Where will RNAi fit in the era of finite therapies?

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HepDart 2019

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Disclosures

- I am an employee and shareholder in Arrowhead Pharmaceuticals, Inc.

- Given that this is an invited lecture, the opinions expressed can be considered to represent my own and not those of Arrowhead or Janssen.

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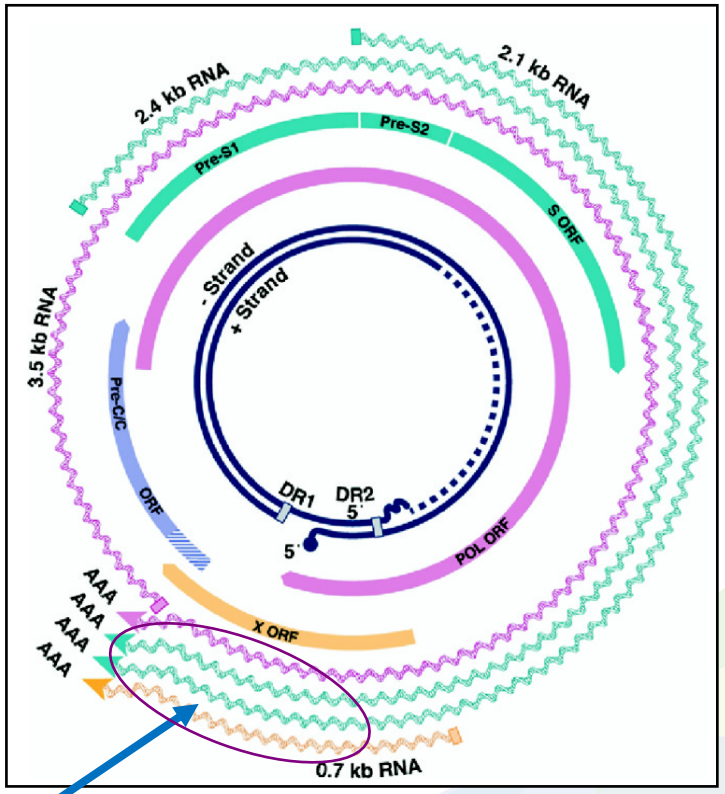
Thinking in 2011 - All HBV RNA Derived from cccDNA Targetable with One siRNA – An All Targets DAA?

- All cccDNA-derived HBV transcripts, including pregenomic RNA, overlap and share the same polyadenylation termination signal.

HBV Transcript Map



Single siRNA can reduce all HBV proteins

Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

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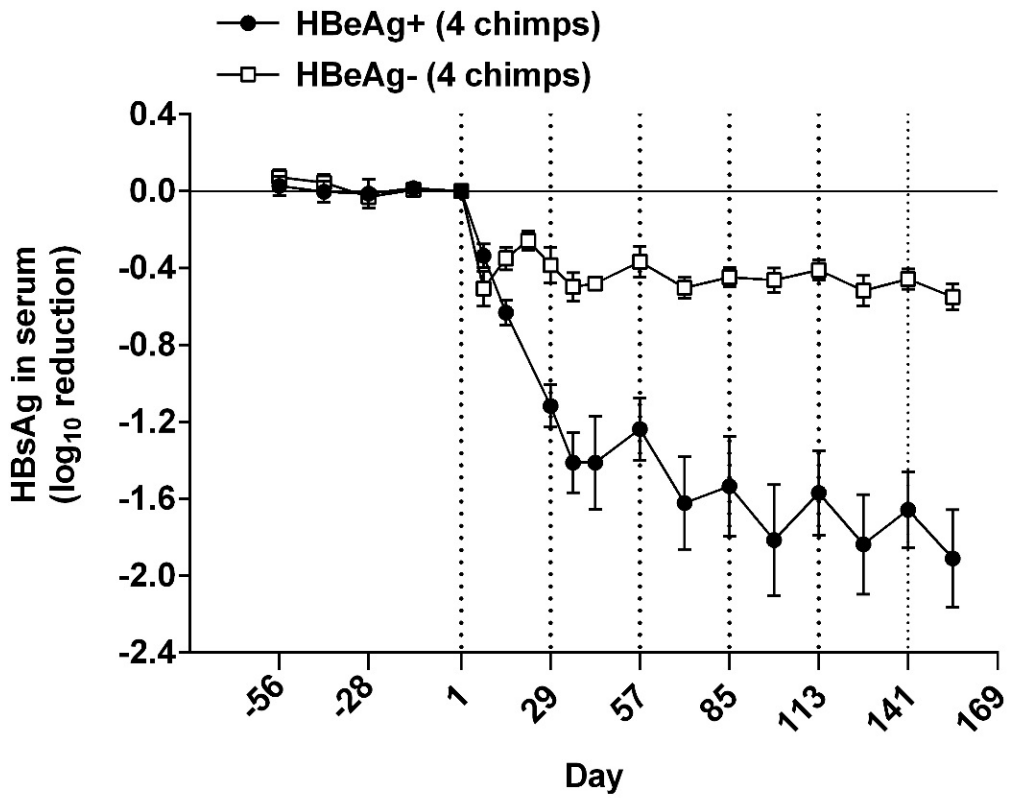
Differential HBsAg Reduction Observed in Chimpanzees with ARC-520



HBeAg-
0.5 - 0.9 log_{10} reduction at nadir

HBeAg+
1.5 - 2.7 log_{10} reduction at nadir

HBeAg positive responded better than HBeAg negative chimps

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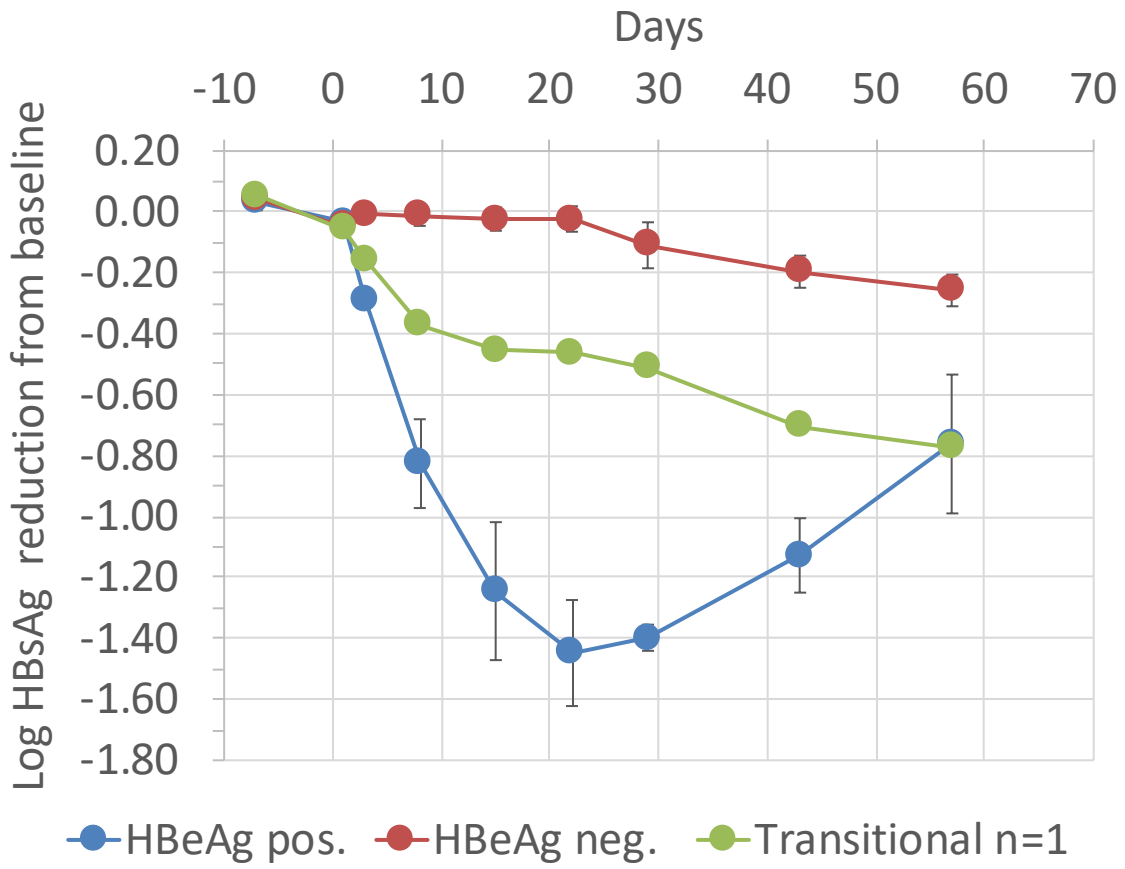
Wooddell, Yuen et al, Sci Trans Med 2017

Differential Response Also Seen in Treatment Naïve Chronic HBV Patients

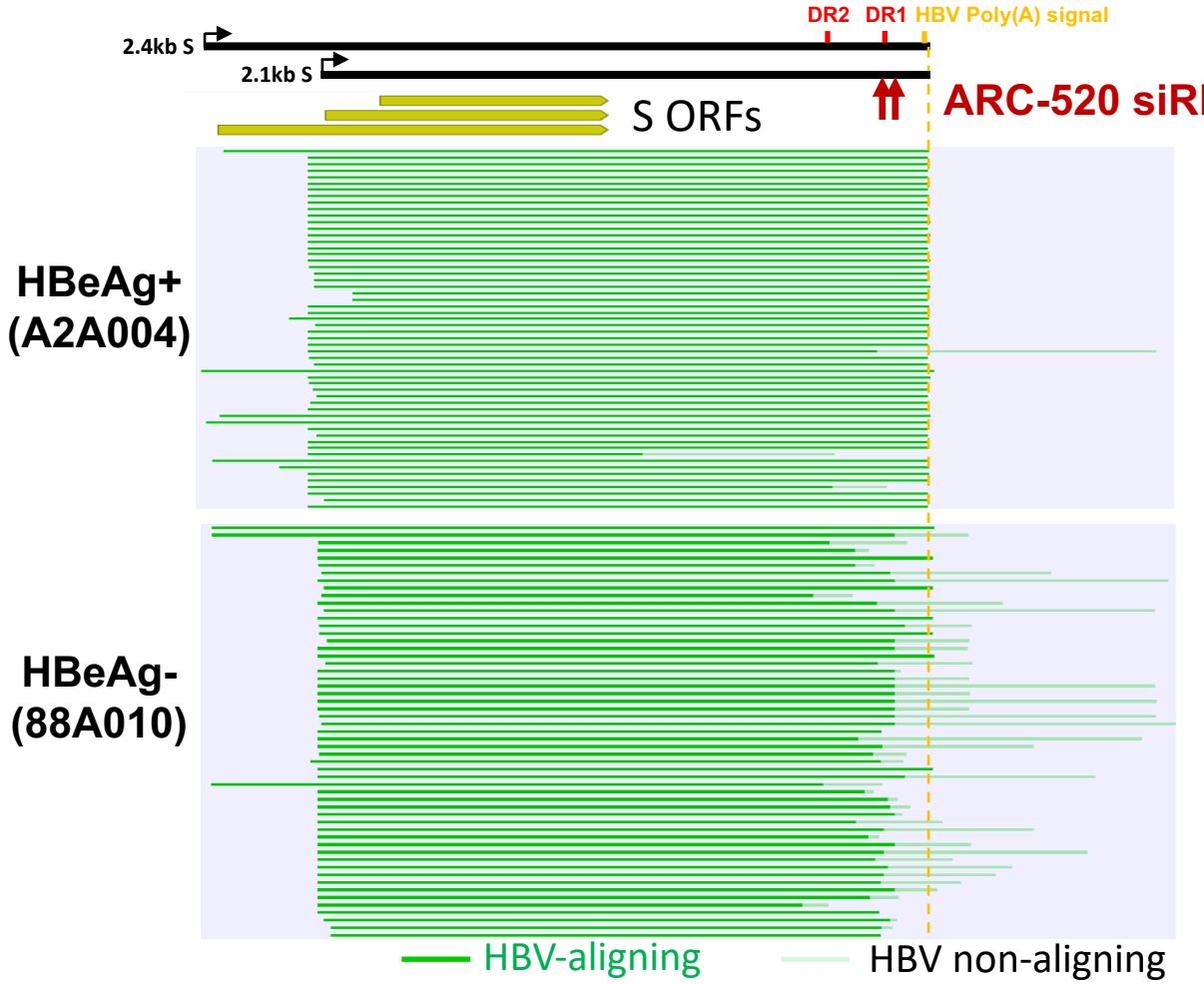


- Deep knockdown of HBsAg in HBeAg positive patients after a single dose

Wooddell, Yuen et al, Sci Trans Med 2017

HBV Transcripts in HBeAg+ vs. HBeAg- Chimps

PacBio Single Molecule Real-Time (SMRT) Sequencing



HBeAg+

- **Most S transcripts terminate near HBV poly(A) signal as expected**

HBeAg-

- **Majority of S transcripts are fused at the 3' end to chimp sequence**
- **Fusion points typically between DR2 and DR1. Expected if transcripts arose from integrated HBV dslDNA**

S transcripts in HBeAg- chimps often lack target sites for ARC-520

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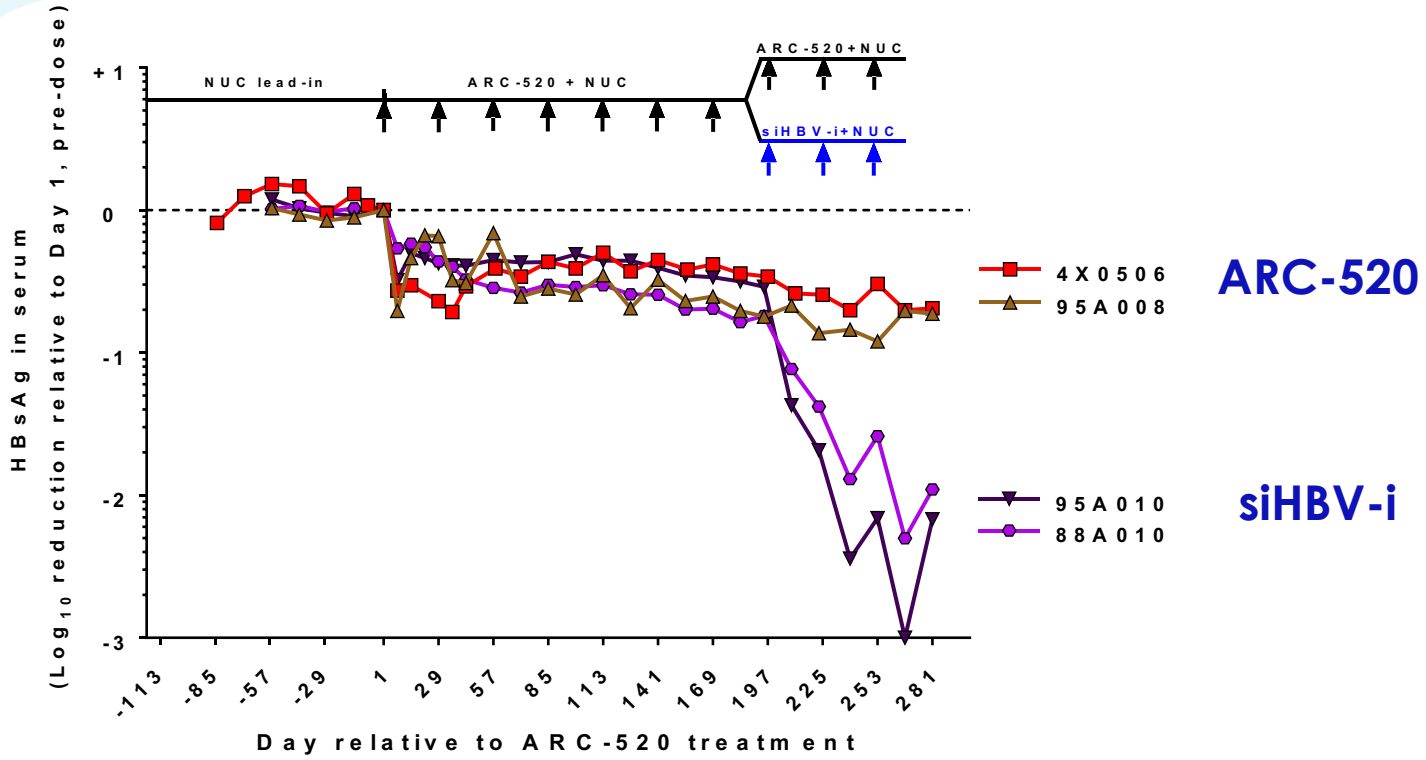
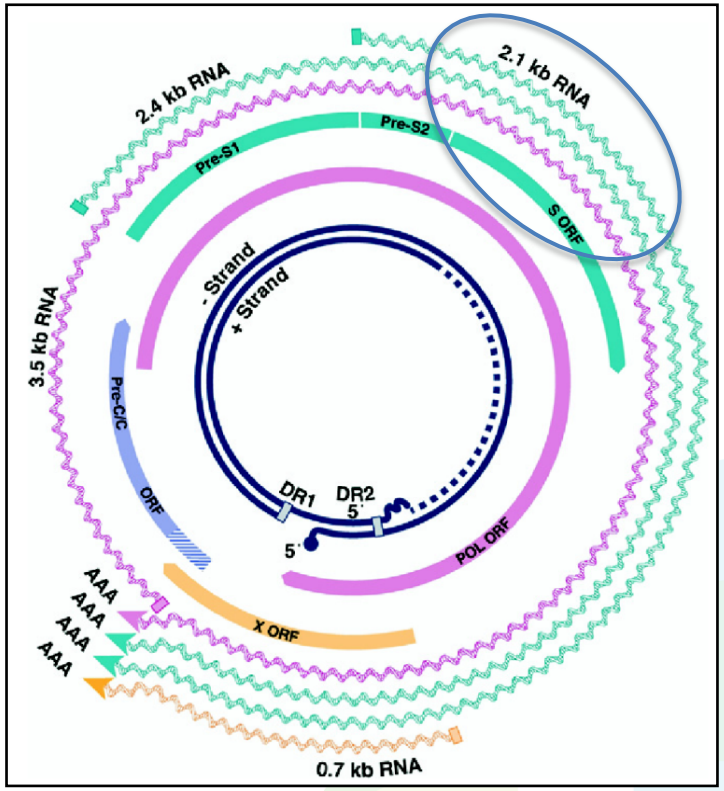
Wooddell, Yuen et al, Sci Trans Med 2017

siRNA Designed to Target RNA Derived From HBV Integration Products in HBeAg- Chimps



ARC-520

siHBV-i



- siHBV-i targets HBsAg RNA even if expressed from integrated HBV DNA
- siHBV-i gave deep reductions in HBsAg in HBeAg- chimps, similar to those observed using ARC-520 in HBeAg+ chimps

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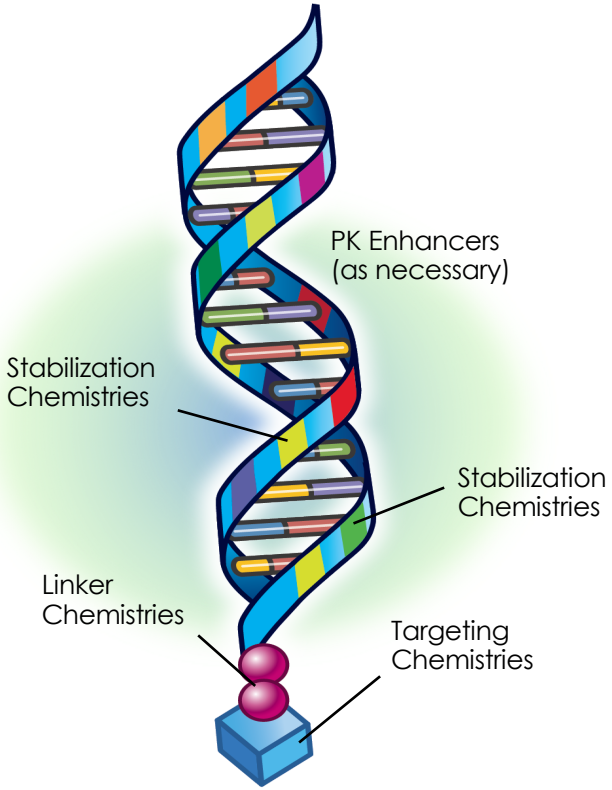
Wooddell, Yuen et al, Sci Trans Med 2017

JNJ-3989: Key Design Elements for the Current Generation

The Wish List:

- Addresses full HBV transcriptome
  - Works for cccDNA *and* integrated-derived transcripts
- Powerful HBsAg reduction
- Subcutaneous dosing
- Multiple triggers to avoid resistance development and broaden coverage
  - We seem to be the only RNAi employing this strategy and the need is still theoretical
- Efficacy and safety in HBV patients

Targeted RNAi Molecules - TRiM™ Platform



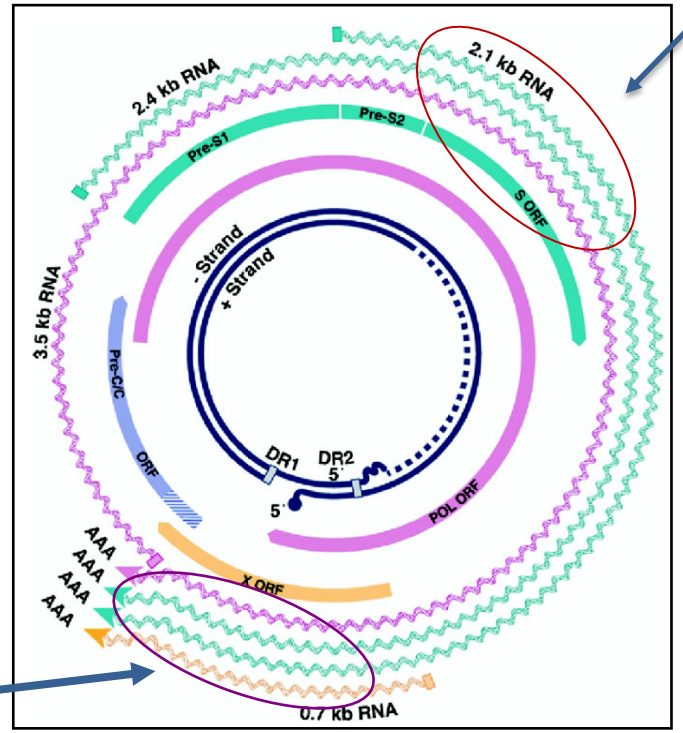
- Growing libraries of targeting agents, linkers, stabilization chemistries, and PK enhancers enable modular approach… in a simple structure:
  - Faster time to clinical candidates
  - Multiple routes of administration
  - Simplified manufacturing at reduced cost
  - Wide safety margins
  - Taking RNAi to the liver, lung, and other tissues

Importance of Integrated DNA as mRNA Source has Changed RNAi Strategy

- All HBV transcripts, including pregenomic RNA, overlap and terminate with the same polyadenylation signal

New S Trigger

HBV Transcript Map



Single siRNA can reduce all mRNA from cccDNA but can miss integrated-derived mRNA

Ghany & Liang (2007), *Gastroenterology* **132**: 1574-1585

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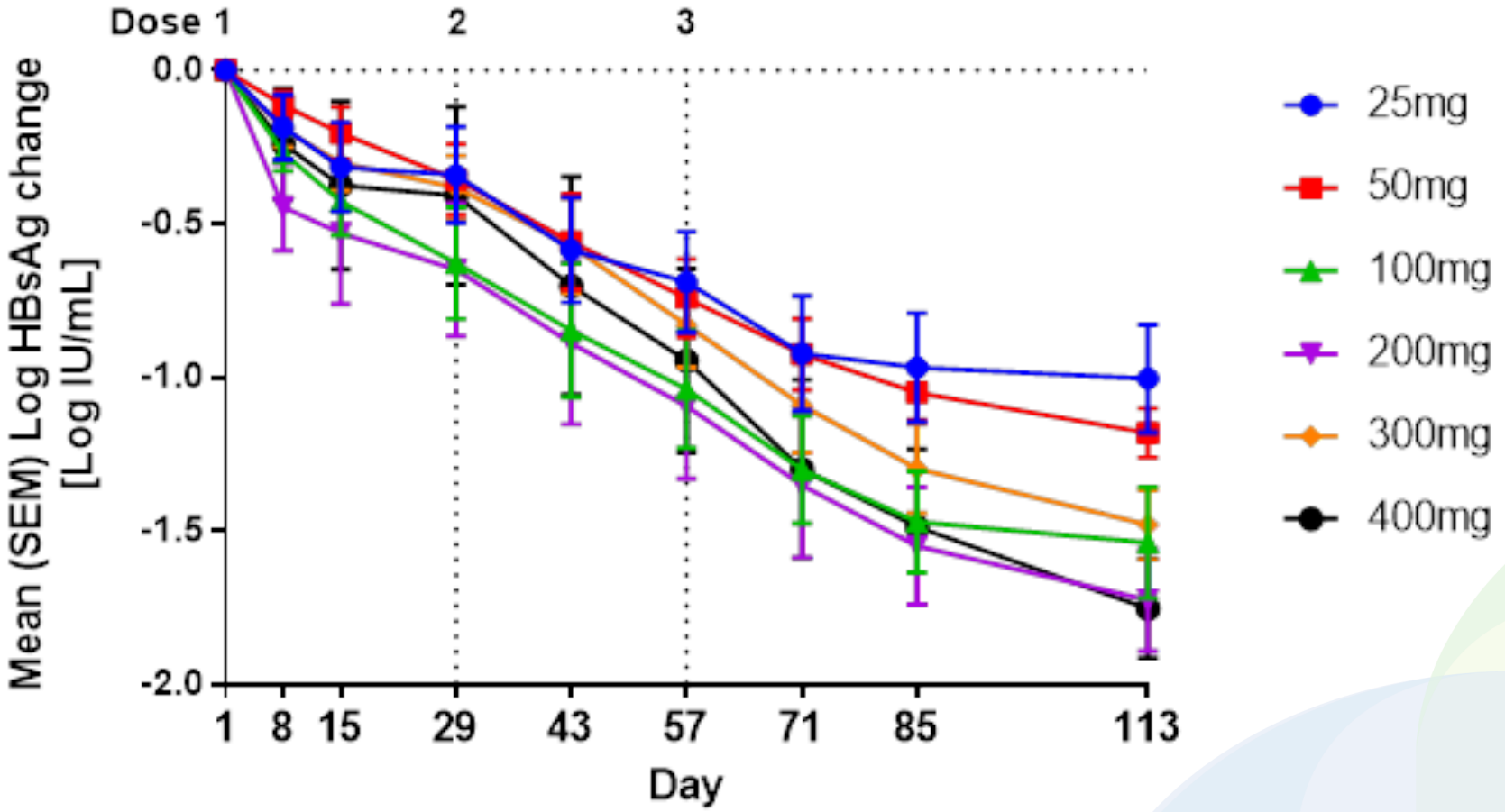
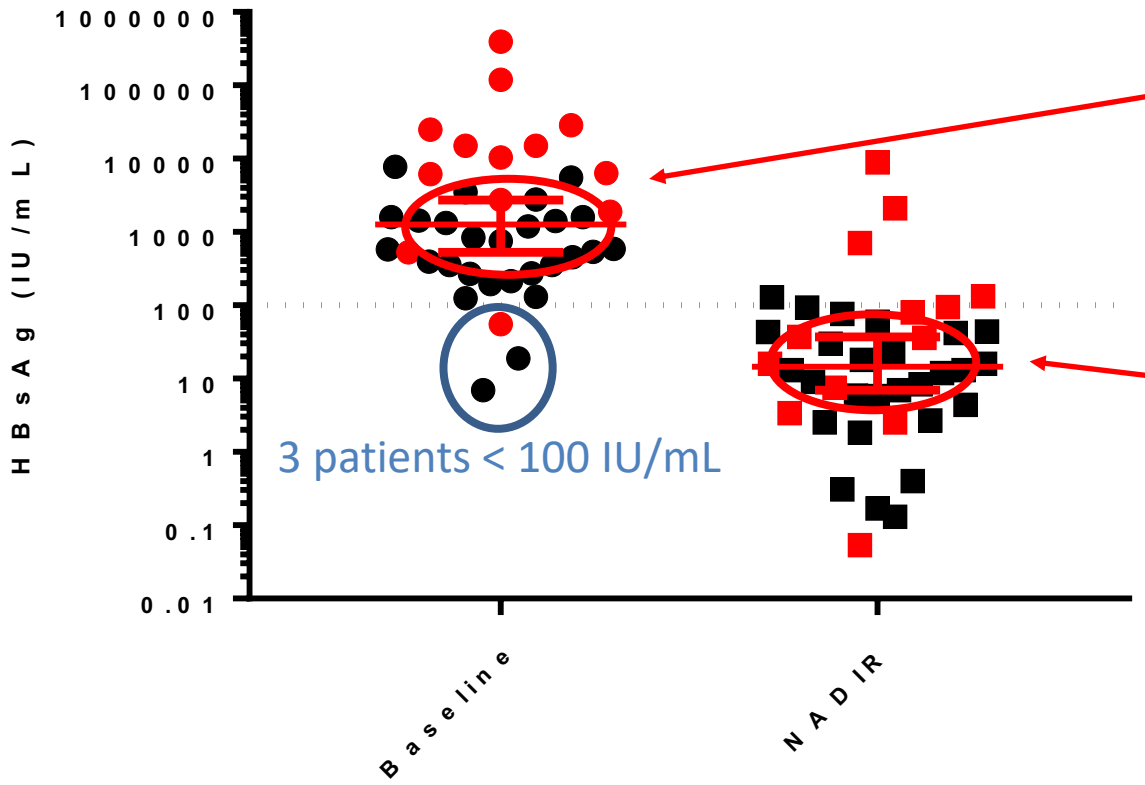
Monthly JNJ-3989 plus a NUC generates strong HBsAg knockdown



Gane Edward, et al. AASLD 2019

Most Patients Achieve HBsAg <100 IU After 3 Monthly Doses of 100-400 mg



Baseline

Median: 1263 IU/mL
Min: 7.0 IU/mL
Max: 392,800 IU/mL

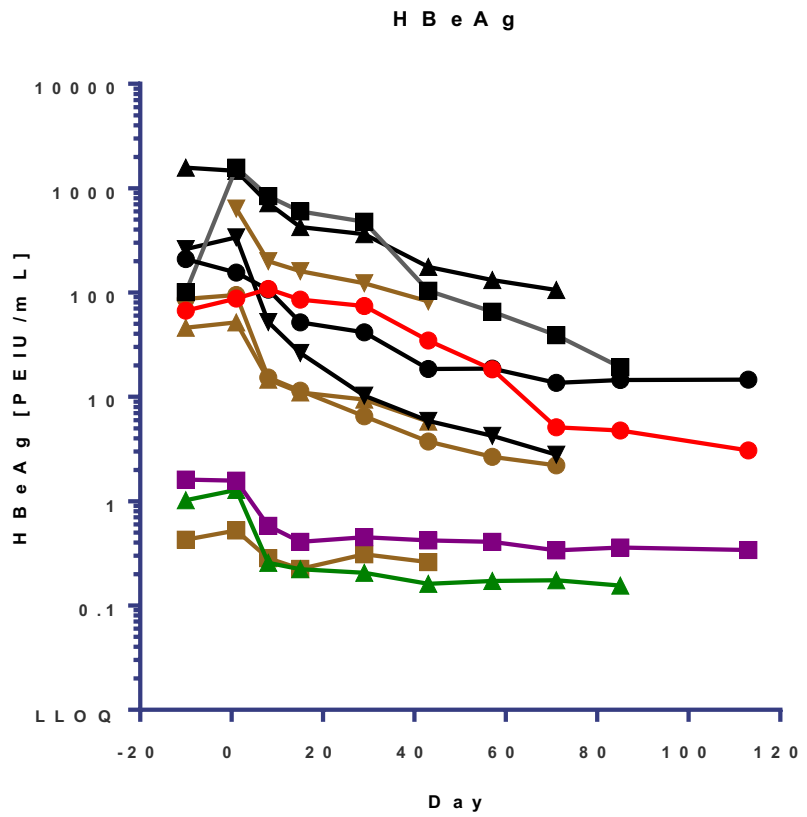
NADIR

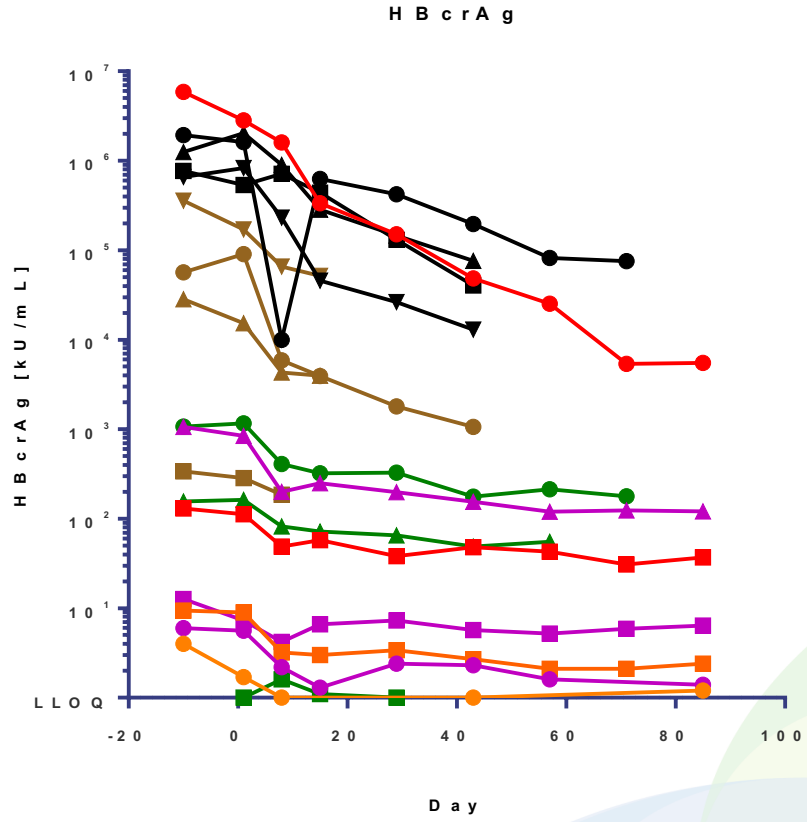
Median: 14.5 IU/mL
Min: 0.05 IU/mL
Max: 8950 IU/mL

Red Points: HBeAg positive patients
Black Points: HBeAg negative patients

Yuen MF et al. ILC 12 April 2019, PS-080

Individual HBeAg and HBcrAg Also Showing Response

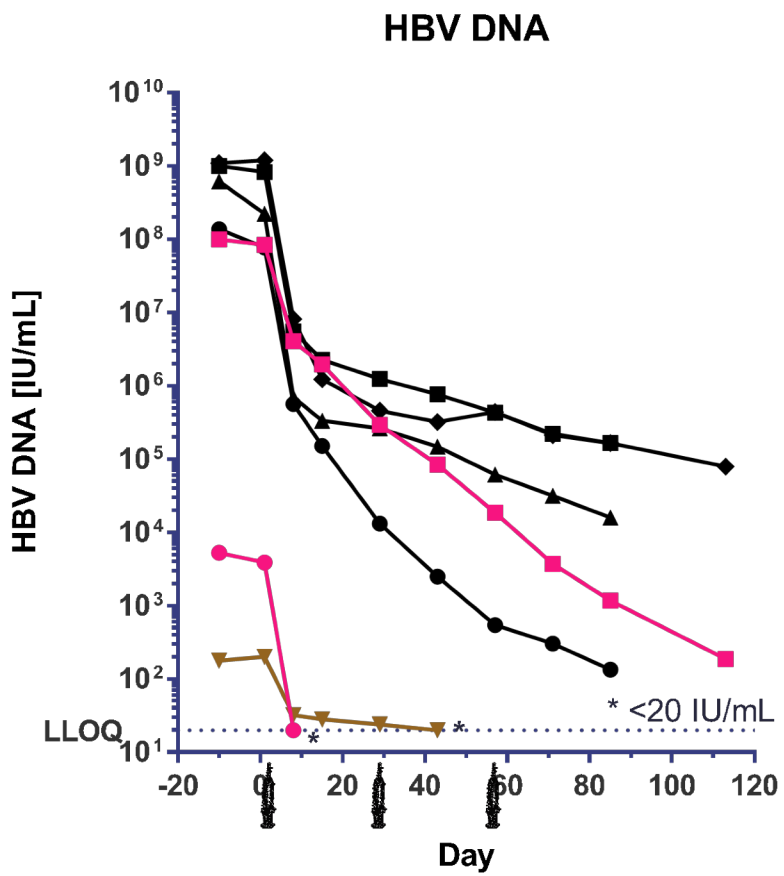


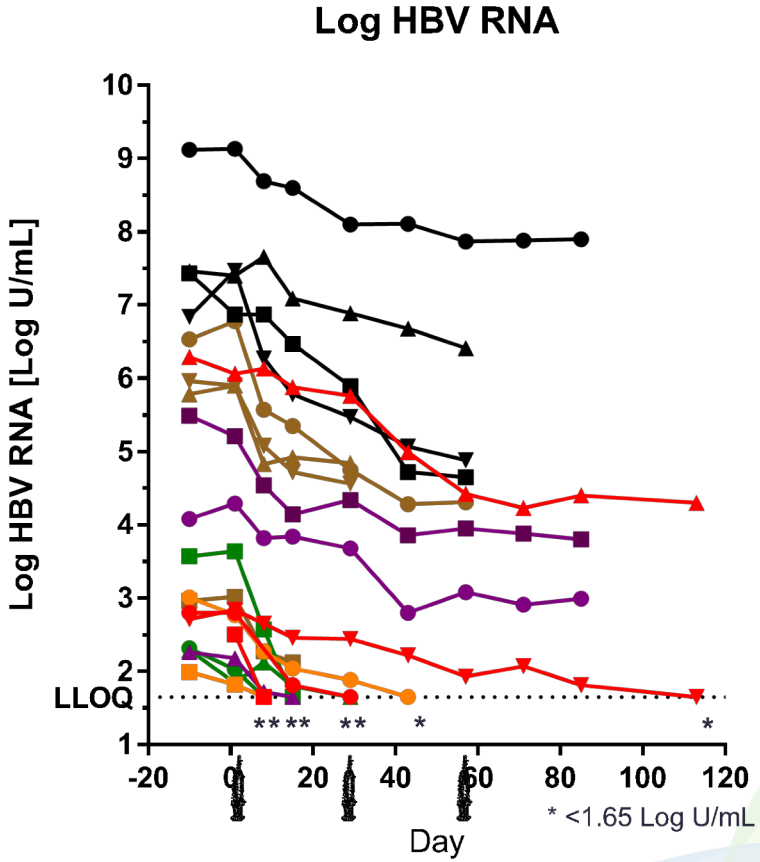


Colors in graphs indicate cohorts as follows: Red (C2b), orange (C3b), purple (C4b), green (C5b), black (C8), brown (C9)

Gane Edward, et al. AASLD 2018

Individual HBV DNA and RNA Also Reduced





Colors in graphs indicate cohorts as follows: Red (C2b), orange (C3b), purple (C4b), green (C5b), black (C8), brown (C9)

Gane Edward, et al. AASLD 2018

Early Data on Safety and Tolerability Encouraging

	JNJ-3989 3x Q4w, cohort, dose						
Possibly or probably drug-related AEs in ≥2 patients[a], n	1b	1c	2b	3b	4b	5b	All patients
	25 mg N=8	50 mg N=8	100 mg N=8	200 mg N=8	300 mg N=8	400 mg N=8	N=48
Injection site discoloration, injection site erythema, injection site bruising	1 Mild	0	0	0	2 Mild	2 Mild	5
Fatigue	1 Mild	0	1 Mild	0	0	1 Mild	3
Blood creatine phosphokinase elevated	1 Mild	0	0	0	1 Severe	0	2
Hot flush, flushing	0	1 Mild	0	0	0	1 Mild	2
Blood bilirubin increased, hyperbilirubinemia	0	0	0	1 Mild	1 Mild	0	2
Pruritus	1 Mild	0	1 Mild	0	0	0	2

[a]MedDRA preferred term aggregated based on similarity.
AE: adverse event; Q4w: every 4 weeks.

Gane Edward, et al. AASLD 2019

What Can We Say Today?

- RNAi against HBV (properly designed) can stake a strong claim as a cornerstone therapy for the foreseeable future
  - It can achieve powerful HBsAg reduction, including from HBeAg neg
  - It can address key viral antigens, DNA and pgRNA derived from cccDNA
  - JNJ-3989 has shown itself agnostic as to patient type HBeAg pos/neg, NUC experienced/naïve – and at least genotypes B, C and D (likely all)
  - It looks like most subjects (? all with more doses) will achieve HBsAg <100 IU
- JNJ-3989 has been well tolerated to date
  - It was also well tolerated when a CAM (JNJ-6379) was added (AASLD 2019)
  - No a priori reason to expect added tolerability issues with other drug classes
- 3 monthly doses is not enough as a finite approach, at least if NUCs are continued

And Still to Learn…….

- How long do we need to treat ?
- What is the best combination and do they need to be sequenced ?
- Do we need to stop NUCs to see best results ?
- How often will we see on-treatment HBsAg clearance vs delayed clearances with finite therapies ?
  - HBsAg clearance often occurs post-treatment over years with interferon, NUC stoppage and in the 2 patients clearing after ARC-520
- And – the ringer – are we missing neo-antigens with our current assay methods and if so, do they matter ?

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Thank you !

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