



# Session IV: The Role of Biomarkers in Drug Development

**Moderators:**

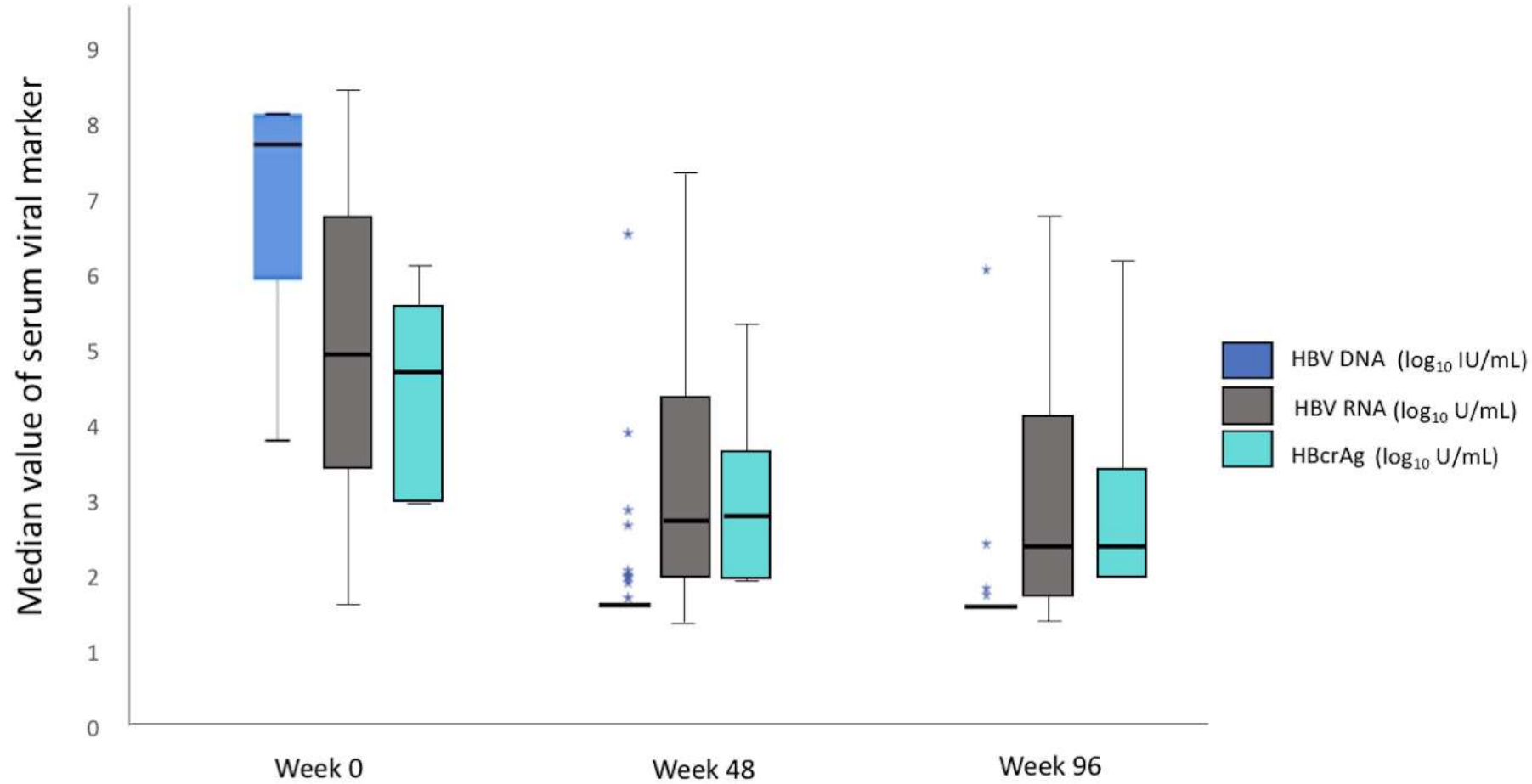
**Oliver Lenz, *Janssen Pharmaceuticals***

**Man-Fung Yuen, *The University of Hong Kong***

# Introduction

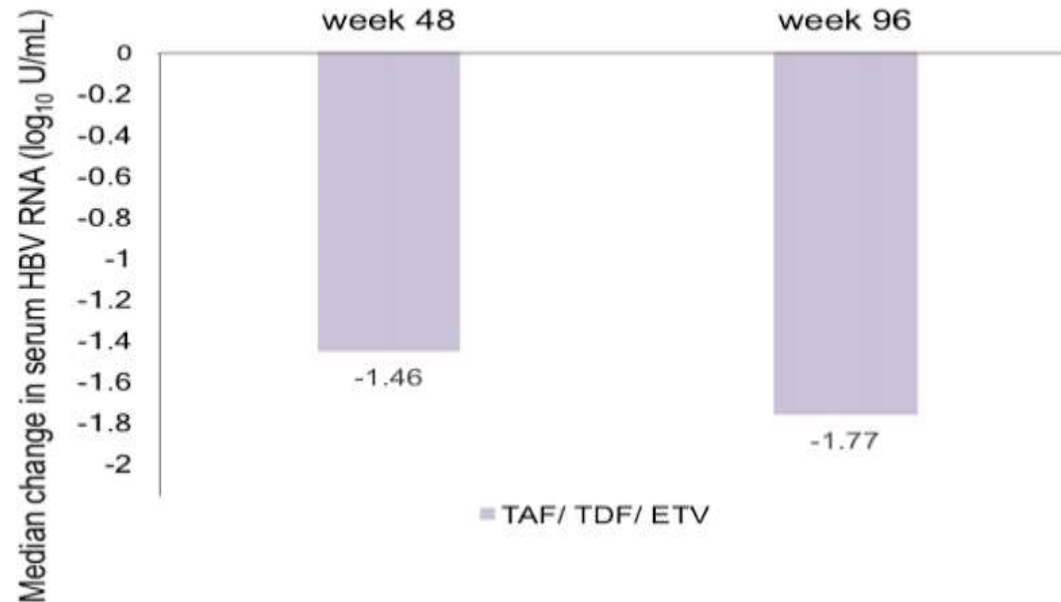
- HBV pgRNA and HBcrAg are mainly cccDNA driven viral markers
- Drugs affecting HBV DNA synthesis and/or pgRNA & other mRNAs
  - Nucleos(t)ide analogue
  - siRNA/ ASO
  - CpAM

# 2-year NUC treatment effects on HBV RNA and HBcrAg

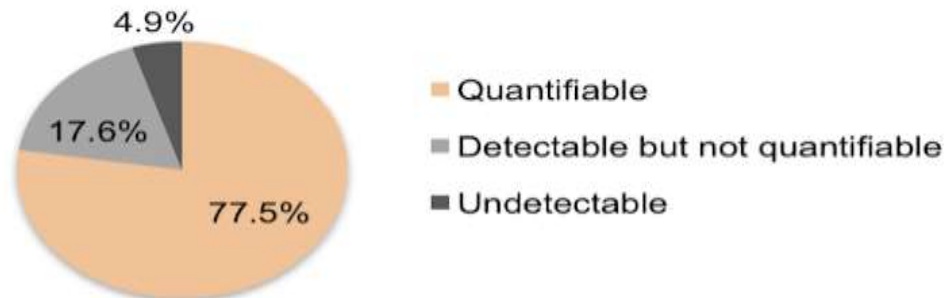


# High rate of HBV RNA detectability using a highly sensitive assay

## Changes of HBV RNA after 2 years of antiviral treatment



### Serum HBV RNA at week 96 of NA



# Continuous HBcrAg level decline on long-term NUC treatment

Treatment - naïve Chinese CHB patients treated for entecavir in the real world setting for up to 7 years

HBcrAg measurement at baseline, year 1, 5 and 7

Annual decline: 0.244 log KU/mL/year (p = 0.001)

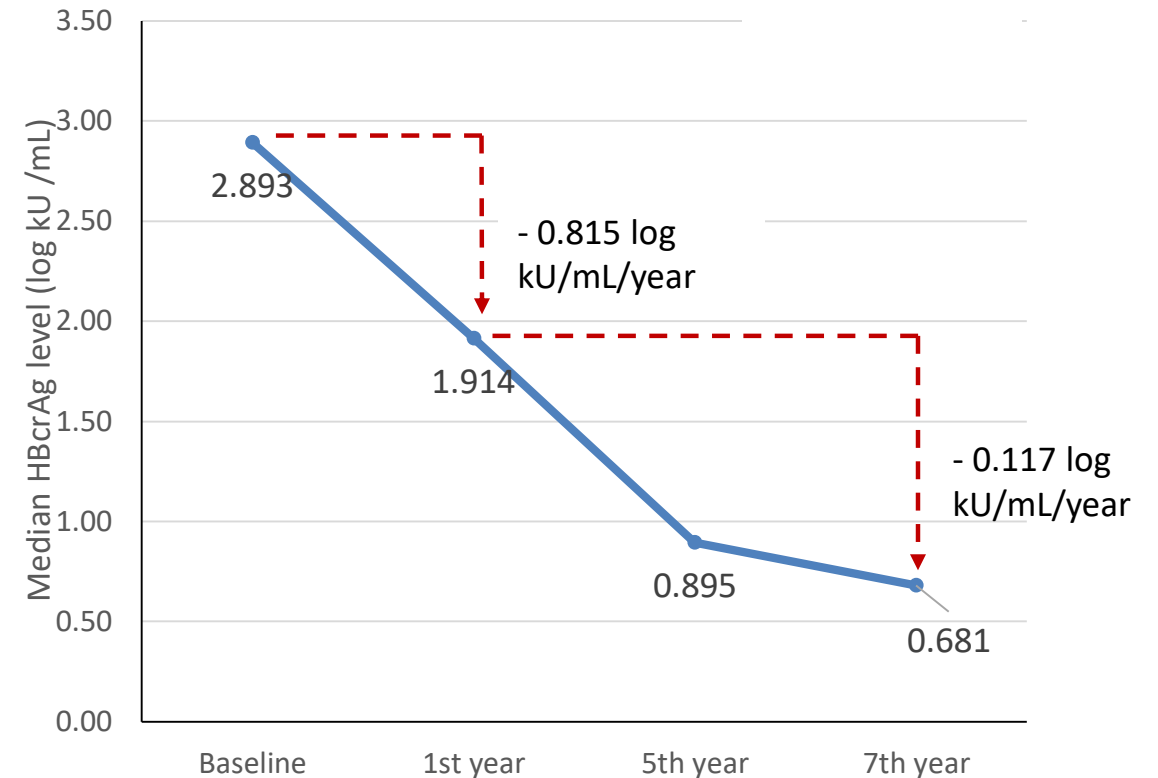
Median levels:

baseline 2.9 KU/mL

1<sup>st</sup> year 1.9 KU/mL

5<sup>th</sup> year 0.9 KU/mL

7<sup>th</sup> year 0.7 KU/mL

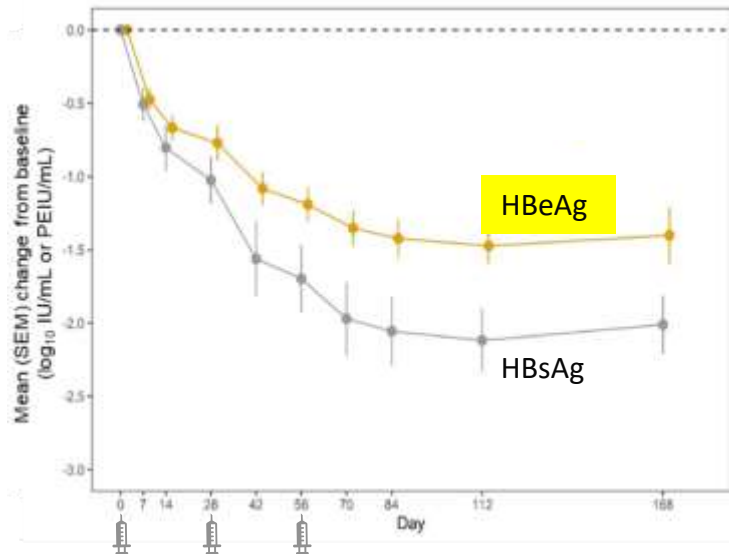


# Unmet need of new DAAs for HBV RNA and HBcrAg reduction

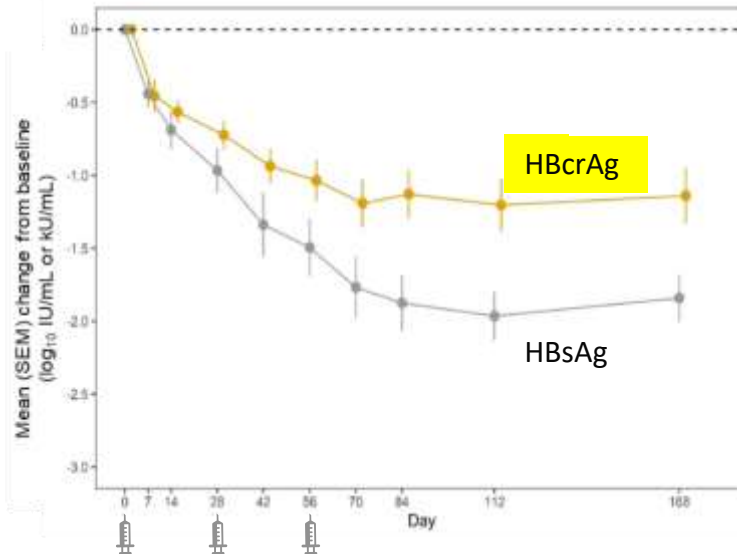
- Under long-term NUC treatment
  - Annual decline in HBcrAg levels is low (<0.25 log KU/mL/year)
  - Majority of patients had detectable and quantifiable HBV RNA
- DDAs with MOA expected to exert effects on HBV RNA and HBcrAg
  - siRNA
  - ASO
  - CpAM

# Effect of JNJ-3989 (siRNA) and NUC on viral markers

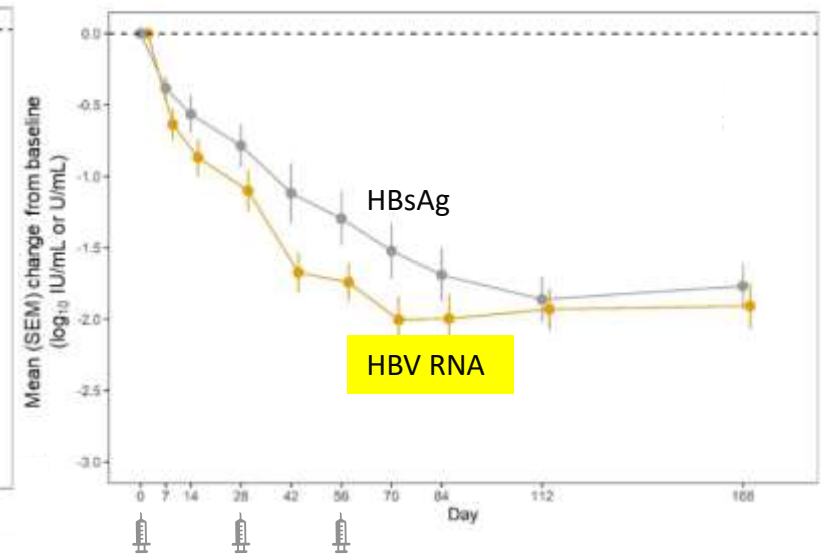
Mean change of viral markers, comparing HBeAg with HBeAg, HBcrAg and HBV RNA from Day 0 to Day 168 (N=40)\*



	Mean (SE); n change at Day 112
HBsAg, IU/mL	-2.11 (0.21); 12
HBeAg, PEIU/mL	-1.41 (0.12); 12



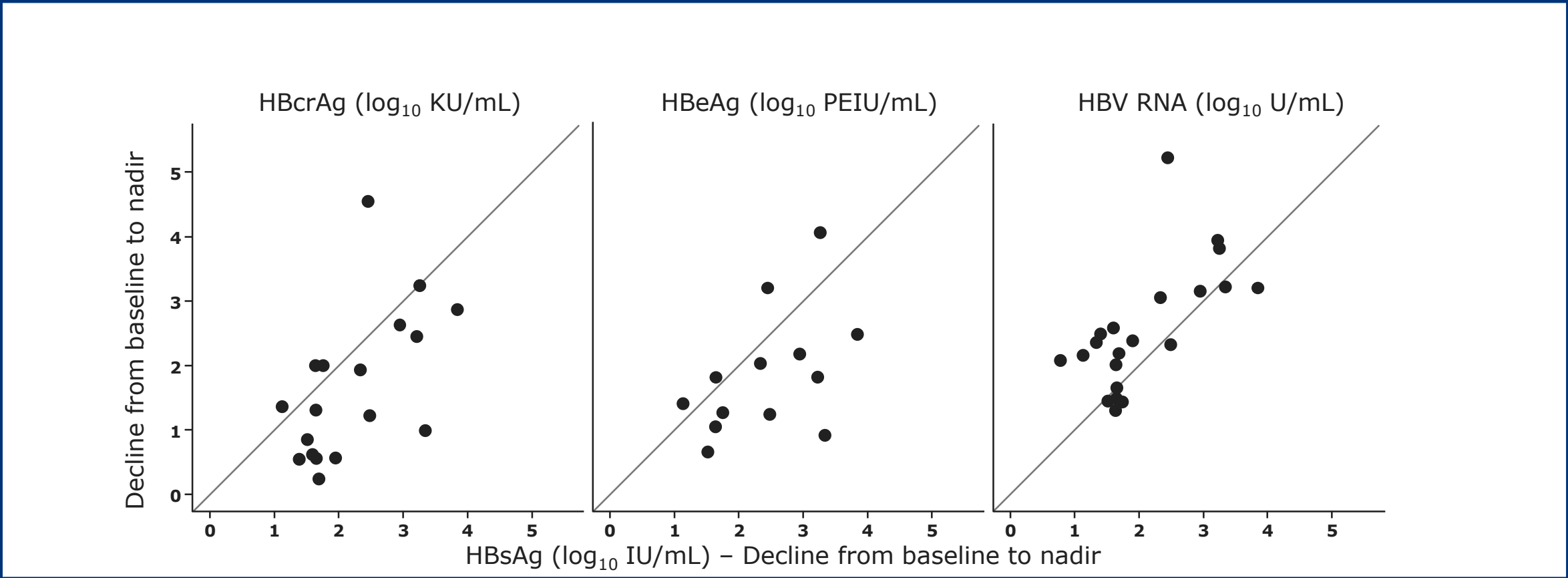
	Mean (SE); n change at Day 112
HBsAg, IU/mL	-1.97 (0.16); 18
HBcrAg, kU/mL	-1.20 (0.17); 18



	Mean (SE); n change at Day 112
HBsAg, IU/mL	-1.86 (0.15); 21
HBV RNA, U/mL	-1.93 (0.14); 21

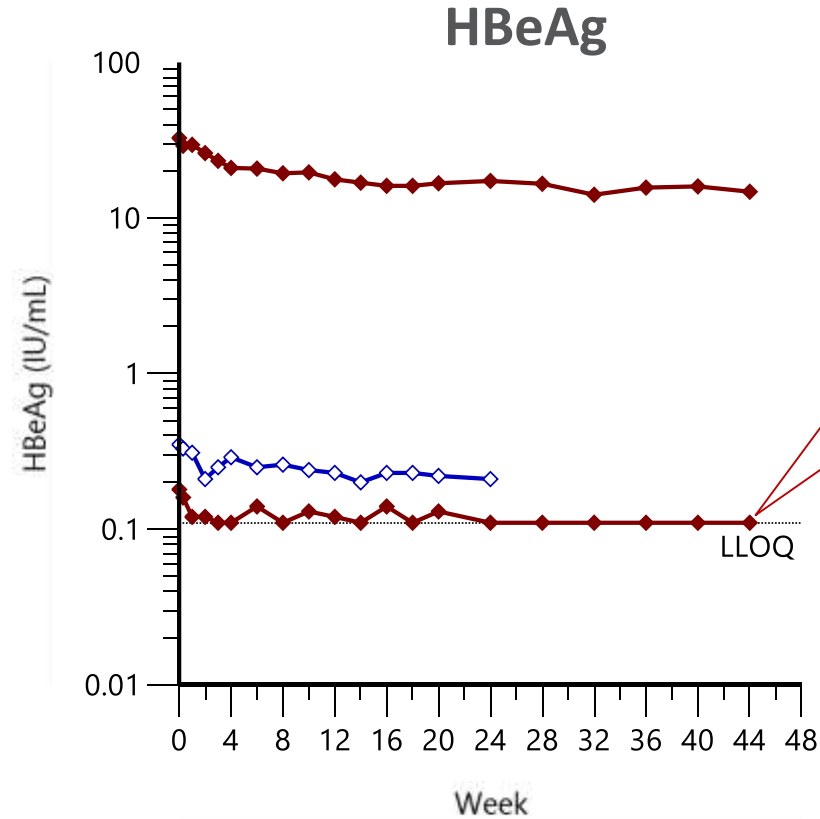
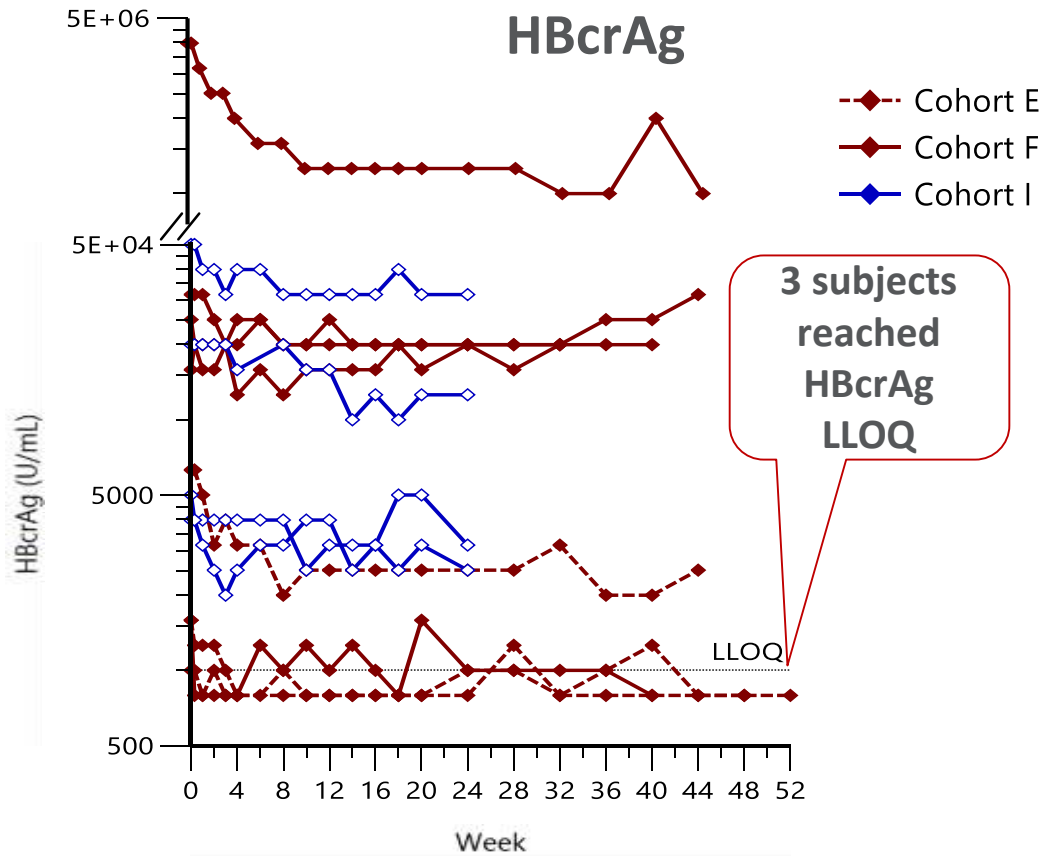
Reductions in HBsAg and HBV RNA were generally to be more pronounced compared with HBeAg and HBcrAg

# Positive correlations between HBsAg decline and HBeAg, HBcrAg and HBV RNA





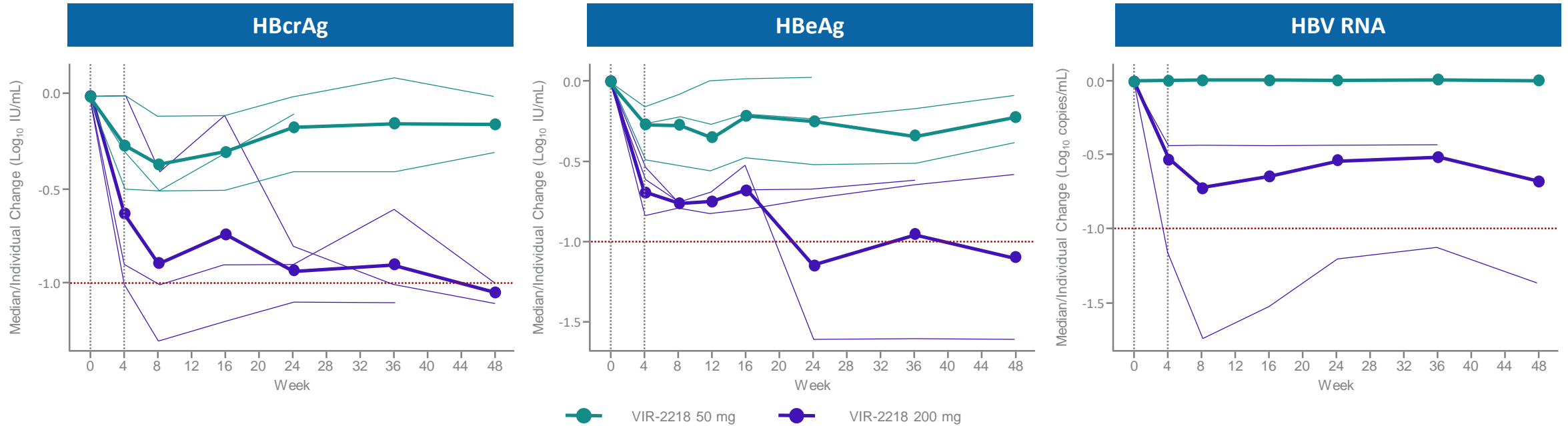
# Effect of AB-729 (siRNA) and NUC on viral markers



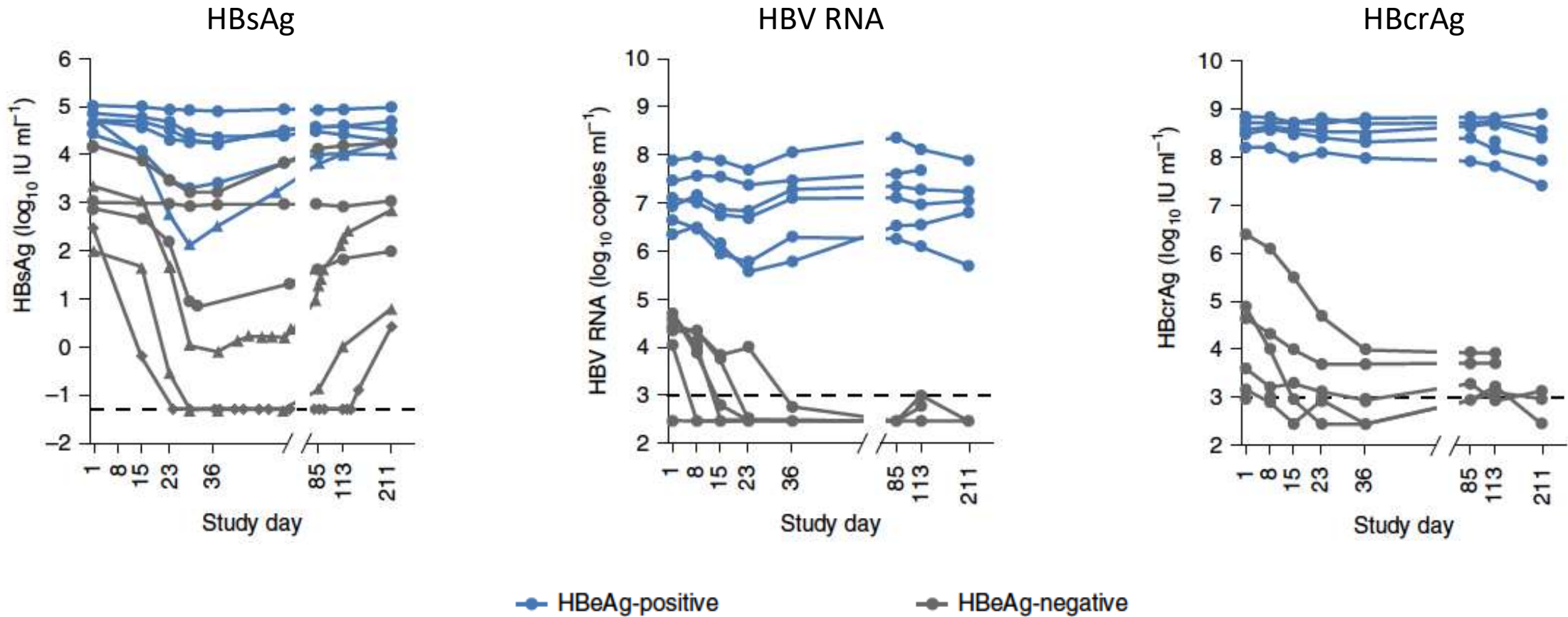
Cohort	N	Mean (SE) Baseline HBcrAg	Max HBcrAg decline
E	3	2,965 (1,681) U/mL	-0.5 log <sub>10</sub> U/mL
F	5	811,049 (792,522) U/mL	-0.6 log <sub>10</sub> U/mL
I	4	19,766 (10,756) U/mL	-0.3 log <sub>10</sub> U/mL

Cohort	N	Baseline HBeAg (IU/mL)	Max HBcrAg decline to date
F	2	0.18, 32.7	-0.4 log <sub>10</sub> U/mL
I	1	0.35	-0.2 log <sub>10</sub> U/mL

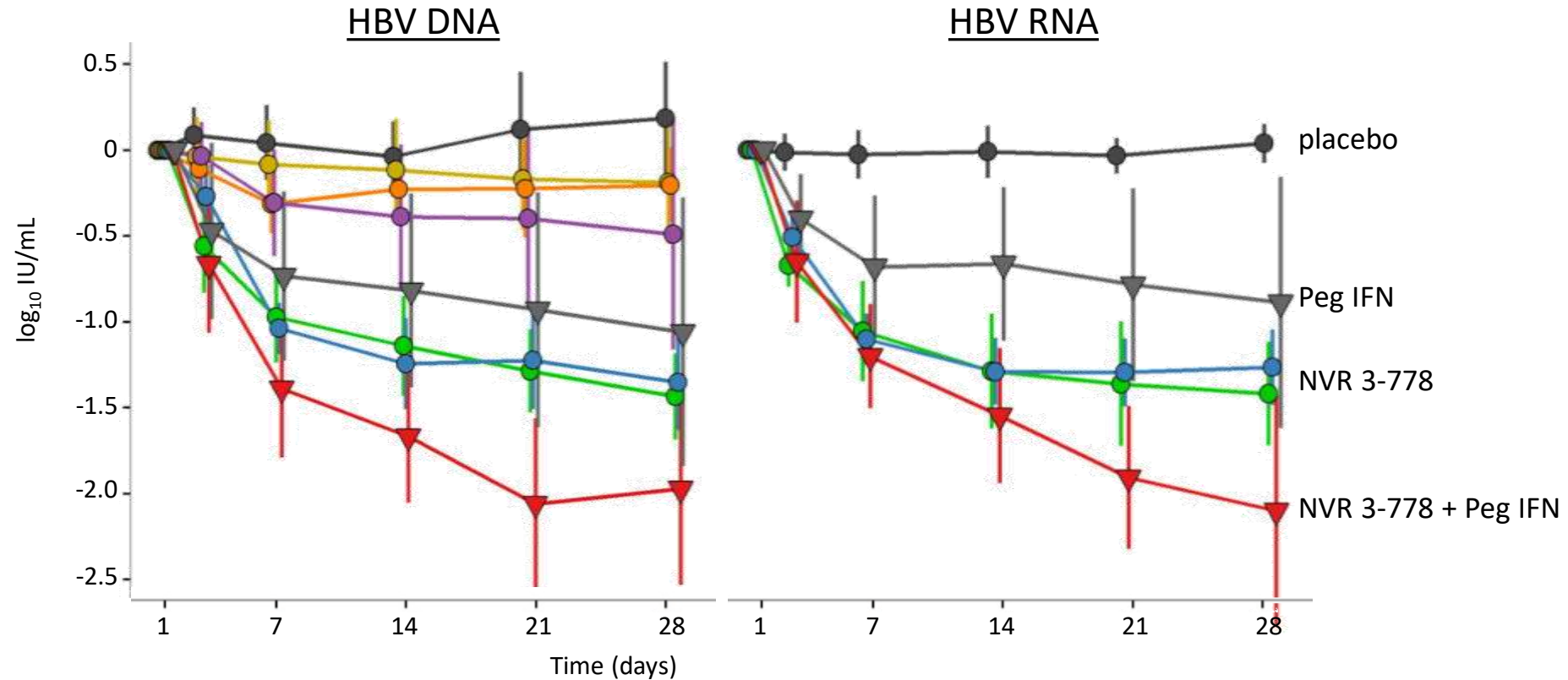
# Effect of VIR-2218 (siRNA) and NUC on viral markers



# Effect of Bepirovirsen (ASO) on viral markers

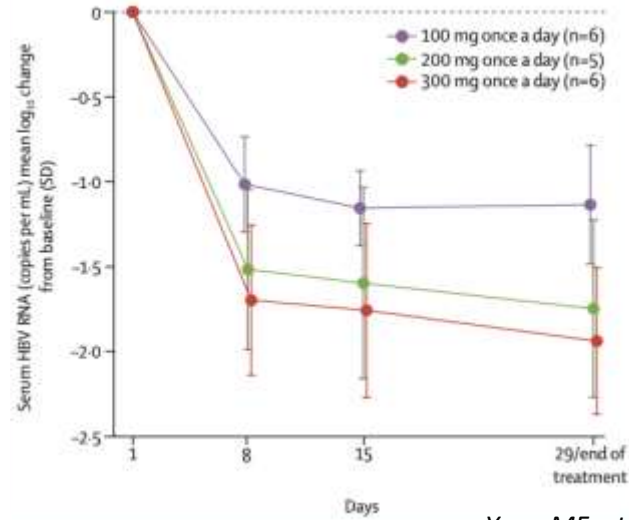


## Effect of 4-week CpAM (NVR 3-778) + Peg IFN on HBV RNA



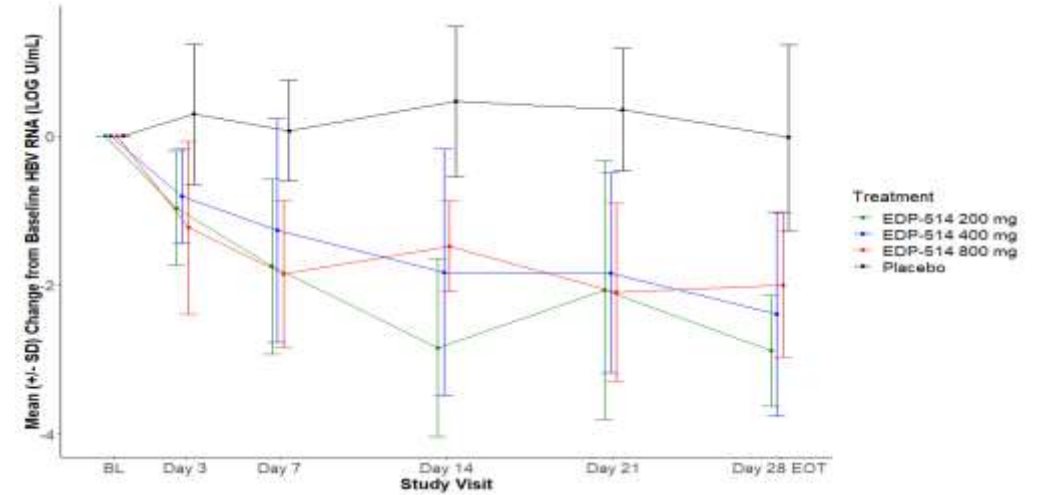
# Effect of 4-week newer different CpAMs on HBV RNA

**ABI-H0731 (Vebicorvir)**



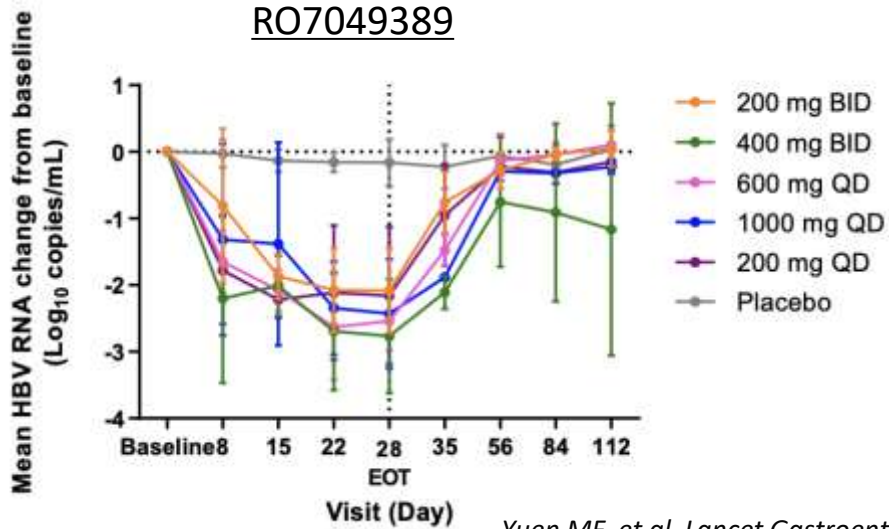
Yuen MF, et al. *Lancet Gastroenterol Hepatol* 2020;5:152-66

**EDP-514**



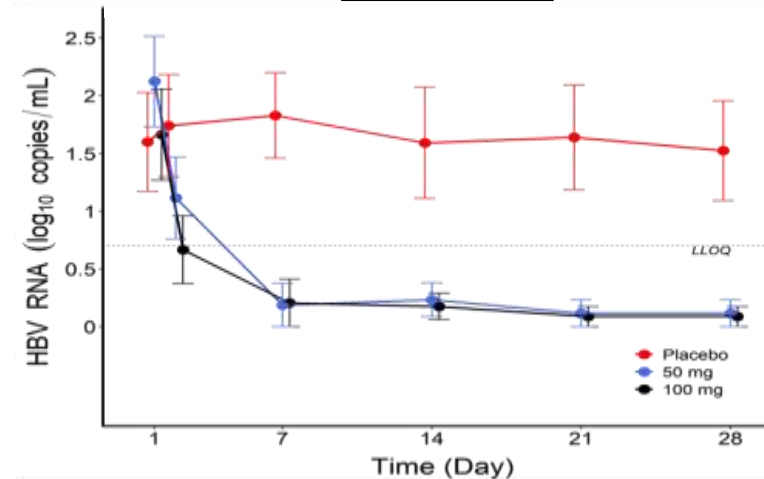
Yuen MF et al. *AASLD* 2021;74;505A-506A

**RO7049389**



Yuen MF, et al. *Lancet Gastroenterol Hepatol* 2021;6:723-32

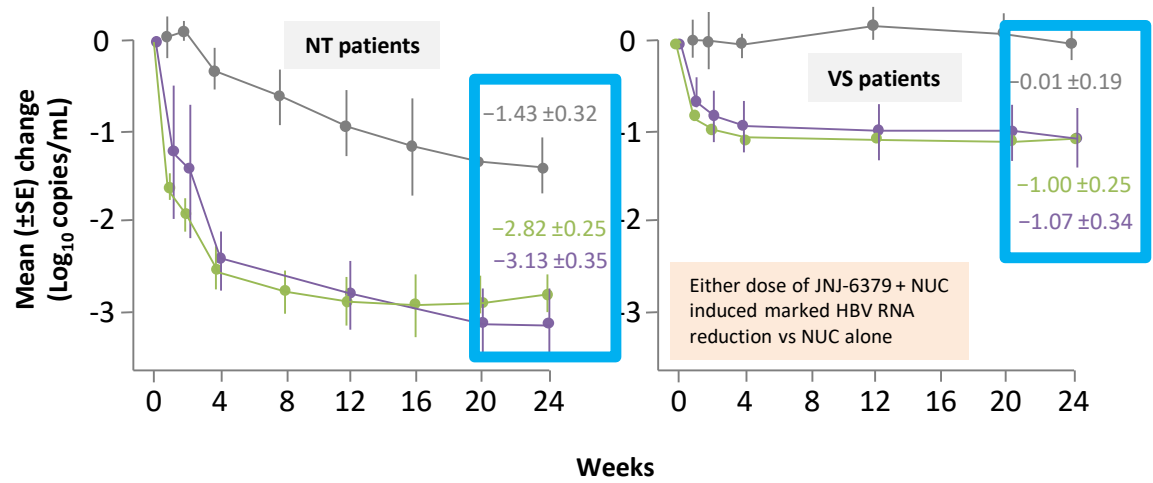
**ALG-000184**



Gane E et al. *AASLD* 2021;74;516A-517A

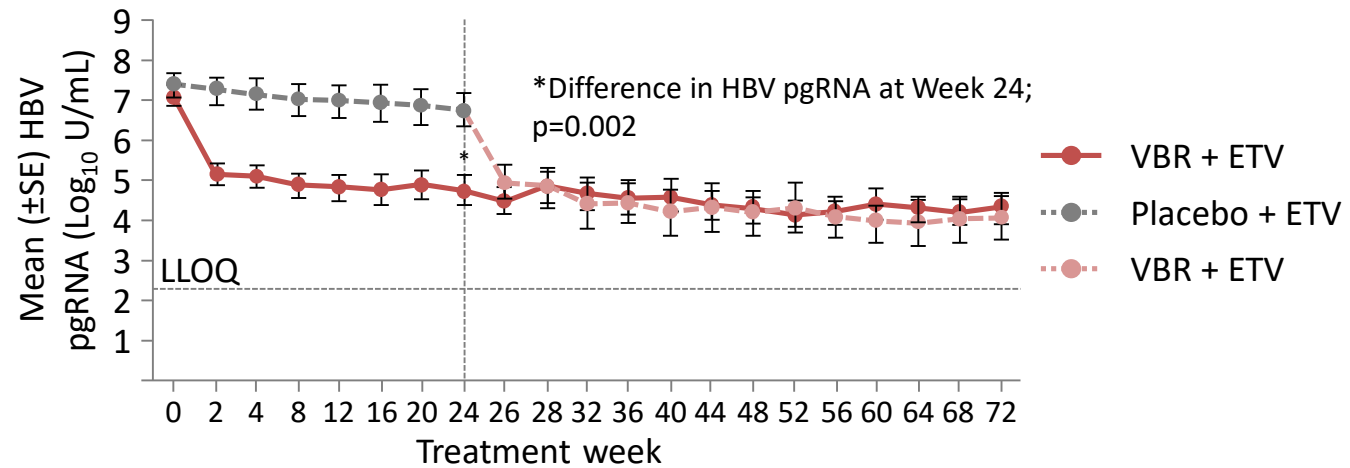
# Effect of 24-week JNJ 6379 & Vebicorvir on HBV RNA

Mean  $\pm$ SE change from baseline in HBV RNA through Week 24 (HBeAg+ and -)



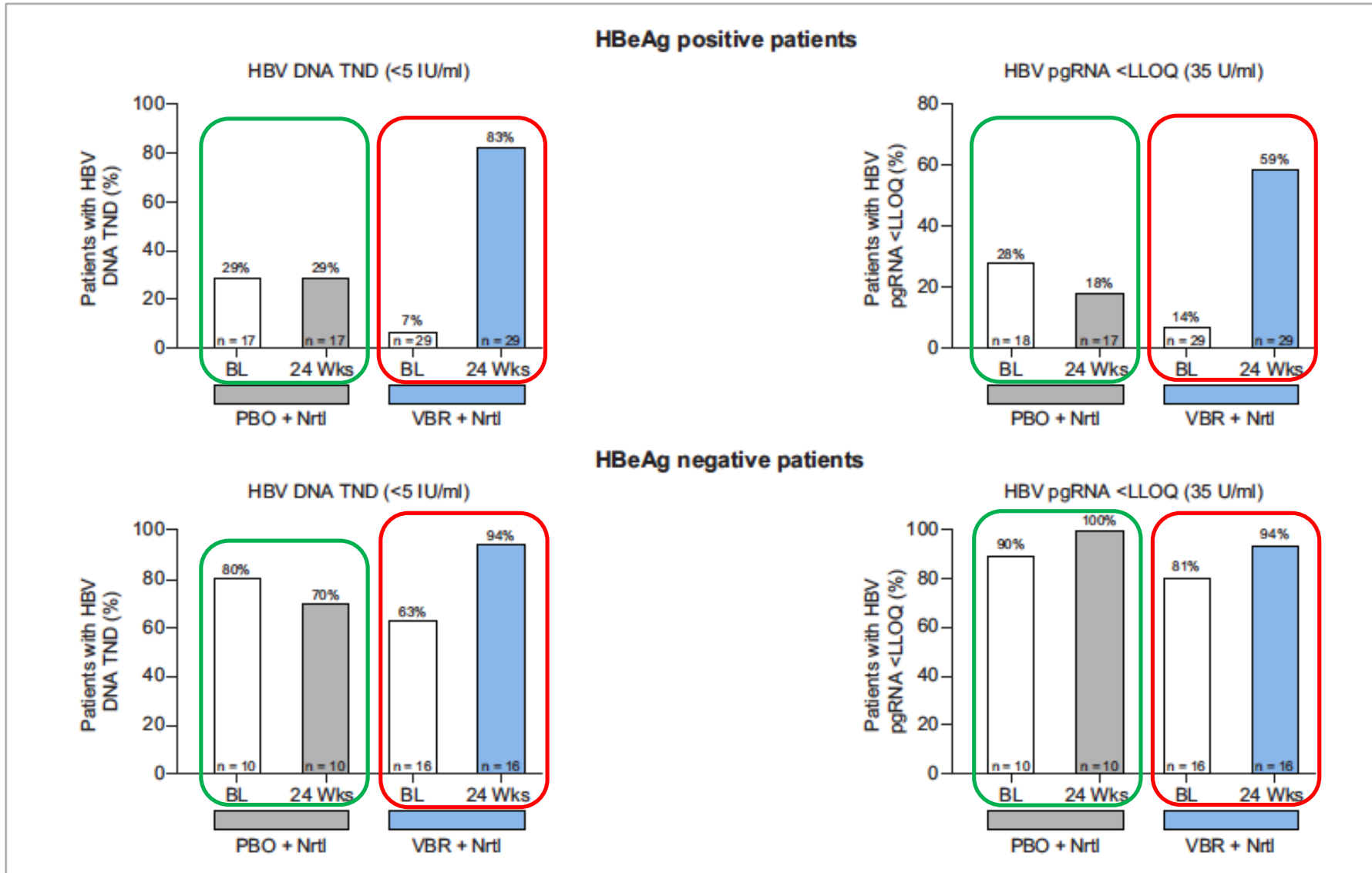
Janssen H, et al. EASL dILC2020. #BP12

pgRNA in treatment-naive patients



Yuen MF, et al. EASL dILC2020. #LBP30

# Effect of 24-week ABI-H0731 (Vebicorvir) on HBV RNA and HBcrAg (in NUC-treated patients)

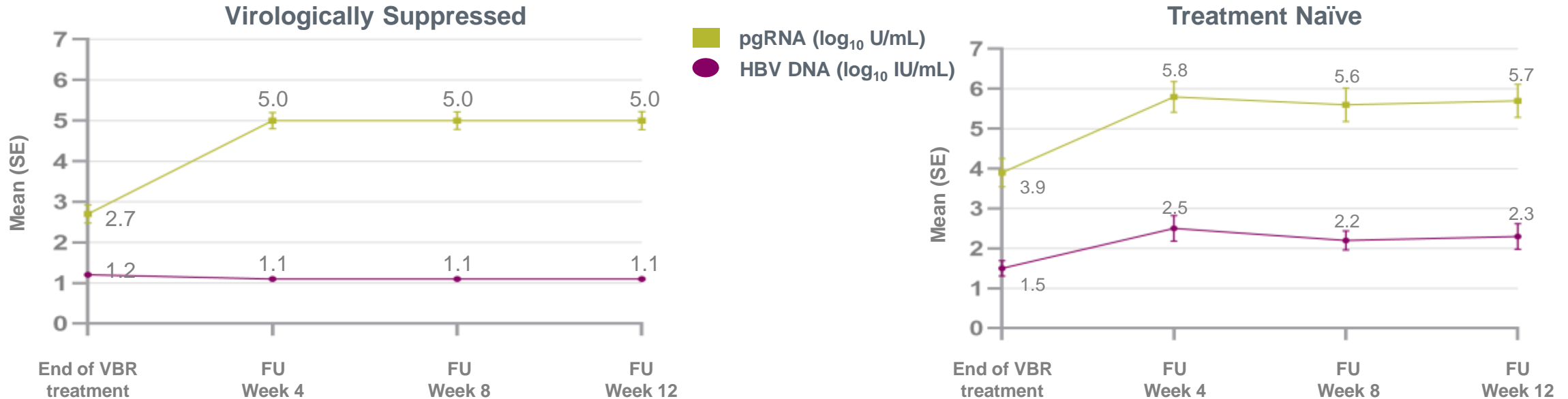


**HBcrAg (LSM BL to wk 24)**

HBeAg +ve  
VBR + NA -0.164  
PBO + NA -0.13

HBeAg -ve  
VBR + NA -0.073  
PBO + NA -0.056

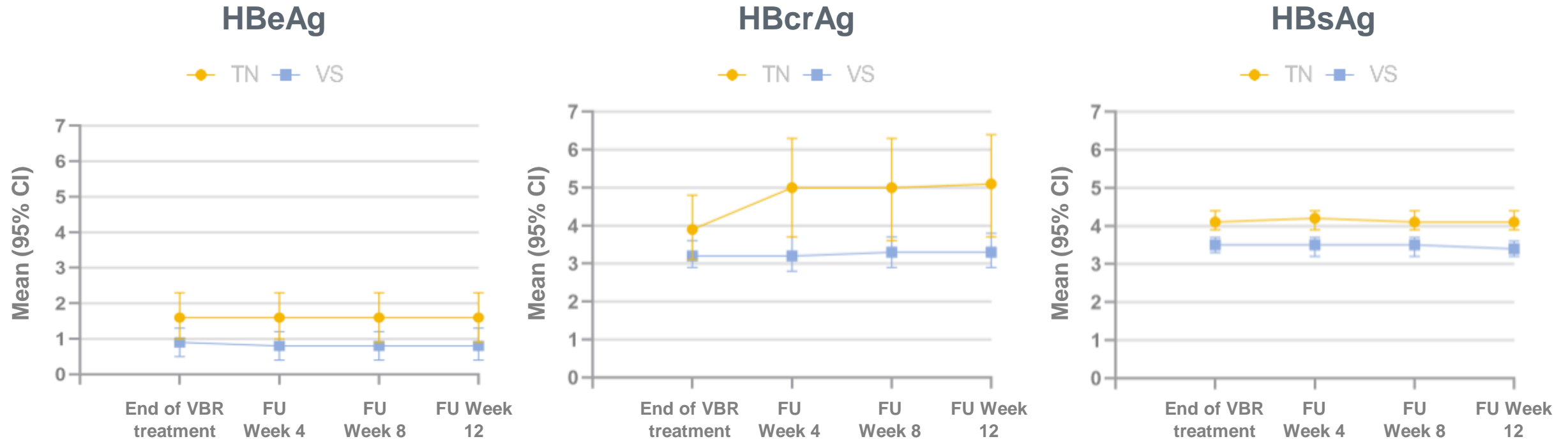
# Effect of withdrawal of ABI-H0731 (Vebicorvir) on HBV RNA in NUC-treated and -untreated HBeAg +ve patients



- Four weeks after VBR discontinuation, pgRNA increased by approximately 2 log<sub>10</sub> U/mL in both VS and TN patients
- At the same timepoint, HBV DNA exhibited a mean (SD) increase of 1.0 (0.85) log<sub>10</sub> IU/mL in TN patients but remained unchanged in VS patient



# Effect of withdrawal of ABI-H0731 (Vebicorvir) on HBcrAg in NUC-treated and -untreated patients



- There were no statistically significant changes in HBeAg, HBcrAg, or HBsAg levels in either treatment group after VBR discontinuation, although numerical 1 log increase in HBcrAg levels in TN patients

# Conclusions

- HBV RNA and HBcrAg are important HBV markers for monitoring for both disease outcome and drug treatment
- Although NUC is able to reduce both markers, a considerable proportion of patients still have detectable levels
- New DAAs are able to further reduce HBV RNA and HBcrAg
  - Associate with clinical benefit (enhance the chance of sustained viral response/ functional cure after stopping therapy)
  - Confirm the target engagement and MOA of DAAs
  - Allow comparison of efficacies of different DAAs

Thank you