THE FORUM
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Liver Safety Monitoring Working Group update

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THE FORUM For Collaborative Research℠

Liver Safety Monitoring Working Group

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Objective: Develop consensus recommendations regarding definitions and criteria to distinguish DILI events vs “therapeutic” flare vs other viral breakthrough/ resistance in HBV treatment trials with newer agent(s)

Liver Safety Assessment in Clinical Trials of New Agents for Chronic Hepatitis B

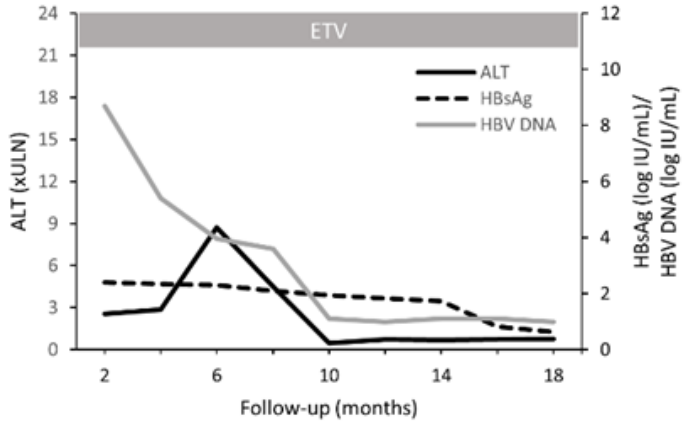
- **Journal of Viral Hepatitis (accepted 9/15/19)**

Table 1 – Types of flares

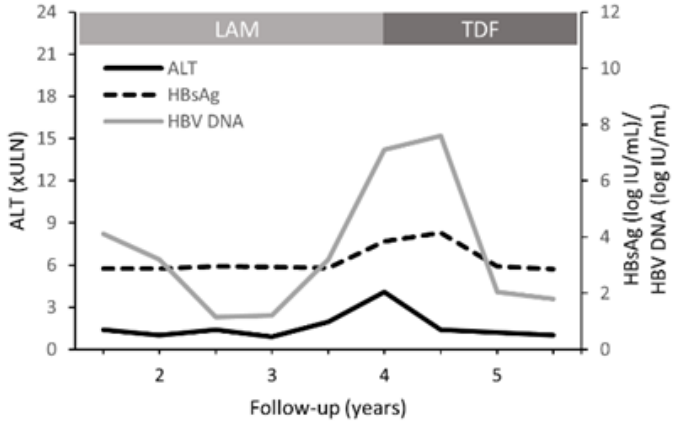
Host mediated	**Spontaneous-** enhanced host immunity to infected hepatocytes; frequently preceded by surge in HBV replication; variable ALT **Treatment related**- enhanced host immunity to infected hepatocytes Early < 12 wks; variable ALT Late > 12 wks; variable ALT	HBeAg (or HBsAg) loss in some; severe flare may require rescue NRTI Early flare associated with ↓ HBV replication; continue therapy if no ↑ Bili or INR HBeAg (or HBsAg) loss in some; continue therapy if no ↑ Bili or INR
Virally mediated	**On-Treatment** - redetection of previously suppressed HBV-DNA Late > 12 wks; variable ALT **Post-treatment**: redetection of HBV-DNA within 48 weeks of therapy completion	Non-compliance associated with resurgence of wild-type HBV; may respond to resumption of Rx. Drug resistant breakthrough associated with viral variants Severe may require rescue NRTI
Idiosyncratic drug toxicity	**Timing**: occur at any time; independent of drug dose or other host factors **Phenotype**: Variable ALT; some with ↑Alk phos or bili	Variable phenotype makes diagnosis difficult Serum ALT > 10 x ULN or ↑T. bili or INR require immediate drug d/c Potentially severe in adv fib

Figure 1: Types of ALT flares

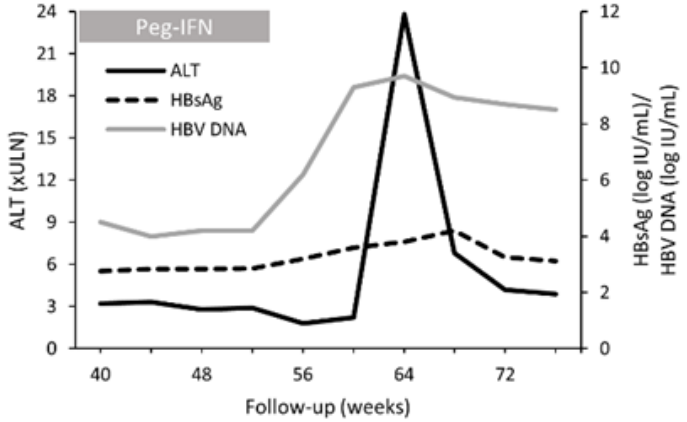
A. On-treatment flare



B. Resistance-induced flare



C. Post-treatment flare



JVH Manuscript

- **Table 2- Incidence of ALT elevations with Tenofovir and PegIFN a2a**
- **Table 3- Recommended Exclusion criteria for Clinical Trials**
  - **Phase ½- Exclude advanced fibrosis/ cirrhosis**
  - **Phase 3- Exclude decompensated cirrhosis**
- **Table 4/5- Management of liver safety signal in NRTI suppressed and naïve patients based on x ULN (BL)**

Table 6: Recommended evaluation of liver safety signal

1st Line (Initial)		2nd line (If needed)	
Etiology	**Evaluation**	**Etiology**	**Evaluation**
Liver directed history	Travel, alcohol use Exercise, con meds, HDS use	Autoimmune	ANA, SmAb, IgG, IgM, IgA
Acute HAV	Anti-HAV (IgM)	Ischemia	Vitals, echocardiogram
Acute HCV	Anti- HCV, HCV RNA	Illicit hepatotoxins	Urine drug screen
Muscle injury	CPK, aldolase	Acute HDV	Anti-HDV
Alcohol	Serum PeTH Urine ETG	Acute HEV	Anti- HEV IgM, IgG
Pancreaticobiliary	Ultrasound (CT/ MRI)	CMV, EBV, HSV	EBV-DNA, CMV-DNA, HSV-DNA
		Cholestasis of sepsis	Medical history