	0 (0.0)	5.0
ALT >2.0x ULN	26 (15)	23 (89)	2 (7.7)	1 (3.8)	5.5
ALT flare >2.0x ULN*	3 (1.8)	2 (1.2)	1 (0.6)	0 (0.0)	5.0

\*ALT elevation during at least two consecutive visits.

**Abbreviations:** ALT, alanine aminotransferase; DAS, daclatasvir; LED, ledipasvir; OMB, ombitasvir; PAR, paritaprevir; RBV, ribavirin; RTV, ritonavir; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response

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