

# Examining the relationship between transaminase flares, liver dysfunction and functional control of HBV in HBV mono-infected and HBV / HDV co-infected patients

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# Transaminase flares in HBV infection

## Transaminase flares are infrequent but typically well tolerated

Brahmania et al., Clin Gastro Hepatol 2019; Epub Feb 8, 2019

Wirth et al., Hepatol 2018; 68: 1681-1694

Chi et al., J Gastro Hepatol 2016; 31: 1882-1887

Ahn et al., Dig Dis Sci 2018; 63: 3487-3497

Seo et al., Clin Mol Hepatol 2017; 23: 154-159

Nagakoya et al., Hepatol Res 2016; 46: E89-E99

## Two major types:

### Host (immune) mediated **(most common)**

- associated with improved virologic response, HBsAg loss and functional cure
- considered a result of clearance of hepatocytes containing cccDNA and or integrated HBV DNA

### Viral mediated

- occurs with viral rebound
- usually associated with development of NUC resistance or PC / PCB mutation

# Safety and prognostic value of ALT flares (available published data)

## In the absence of therapy:

- ALT flares associated with HBV DNA declines and HBeAg seroconversion

Brahmania et al., Clin Gastro Hepatol 2019; Epub Feb 8, 2019

## During NUC therapy:

- host mediated ALT flares associated with HBeAg seroconversion and HBsAg decline / loss

Jeng et al., J Vir Hep 2018; 25: 421-428

Wong et al., Liv Int 2018; 38: 176901769

Seo et al., Clin Mol Hepatol 2017; 23: 154-159

Chi et al., J Gastro Hepatol 2016; 31: 1882-1887

## During pegIFN:

- ALT flares associated with HBsAg loss and functional control and cure

Wirth et al., Hepatol 2018; 68: 1681-1694

Yano et al., Biomed Repts 2017; 7: 275-262

Marcellin et al., Gastroenterol 2016; 150: 134-144

Sonneveld et al., Clin Inf Dis 2013; 6: 100-105

## Rarely symptomatic, perhaps even in cirrhotic patients (limited data)

Wedemeyer et al., Lancet Inf Dis 2019; 19: 275-286

**Analysis is hampered by very low frequency of ALT flares**

# REP 2139-based therapy:

## a novel opportunity for evaluating transaminase flares

52 HBeAg negative patients from the REP 301 and 401 studies

40 HBV, 12 HBV / HDV

Bazinet et al., Lancet Gastro Hepatol 2017; 877-889, Bazinet et al, EASL 2019 Poster FRI-210, FRI-211

Mild to advanced fibrosis (based on Fibroscan) at baseline

All received NAPs in combination with pegIFN

Therapy resulted in high rates of functional control and functional cure of HBV and HDV

Analysis data set of 51 participants examining transaminase elevations during treatment

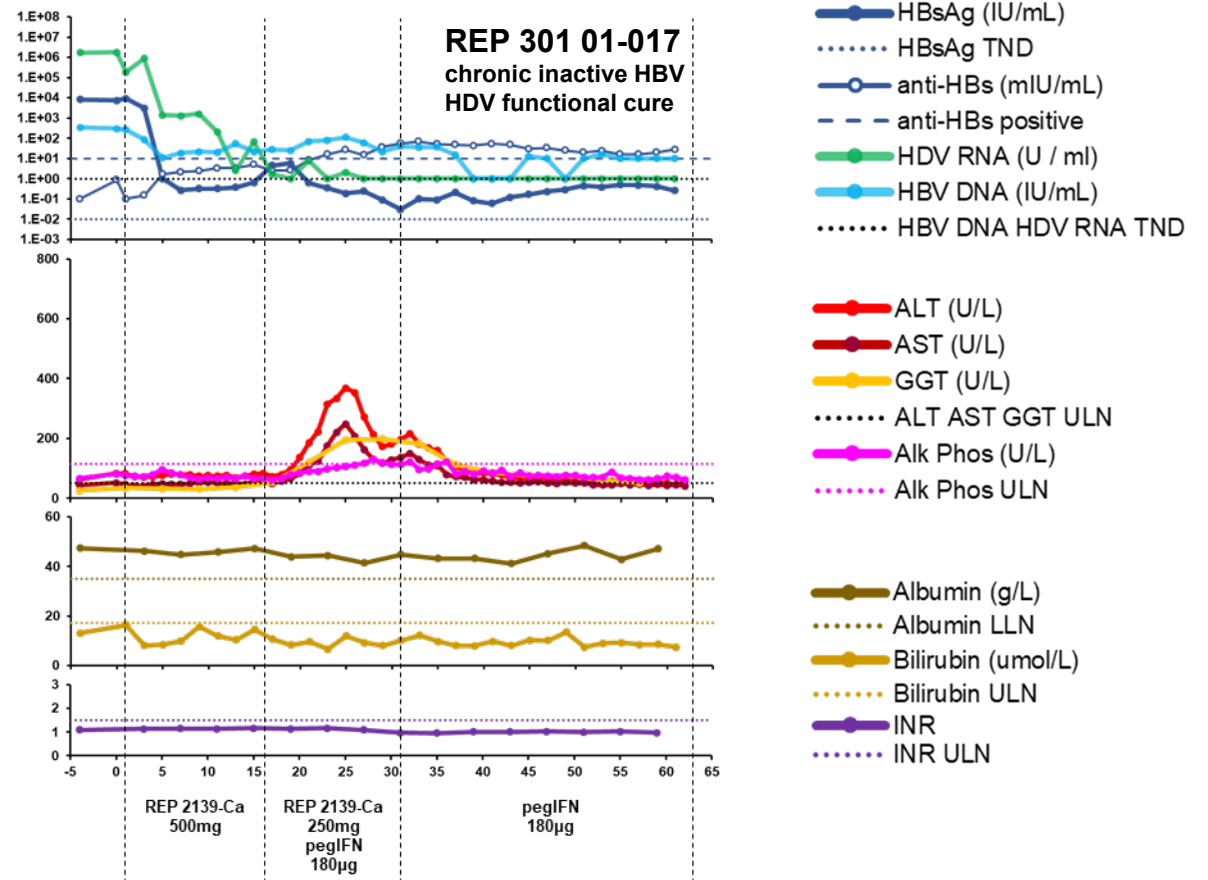
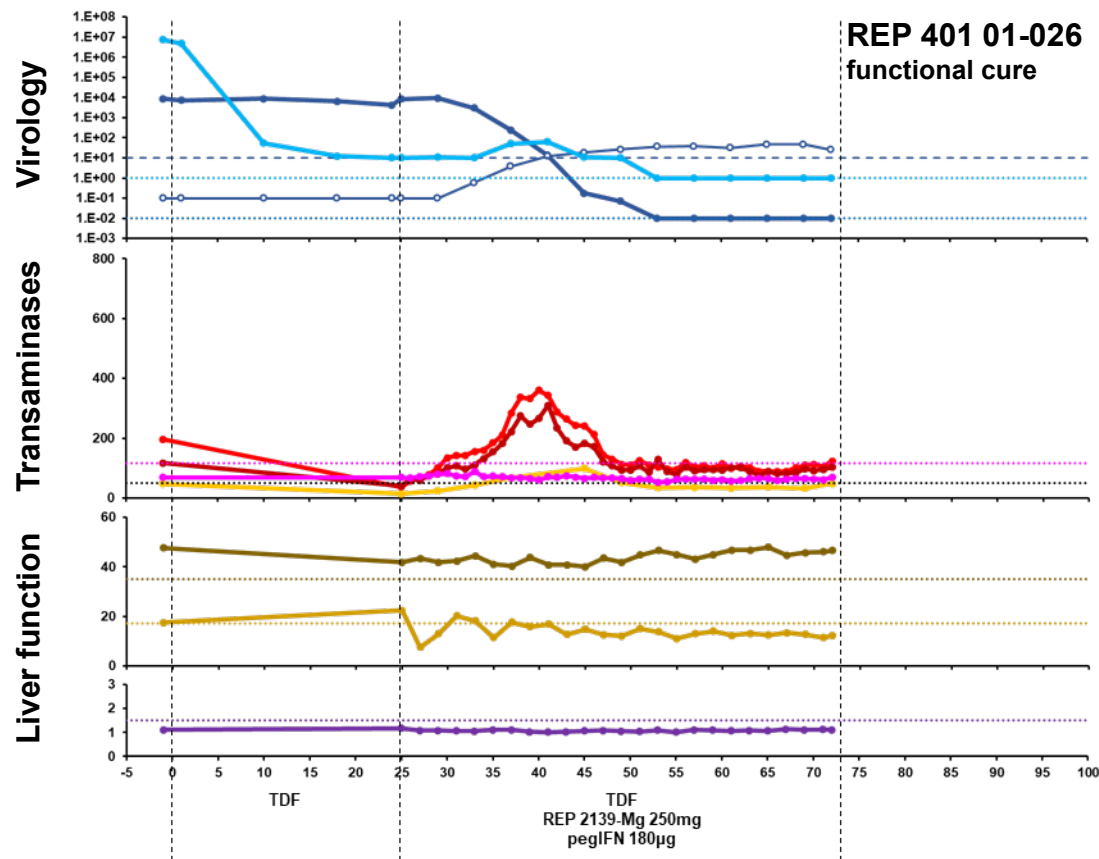
(1 case of pegIFN induced DILI excluded)

Bazinet et al., Lancet Gastro Hepatol 2017; 877-889

**Flares observed in 49/51 participants (96%) with three distinct geometries...**

# Transaminase flare analysis in the REP 301 / 401 studies

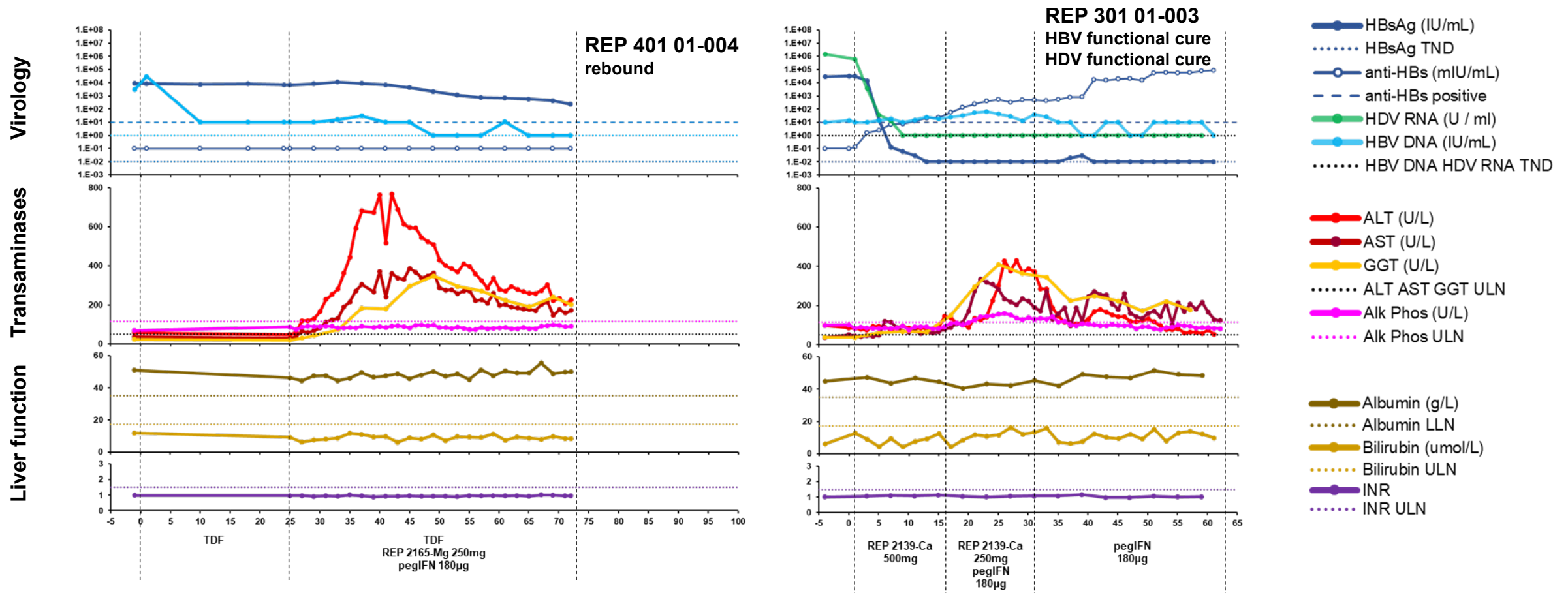
Single flare, self-resolving during therapy (26/51 participants)



- HBsAg (IU/mL)
- HBsAg TND
- anti-HBs (mIU/mL)
- anti-HBs positive
- HDV RNA (U / ml)
- HBV DNA (IU/mL)
- HBV DNA HDV RNA TND
- ALT (U/L)
- AST (U/L)
- GGT (U/L)
- ALT AST GGT ULN
- Alk Phos (U/L)
- Alk Phos ULN
- Albumin (g/L)
- Albumin LLN
- Bilirubin (umol/L)
- Bilirubin ULN
- INR
- INR ULN

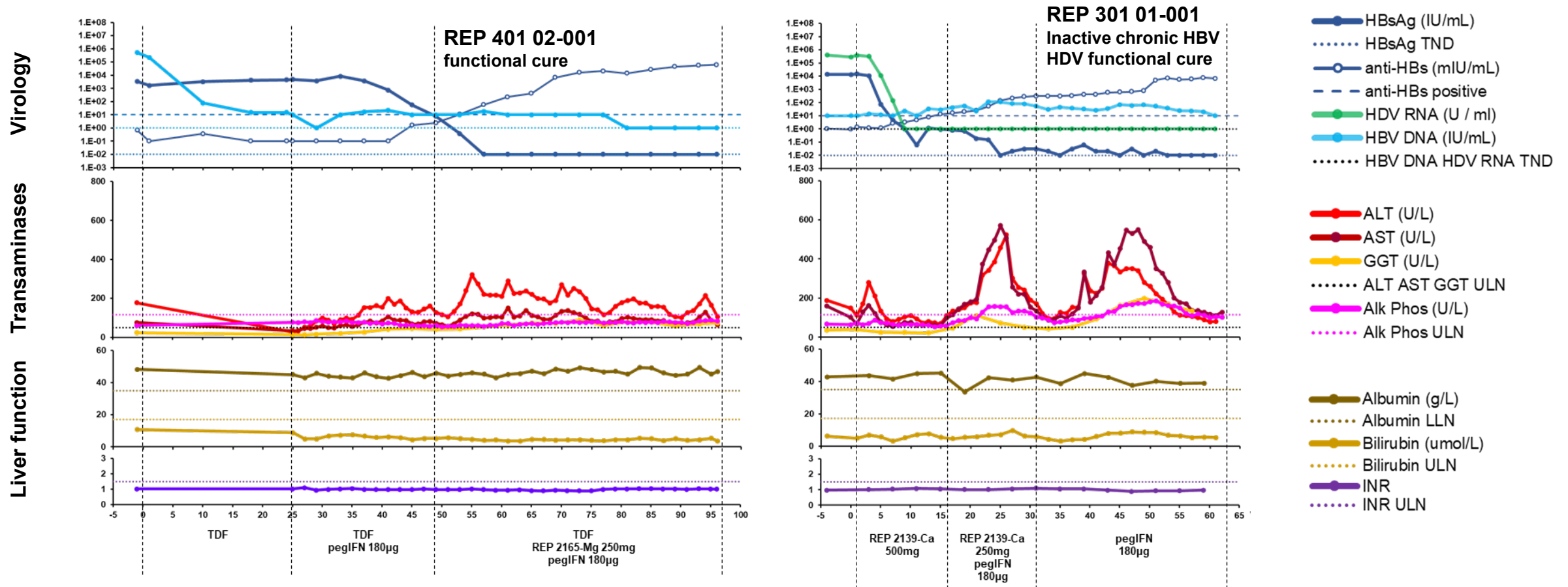
# Transaminase flare analysis in the REP 301 / 401 studies

Single flare, persisting during therapy (9/51 participants)



# Transaminase flare analysis in the REP 301 / 401 studies

Multiple flares during therapy (14/51 participants)

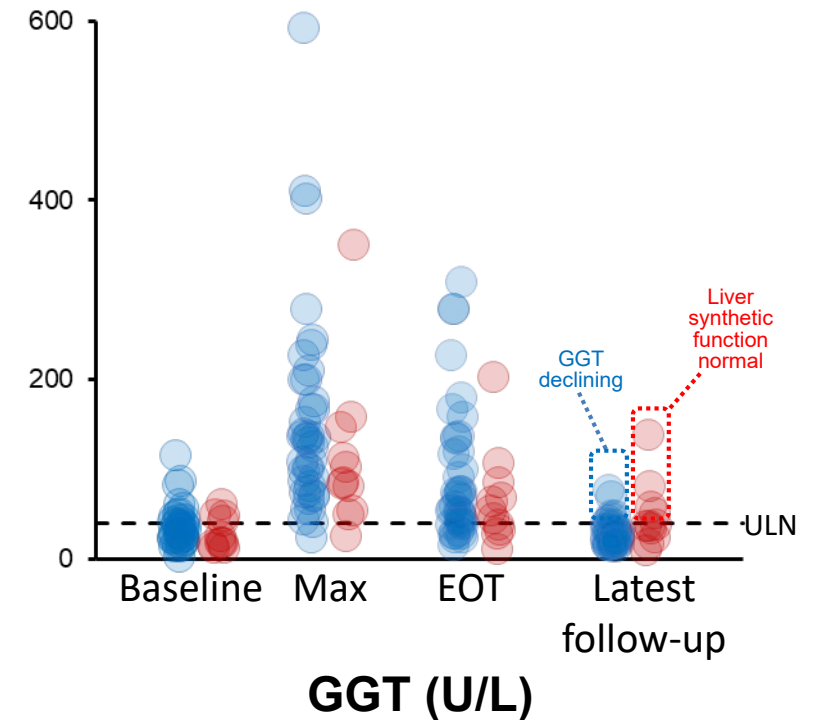
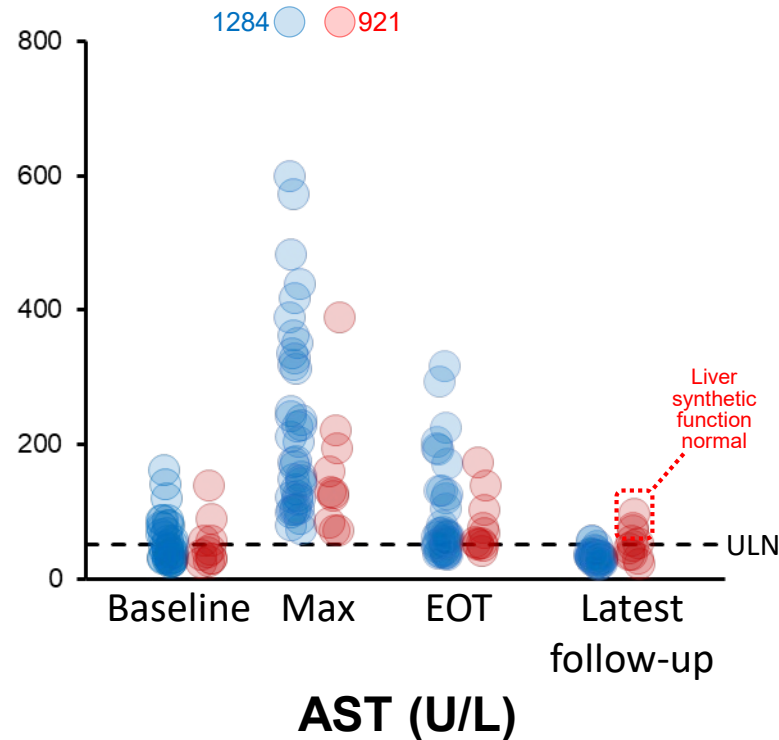
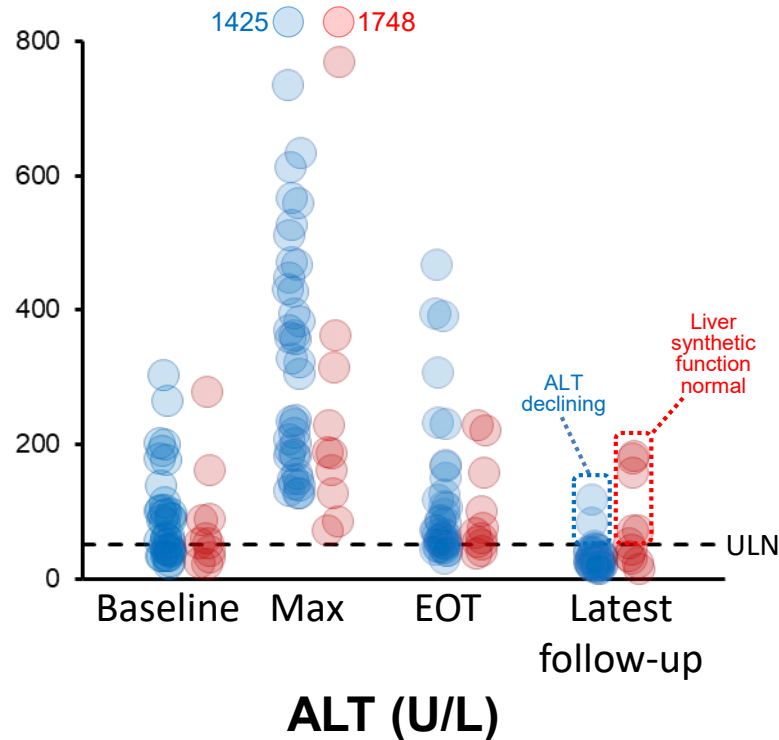




# Transaminase flare analysis in the REP 301 / 401 studies

- Functional control / functional cure
- Rebound

Max = maximum value observed during therapy  
EOT = observed value at end of therapy



Increased flare activity observed regardless of outcome

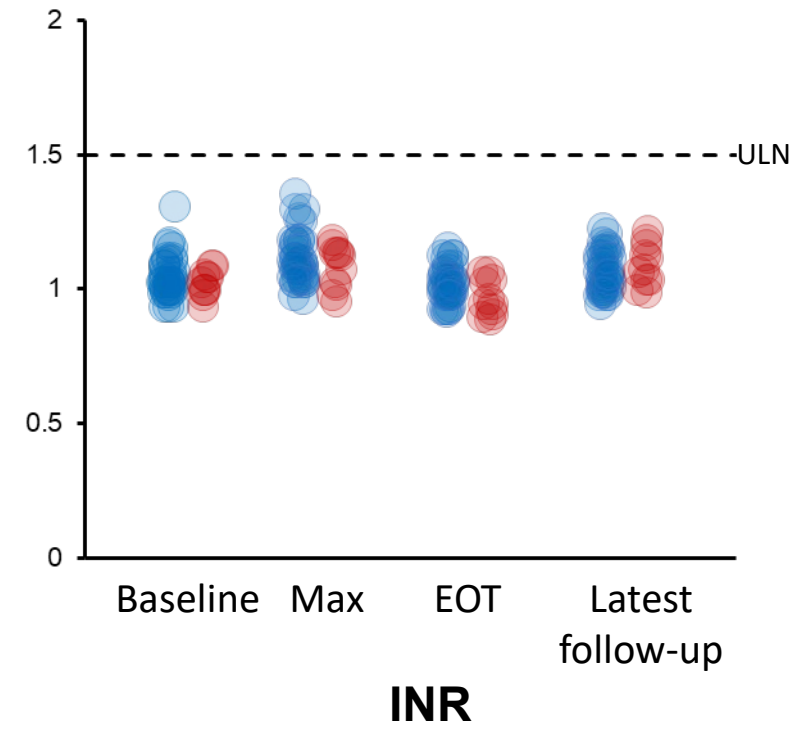
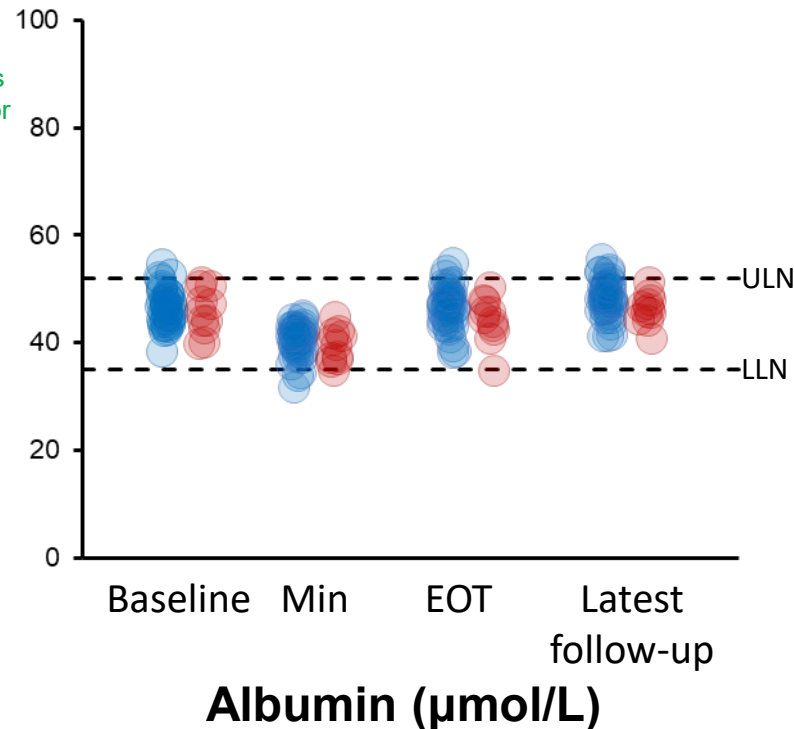
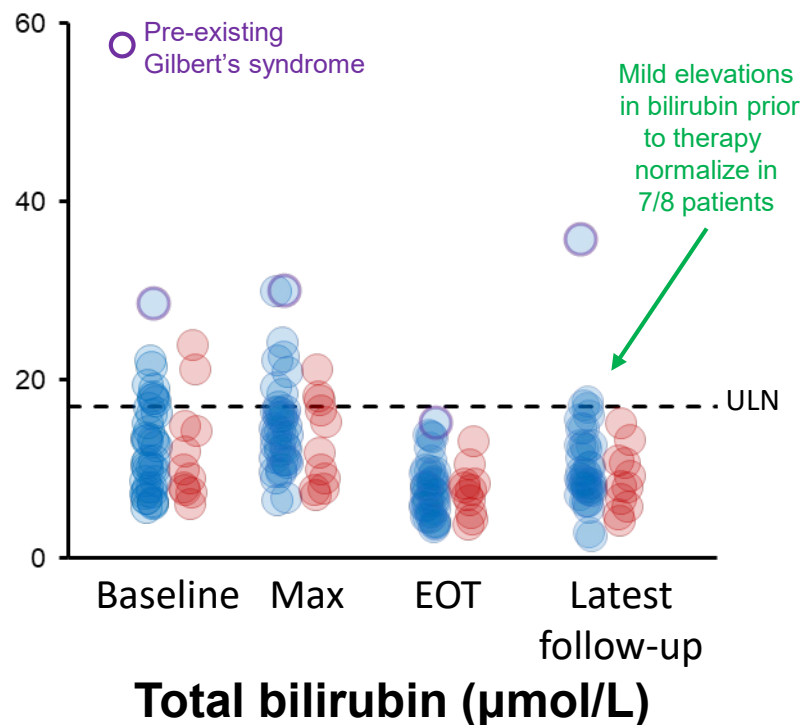
**Transaminases normalize or decline during follow-up with functional control / cure**



# Liver function analysis in the REP 301 / 401 studies

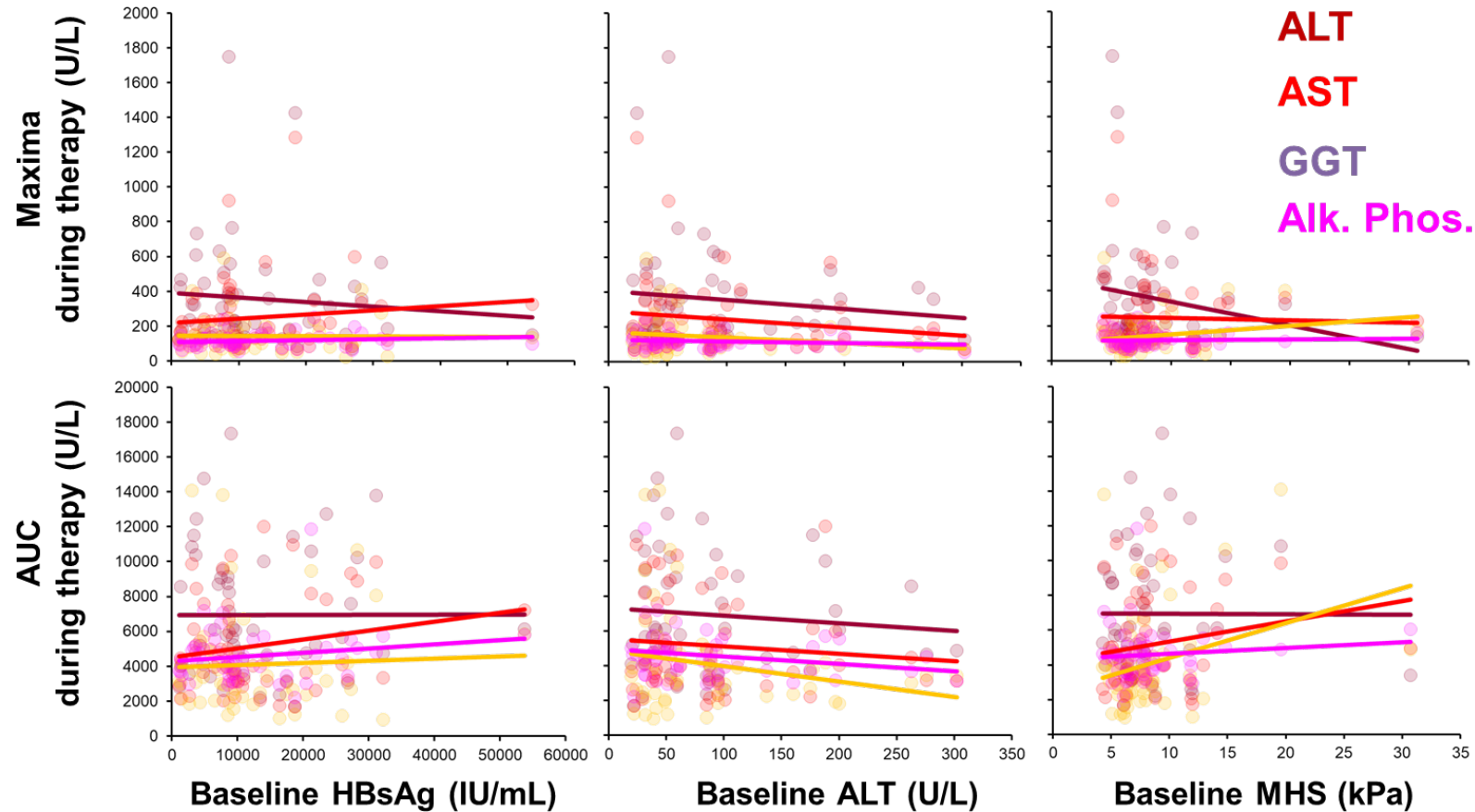
- Functional control / functional cure
- Rebound

Max = maximum value observed during therapy  
Min = minimum value observed during therapy  
EOT = observed value at end of therapy



**Liver function remains normal throughout therapy and follow-up**  
**Transaminase flares are otherwise asymptomatic**

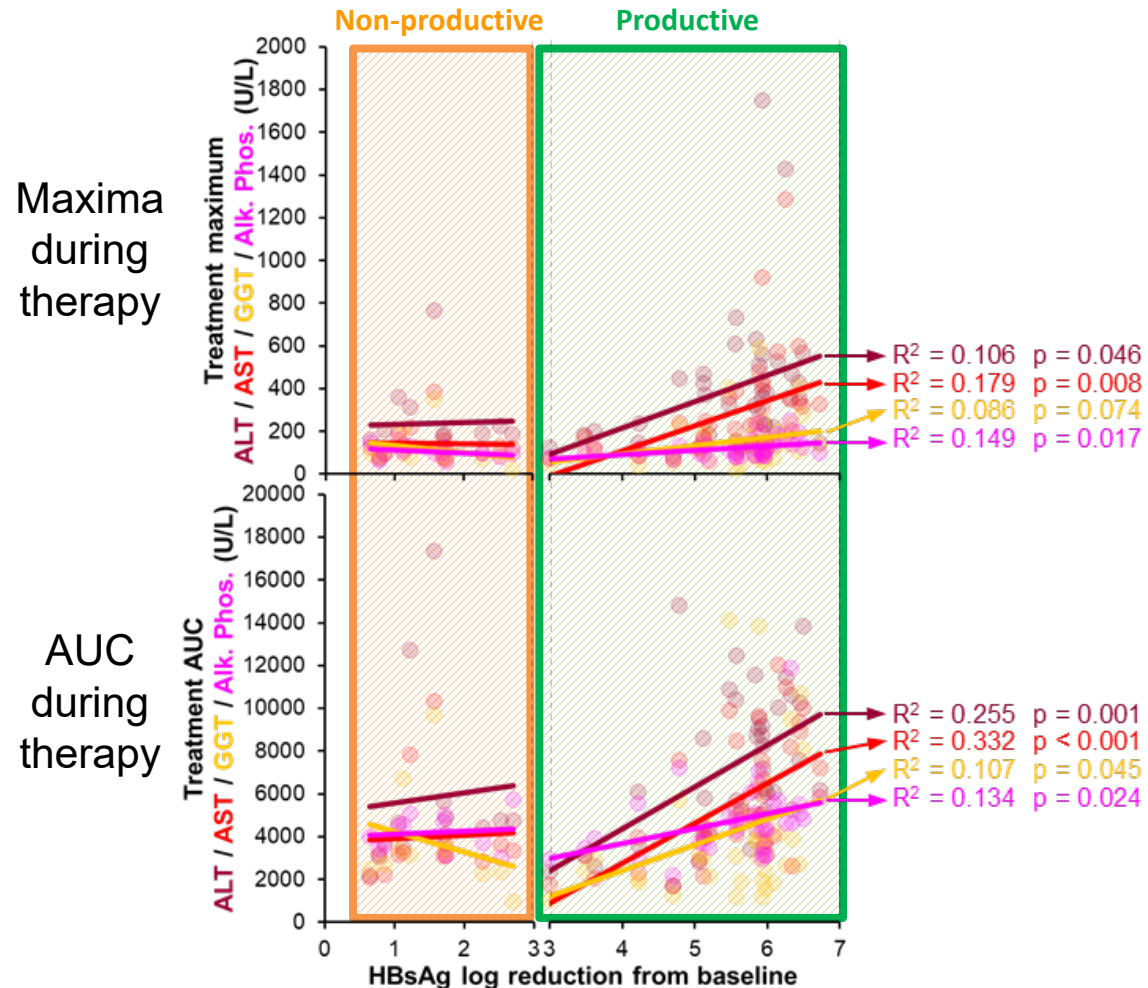
# Impact of baseline on transaminase flares



No correlation between transaminase flares  
and baseline HBsAg, ALT or median hepatic stiffness

# Predicting outcomes during REP 2139-based therapy

Analysis of transaminase maxima and AUC during therapy reveal two flare populations



**“Non-productive flares”**  
(substantial HBsAg still present)  
not correlated with HBsAg response

5 inactive chronic HBV  
8 HBV rebound

**“Productive flares”**  
(occur with clearance of HBsAg below 10 IU/mL)  
correlated with HBsAg response

18 HBV functional cure\*  
17 inactive chronic HBV\*\*  
3 HBV rebound  
(2 withdrew early from therapy)

\*1 REP 401 patient has inactive chronic HBV at 12 weeks of follow-up

\*\*1 REP 401 patient has HBV functional cure at 12 weeks of follow-up

# Summary

Transaminase flares are rare during natural course of infection or with approved therapies  
Safe and correlated with declining HBV DNA, HBeAg seroconversion, HBsAg loss and functional cure

During REP 2139/pegIFN therapy, flares are highly prevalent (96% of participants)  
Not correlated with baseline HBV DNA, HBsAg, ALT or median hepatic stiffness  
Occur in HBeAg negative, HBeAg positive and HBV / HDV co-infection

In 98% of these cases (49/50) liver function remains unaltered  
Flares are otherwise asymptomatic in patients with mild to advanced fibrosis

HBsAg clearance during flares may define their prognostic value:

- < 3 log<sub>10</sub> from baseline (typically > 10 IU/mL): 61% HBV rebound, no functional cure
- > 3 log<sub>10</sub> from baseline (typically 1 – 0.00 IU/mL): 97% HBV functional control / cure\*

\* With completion of therapy

# A collaborative effort !

## Clinical evaluations:

**Montreal, Canada**  
Michel Bazinet

**Dhaka, Bangladesh**  
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**Chişinău, Moldova**  
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Gheorghe Placinta

**Liviu Iarovo**  
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Marion Peters  
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## Clinical virology and assay validation:

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**Los Angeles, USA**  
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**Bobigny, France**  
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**Abbott**  
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## Pre-clinical evaluations:

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**Reno, Nevada, USA**  
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## Mechanistic studies:

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Frauke Beilstein  
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**Ness Ziona, Israel**  
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