HBV-TAG

2021 CONFERENCE

Serum ALT Flares: Good, Bad or just Ugly?

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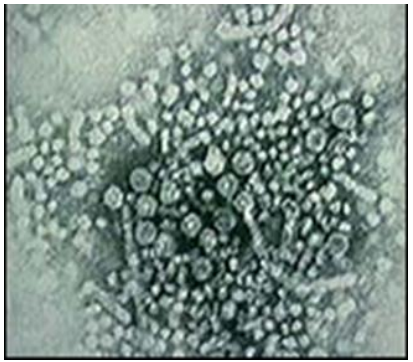
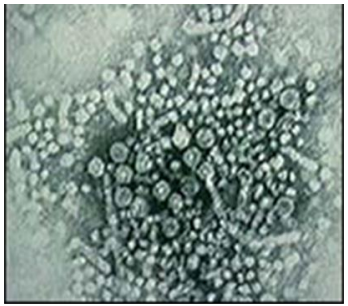
Robert J. Fontana, MD Disclosures

- **Research: Gilead, BMS, Abbvie.**
- **Consultant: Sanofi**

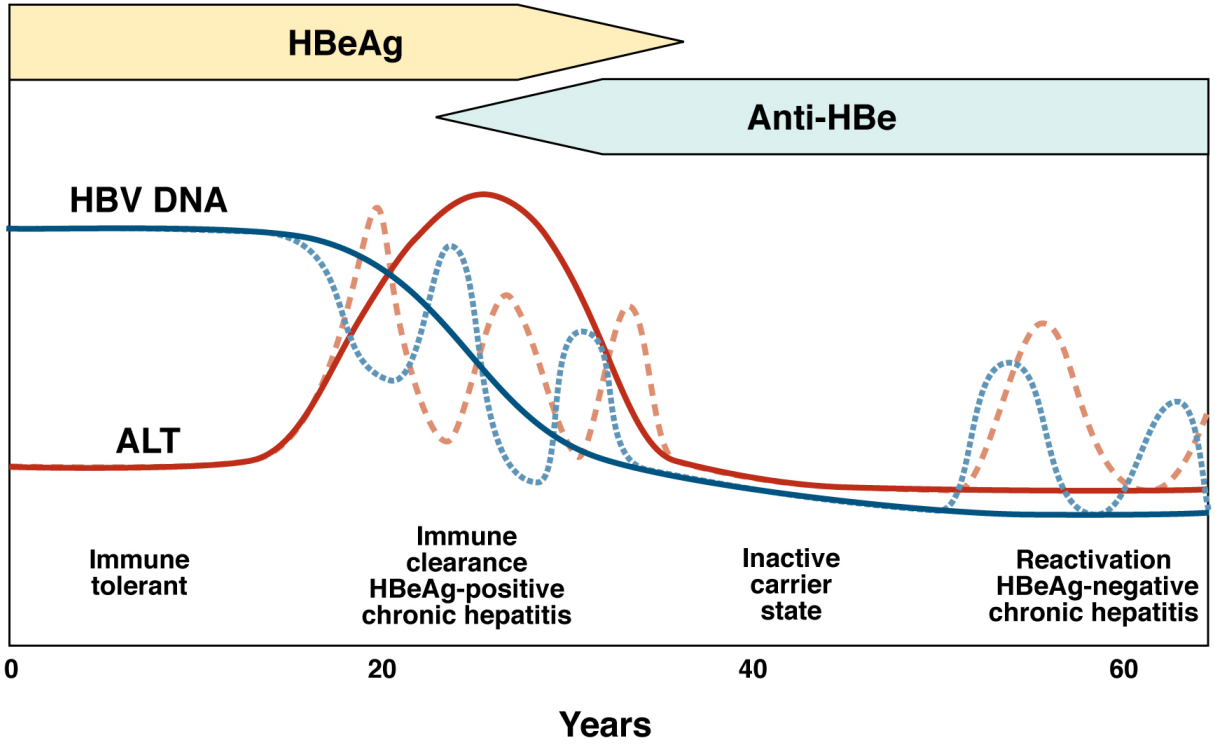


ALT Flares in Chronic HBV

- **Definitions & grading**
- **Host-mediated**
  - **Spontaneous**
  - **On-therapy (Early vs late)**
- **Virally mediated**
  - **On or post-therapy**
- **Idiosyncratic DILI**



Natural History of Chronic HBV



Definition ALT Flare

Grade	Term	Serum ALT (ULN)	Male *
1	Minimal	1x to ≤ 3x	Up to 90
2	Mild	> 3x to ≤ 5x	> 90 to 150
3	Moderate	> 5x to ≤ 10x	> 150 to 300
4	Marked *	> 10 x	> 300

* Male ULN = 30 IU/l Female ULN = 20 IU/l

* Severe if T. bili > 2.5, INR > 1.5 or hepatitis symptoms irrespective of ALT

Liver safety assessment in clinical trials of new agents for chronic hepatitis B

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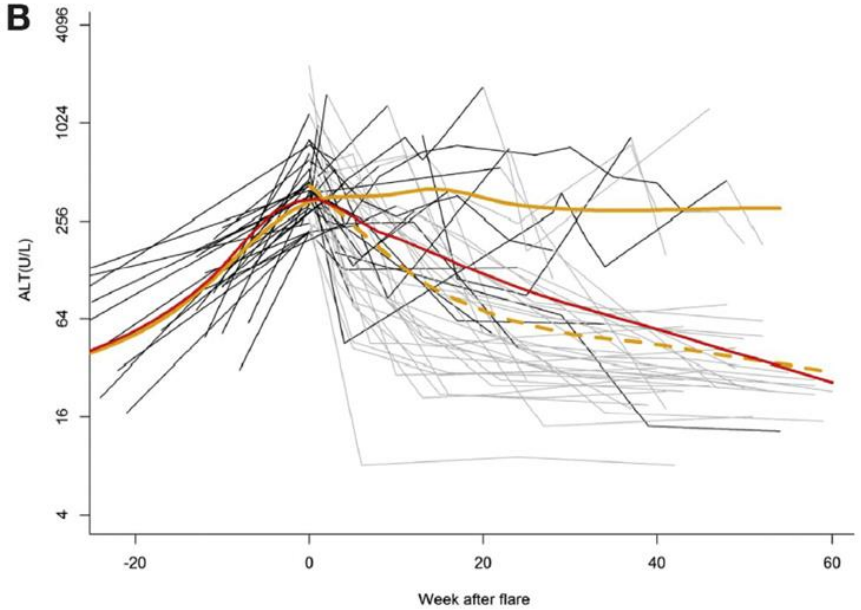
(Fontana JVH 2019: 1-4)

ALT > 10 x ULN in Untreated HBV

5.7% over 4 yrs (n=1587)



Untreated

Treated

Flares associated with ↑HBV DNA decrease and HBeAg loss over 4 year F/U

(Brahmania CGH; 2019: 17)

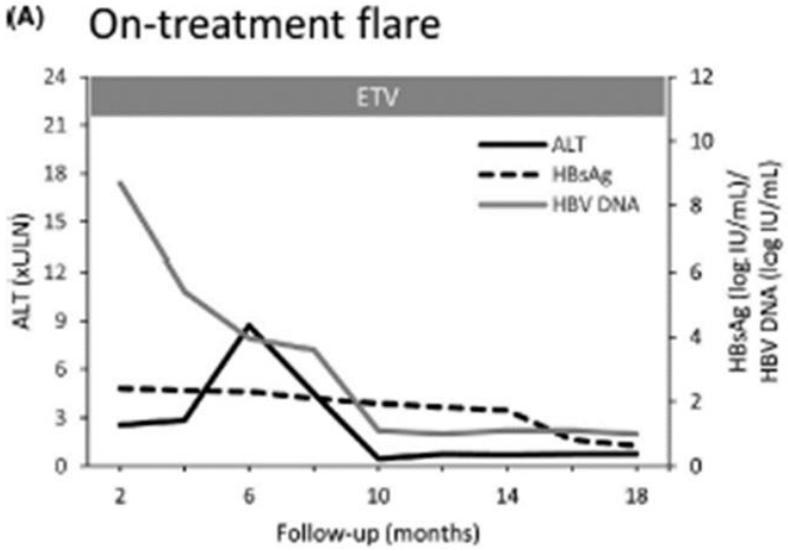
Host Induced ALT Flares

- **Spontaneous**
  - ↑ immunity to infected hepatocytes
    - Higher peak ALT vs viral-induced flares (8-12 x ULN*)
  - Severe flares may require rescue NRTI

- **On-Therapy**
  - ↑ immunity to infected cells (stable or ↓ HBV DNA)
    - Early < 12 wks
    - Late > 12 wks
  - Continue Rx if asymptomatic and ? ALT < 10 x ULN

(Heng C J Gasto Hep 2016; 31: 1882) **(Flink HJ GUT 2005; 54: 1604)**

Host Induced ALT Flares



Early (< 12 wks)

- ? Marker of efficacy
- Usually resolve despite continued Rx
- Rarely severe/ symptomatic

Late (> 12 wks)

- ? Marker of efficacy
- Imminent HBeAg/ HBsAg loss
- Check HBV DNA (resistance)

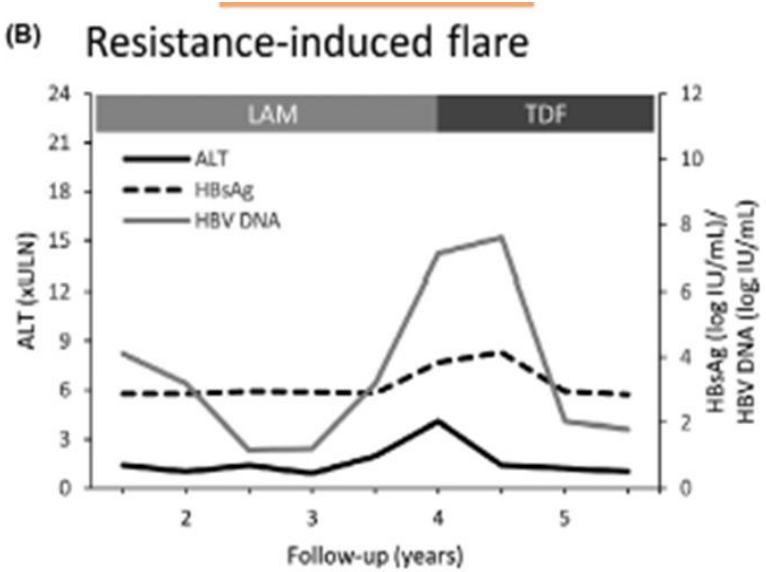
(Fontana JVH 2019: 1-4)

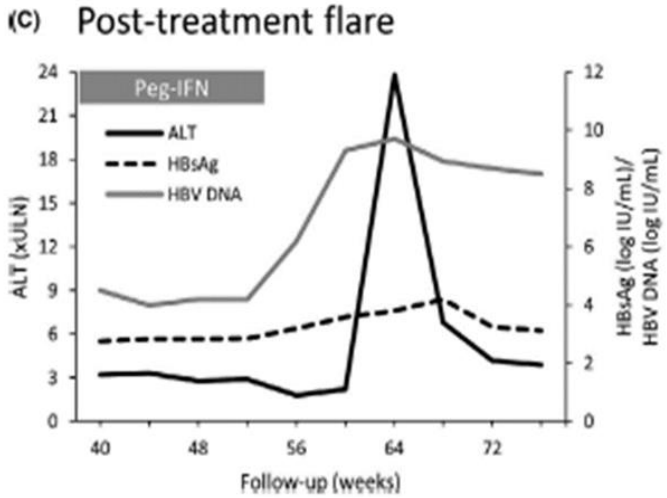
Virus- induced ALT Flares

- **On-therapy**
  - HBV DNA increase precedes ALT increase
    - Non-compliance
    - Drug resistance
  - Generally later & milder than host-induced flares.

- **Post-therapy**
  - ↑ HBV DNA with or without effective immune response
    - Up to 48 wks after discontinuation

Virus-induced ALT Flares





Severe flares may require "rescue" NRTI

(Fontana JVH 2019: 1-4)

New HBV Serum Biomarkers

- **qHBsAg (1 to 4 log $_{10}$) ^**
  - Lld= 0.05 IU/ml; impact by HBV genotype, HBeAg status

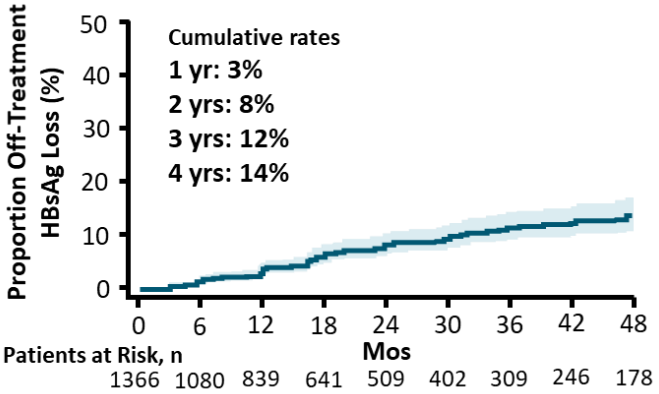
- **HBV-RNA * (1 to 8 log$_{10}$) (Transcription)**
  - Lld= 800 cp/ml
  - Detectable in 30-40%

- **HBcrAg * (2 to 7 log $_{10}$) (Translation)**
  - Lld = 2 log $_{10}$; impact by HBeAg

^ Integrated HBV DNA > cccDNA

NRTI Withdrawal

- **1541 non-cirrhotic HBV patients**
  - HBeAg (-) and undetectable HBV DNA at Nuc withdrawal
- **Primary outcome**
  - Off-treatment HBsAg loss
    - 14% at 4 yrs
  - Retreatment
    - 56% at 4 yrs



(Hirode AASLD 2020; #23)

HBsAg loss & retreatment after NRTI discontinuation

Hazard Ratio (95% CI)	HBsAg Loss	*P*	Retreatment	*P*
Age at baseline				
▪ < 50 yrs	1.0		1.0	
▪ ≥ 50 yrs	1.4	.12	1.6	< .001
Sex				
▪ Female	1.0		1.0	
▪ Male	1.4	.20	1.1	.21
Race				
▪ Asian	1.0		1.0	
▪ Caucasian	5.8	< .001	1.0	.94
NA Type				
▪ ETV	1.0		1.0	
▪ TDF	1.4	.18	0.9	.23
HBeAg at start				
▪ Positive	1.0		1.0	
▪ Negative	1.0	.98	1.1	.51

- 15 (1%) experienced decompensation
- 12 (0.96%) died
  - 9/12 (75%) liver-related

(Hirode AASLD 2020; #23)

Idiosyncratic DILI

- **Unique host response to drugs that is independent of dose, route, or duration**
  - Abberant adaptive immunity
- **Uncommon (< 1%) with most approved drugs**
  - Most common reason for denial, withdrawal, or restriction
  - Significant morbidity & mortality (13% ALF) [1]
- **No reliable means to predict or prevent**

(1 Ann Int Med 2016: 137)

DILI: A Clinical diagnosis
Requires a high index of suspicion

- **Inclusion**
  - Temporal association (most < 6 mon)
    - Dechallenge requires time
  - Drug latency, lab profile (R-value)
    - Polypharmacy common
  - Histology

- **Exclude more common causes**
  - HAV, HBV, HCV, pancreaticobiliary
  - Ischemia, alcohol, autoimmune, NAFLD

- **No objective/ confirmatory test**

Evaluation of ↑ ALT in HBV studies

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

(Fontana JVH 2019; 1-14)

GWAS with individual drugs

Series	Cases	Controls	Locus	OR	MAF
Lumiracoxcib	41	176 treat controls	DRB1*15:01 DQB1*06:02	5.0	15%
Ximelagatran	74	130 treat controls	DRB1*07 DQA1*02	4.4 4.4	8.5%
Lapatanib	37	286 treat controls	DQA1*02	9.0	21%
Amoxicillin-clavulanate	201	532 Pop controls	DRB1*15:01 A*02:01	3.1 2.3	14% 28%
Flucloxacillin	51	282 pop controls	B* 57:01	80	6%
Minocycline	25	6835 pop controls	B* 35:02	29	0.6%

(Daly Nat Genet 2009; 41: 816)
(Kindmark Pharmacogenomics; 2008:8: 186)

(Lucena Gastroenterology 2011; 141)
(Urban J Hepatology 2017)

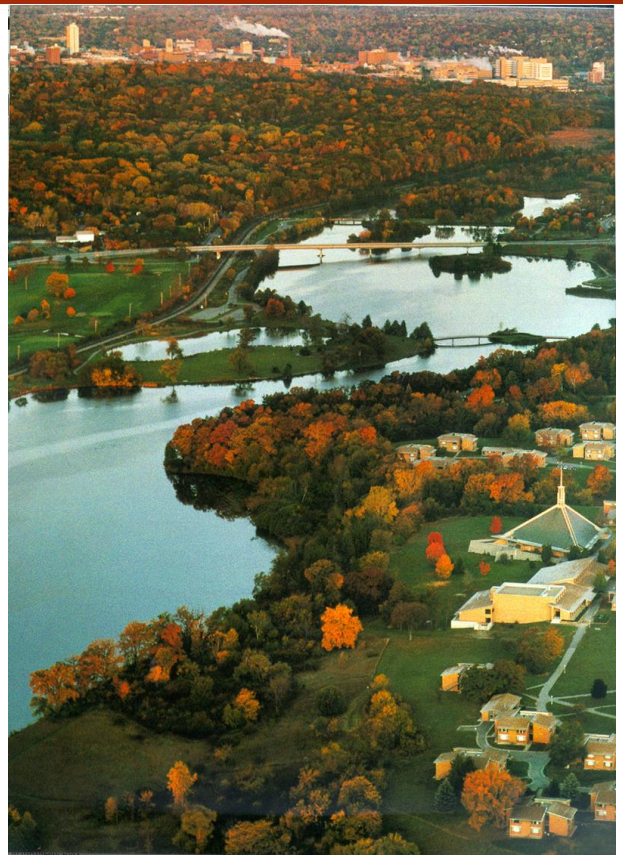
DILI Diagnostic biomarkers

- **Genetic polymorphisms**
  - Drug specific HLA
  - High NPV, low PPV
- **Liver histology**
  - Variable pattern, invasive, risk
- **Blood tests (miR122, GLDH, HMGB1, MCSFR)**
  - ? DILI Specificity
- **In vitro test systems**
  - iPSC (human liver organoids)

Summary ALT Flares in HBV 2021

- **Good: HBsAg or HBeAg loss**
  - Effective immunity ↓ HBV replication
- **Bad: protracted, jaundice**
  - ? Excess or ineffective host immunity
    - NRTI withdrawal, functional cure regimens
    - Avoid cirrhotics (rescue NRTI)
- **UGLY: DILI or other cause**
  - Lab & imaging tests
- **Newer HBV markers**
  - ? Differentiate ? predict

Thank YOU !!!



DILIN
Drug Induced Liver Injury Network

Hepatitis B
Research Network

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