Prolonged RNA interference therapy with ARC-520 Injection in treatment naïve, HBeAg positive and negative patients with chronic HBV results in significant reductions of HBs antigen

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Disclosures

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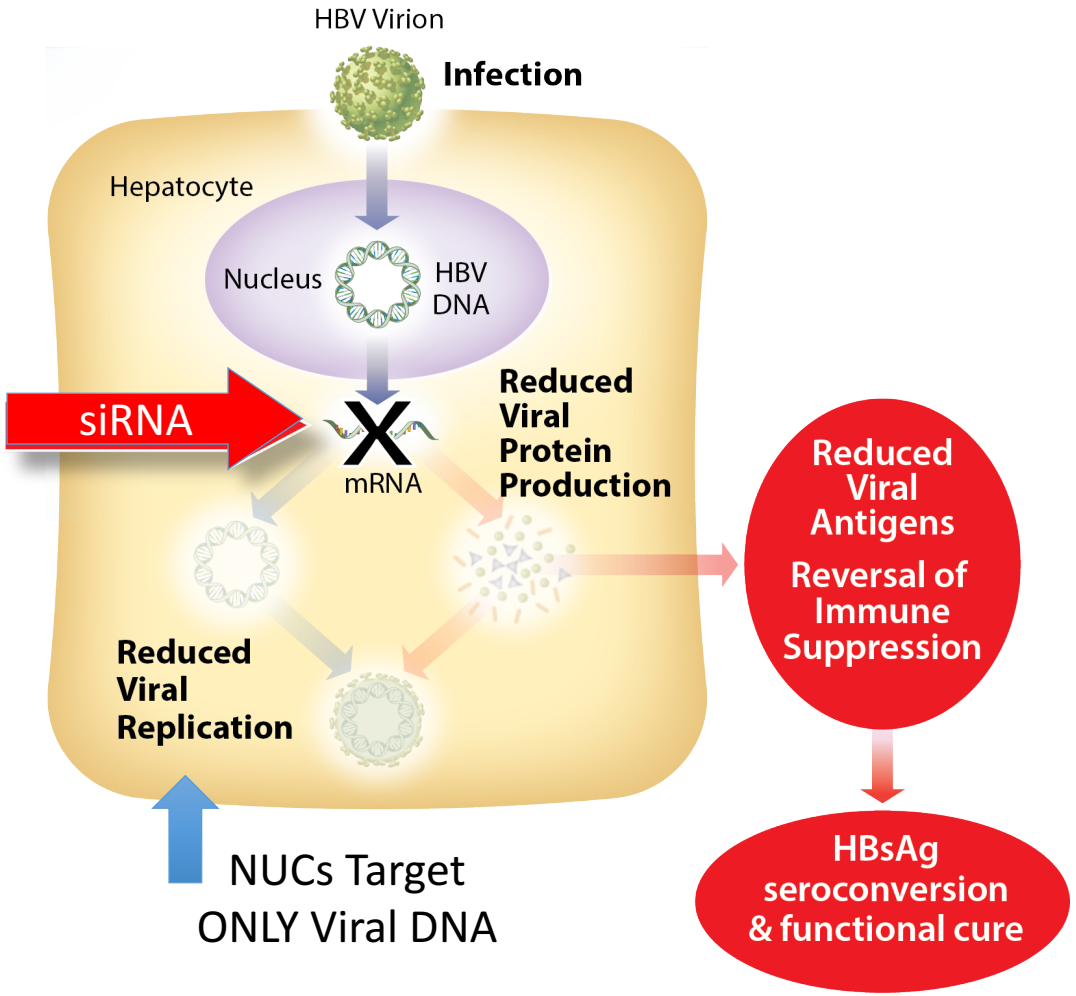
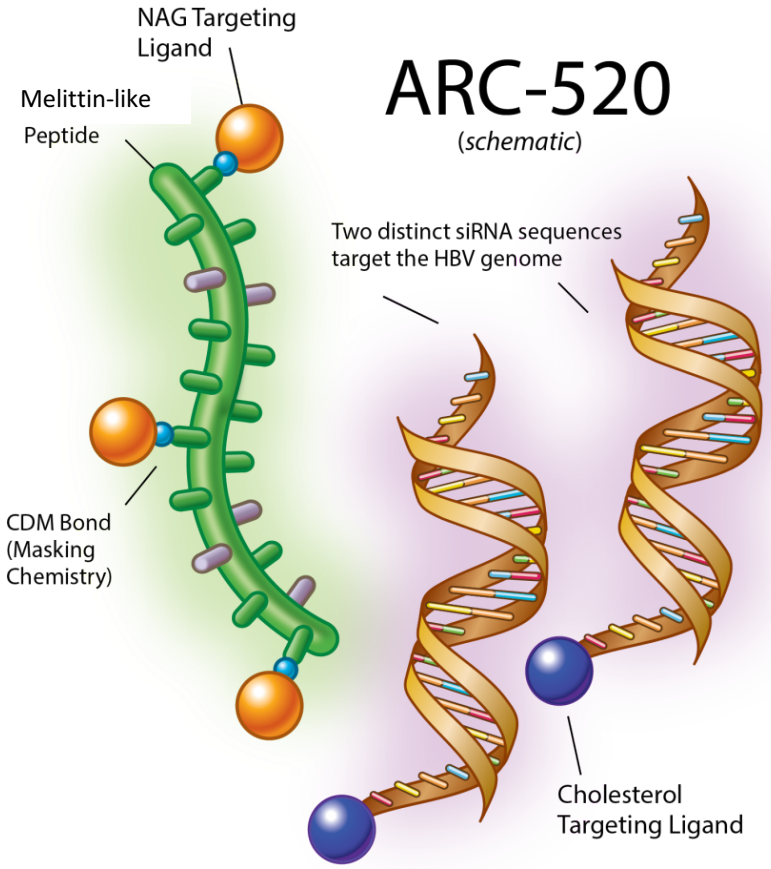
Simplified theory of an HBV RNAi therapeutic



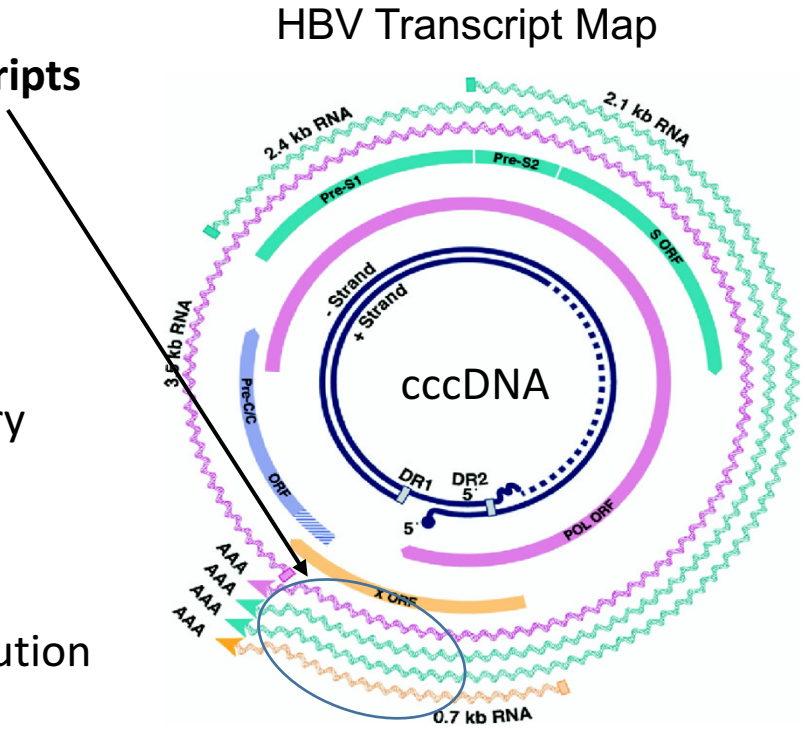
Silence Entire HBV Genome

1. "HBsAg Theory"
   - Reducing HBsAg enables host immune system de-repression and long term control of virus
2. Destabilizing Viral Function
   - Silencing all antigens could destabilize normal viral function
   - Enable host immune system de-repression and long term control of virus

RNA interference therapeutic ARC-520 for chronic HBV infection



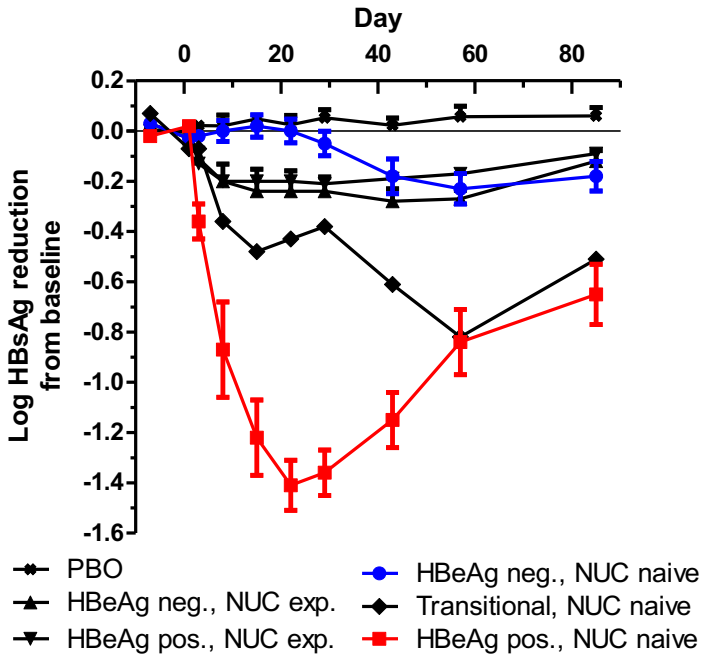
- **Designed to reduce all transcripts from HBV cccDNA**
- **ARC-520 Excipient**
  - Hepatocyte-targeted endosomal escape agent to enhance siRNA delivery
- **ARC-520 API**
  - Mixture of 2 cholesterol-conjugated siRNAs in solution



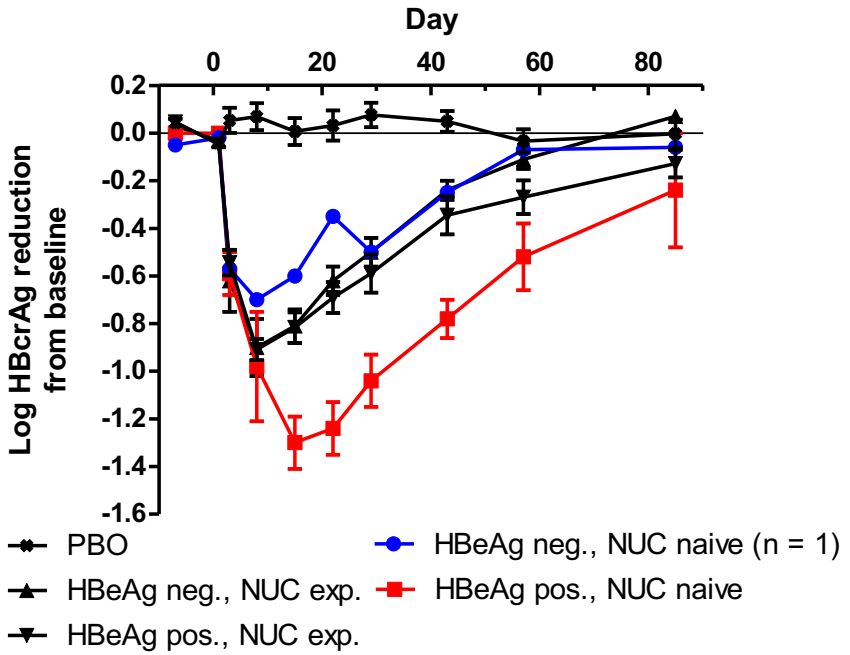
- **As of November 2016, the NAG-MLP containing drug platform was discontinued due to animal toxicology findings, not due to safety signals in humans.**

Previous data from single dose cohort led to new understanding of role of integrated HBV DNA

HBsAg reduction after
4 mg/kg ARC-520 dose



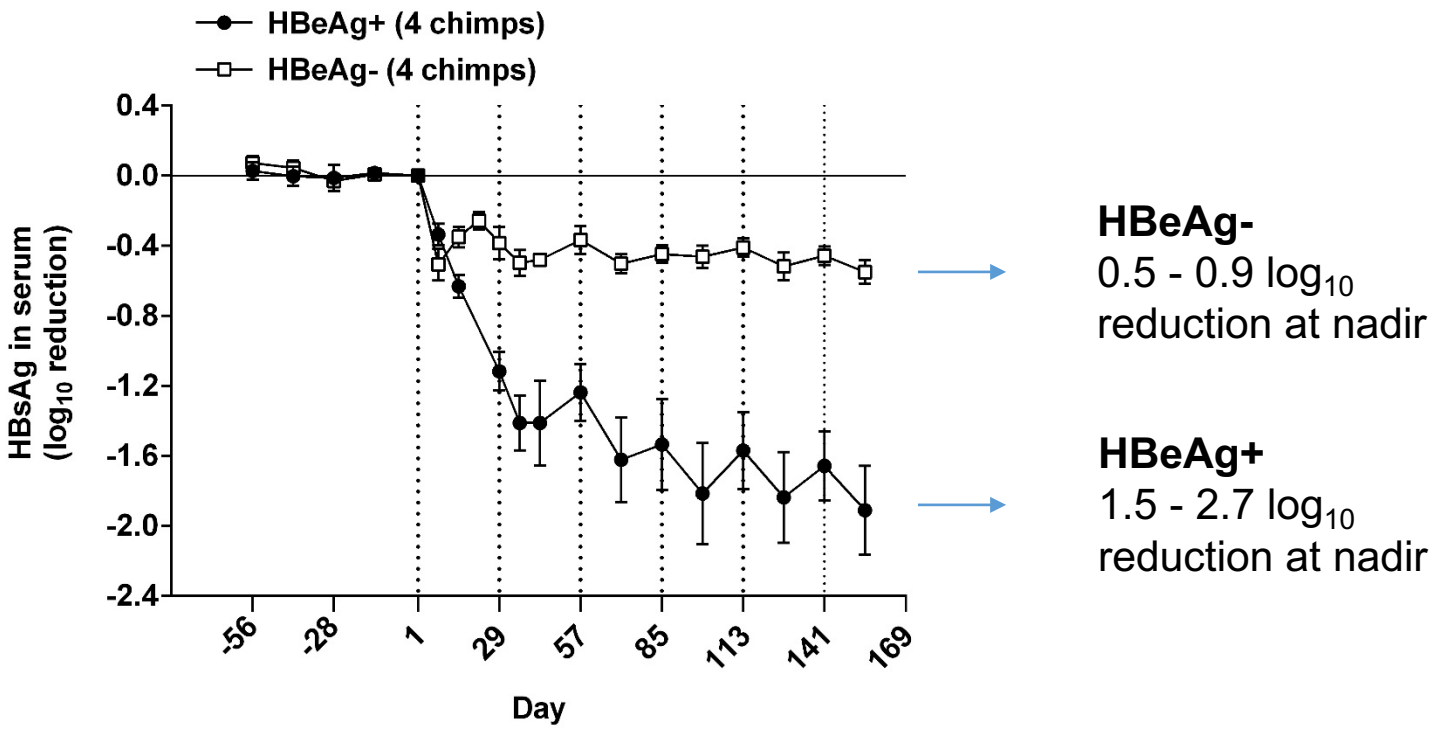
HBcrAg reduction after
4 mg/kg ARC-520 dose



- HBeAg status and previous NUC affect HBsAg response
- HBcrAg data confirms potent antigen reduction in all patients

M.-F. Yuen, H.L.Y. Chan, K. Liu, B.D. Given, T. Schluep, J. Hamilton, C.-L. Lai, S.A. Locarnini, J.Y.N. Lau, C. Ferrari, R.G. Gish. (2016) J Hepatology 64, (Suppl 2): THU-193

Differential HBsAg reduction also observed in untreated chimps



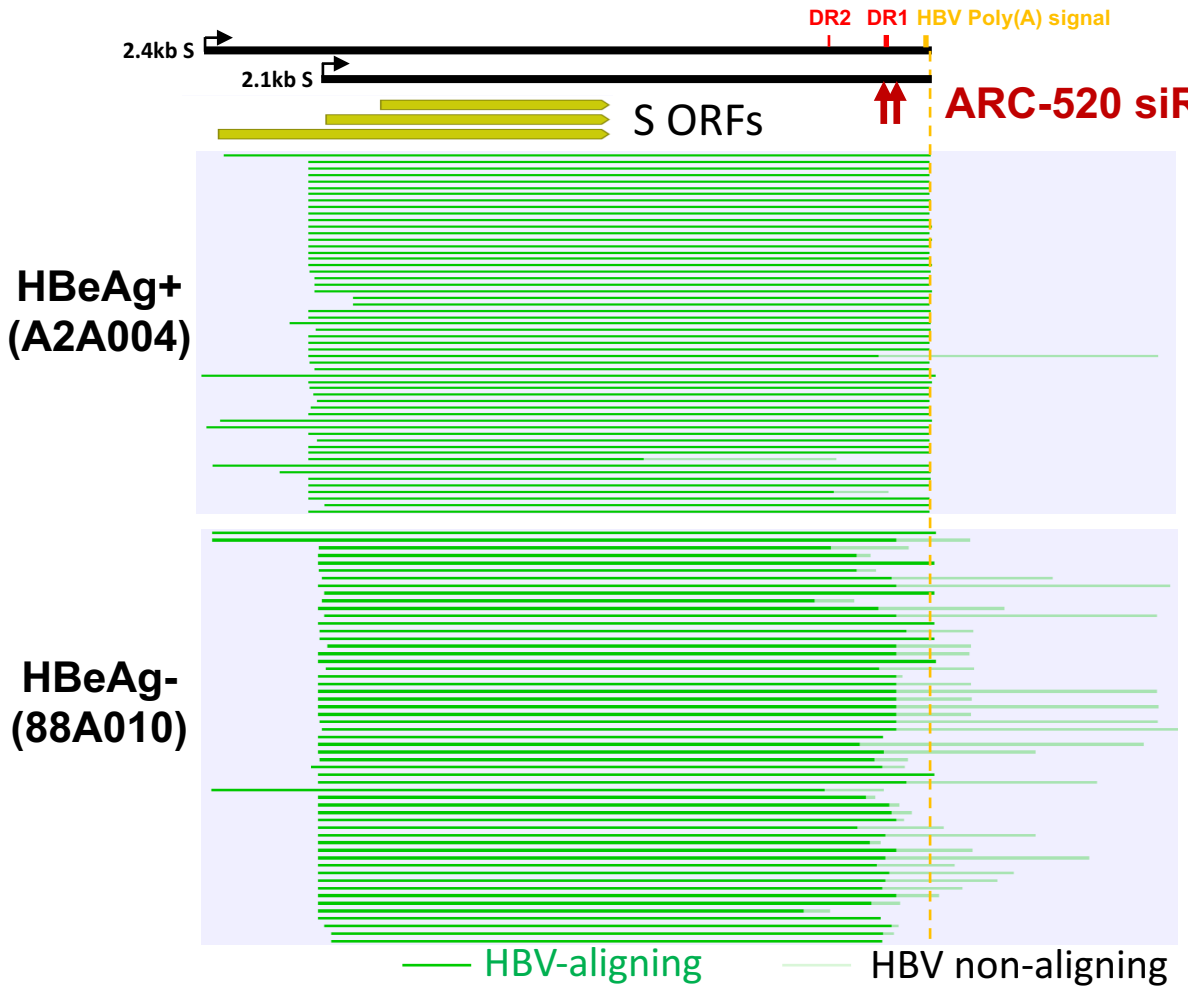
HBeAg-
0.5 - 0.9 log_{10} reduction at nadir

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

- HBeAg positive responded better than HBeAg negative chimps

HBV transcripts differ between HBeAg+ and 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 DR1as expected if transcripts arose from integrated HBV dslDNA

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

Study design Heparc-2001 extension

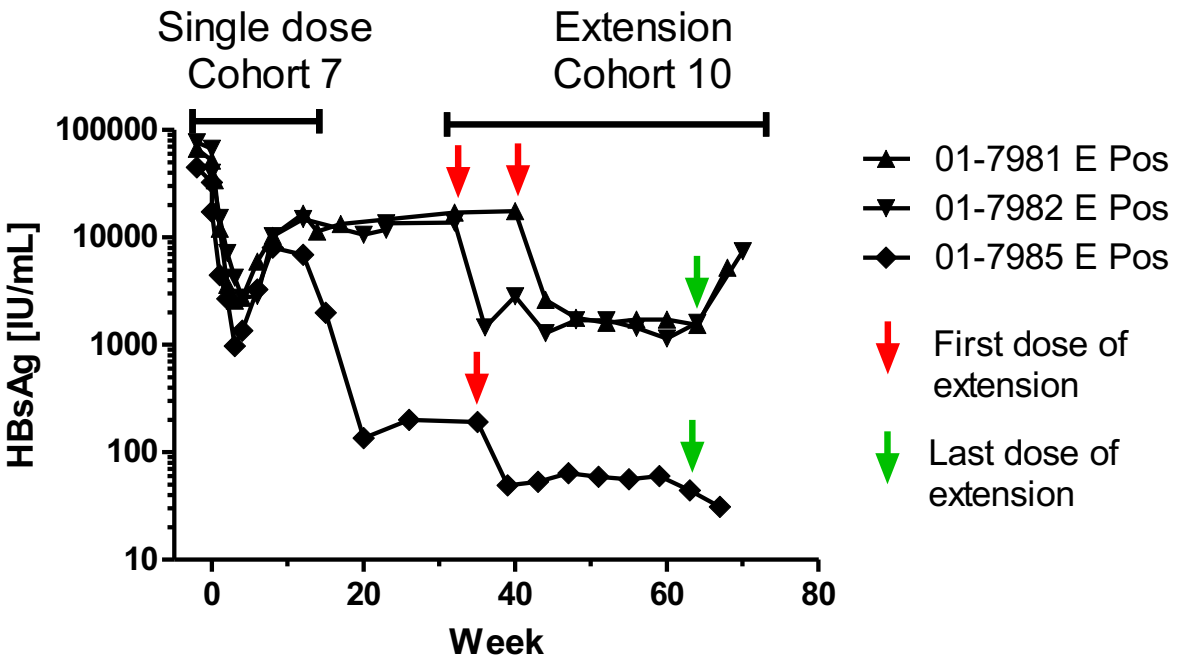
- Treatment naïve chronic HBV patients who previously received a single IV dose of 4 mg/kg ARC-520 and *started* daily entecavir on the same day were eligible (cohort 7)
- 8 CHB (5 HBeAg-neg, 3 HBeAg-pos) were enrolled to receive 4 mg/kg ARC-520 once every 4 weeks with daily entecavir
- Viral DNA and antigen knockdown (KD) were measured at regular intervals
  - qHBsAg
  - HB core-related antigen (qHBcrAg)
  - qHBeAg in HBeAg-pos

Tolerability

- Mean number of ARC-520 doses in the extension was 7.6 with a range of 5 to 9
- 7/8 patients reported at least one mild AE
- No AEs were rated as serious, severe or caused withdrawal
- Most frequent AEs were mild fever and mild flu-like symptoms

Adverse Event	N	Severity
Fever	5	mild
Flu-like symptoms	5	mild
Rash	2	mild
Influenza	1	mild
Haematuria	1	mild
Procedural pain	1	mild
Arthralgia	1	mild
Chest Discomfort	1	mild
Headache	1	mild
Running nose	1	mild
Epigastric discomfort	1	mild
Malaise	1	mild
Temporomandibular joint pain	1	mild

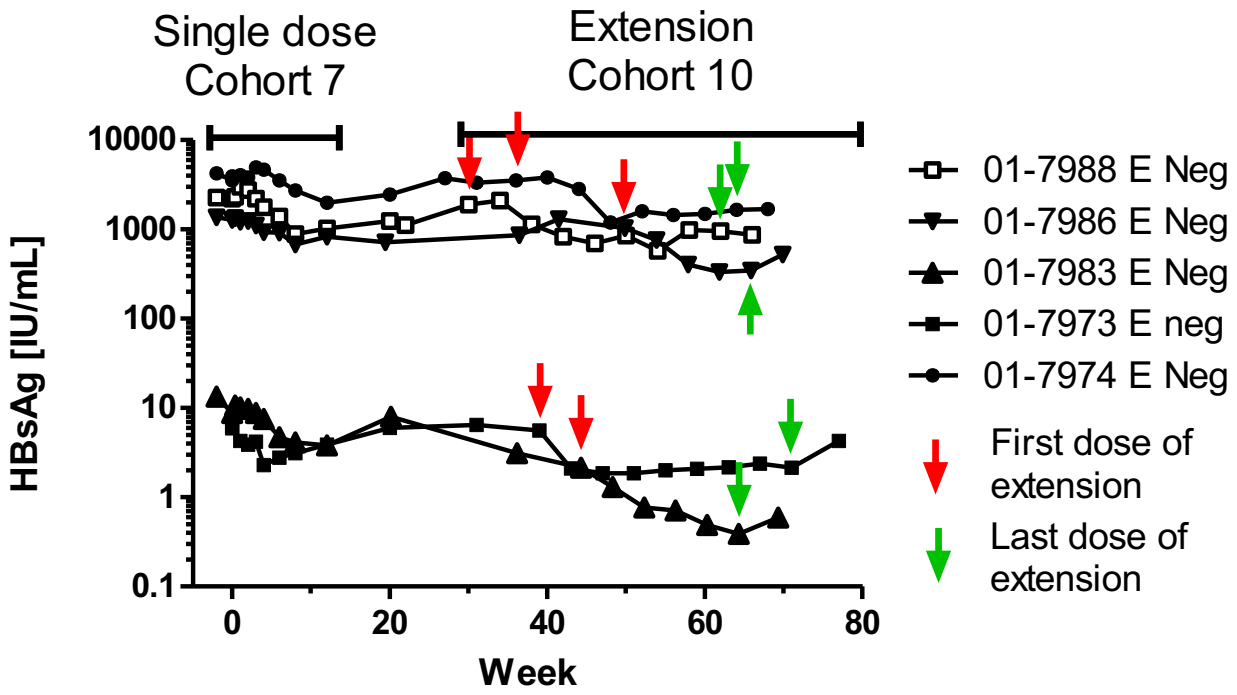
HBsAg reduction in HBeAg positive patients



- In 3/3 patients HBsAg did not return to baseline after single dose of ARC-520
  - Effect persisted for >30 weeks
- Multi-dose re-challenge further reduced HBsAg in all patients
- HBeAg pos patients showed immediate reductions in HBsAg with 1st and 2nd doses
  - Mean max -2.2 Log10
  - Max observed -3.1 Log10

- High levels of HBsAg knockdown achieved with ARC-520
- Similar to observations in HBeAg positive chimps

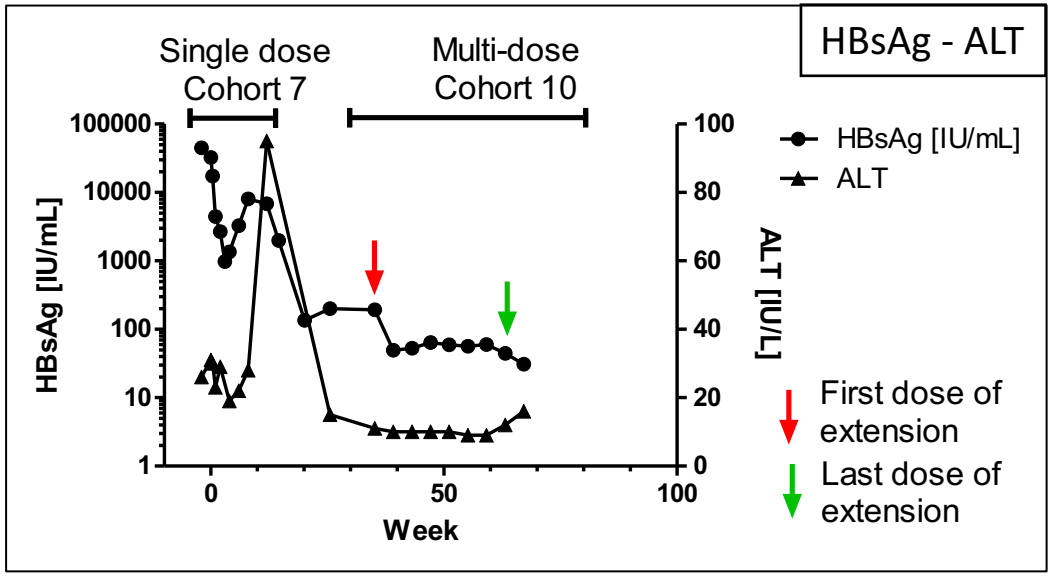
HBsAg reduction in HBeAg negative patients

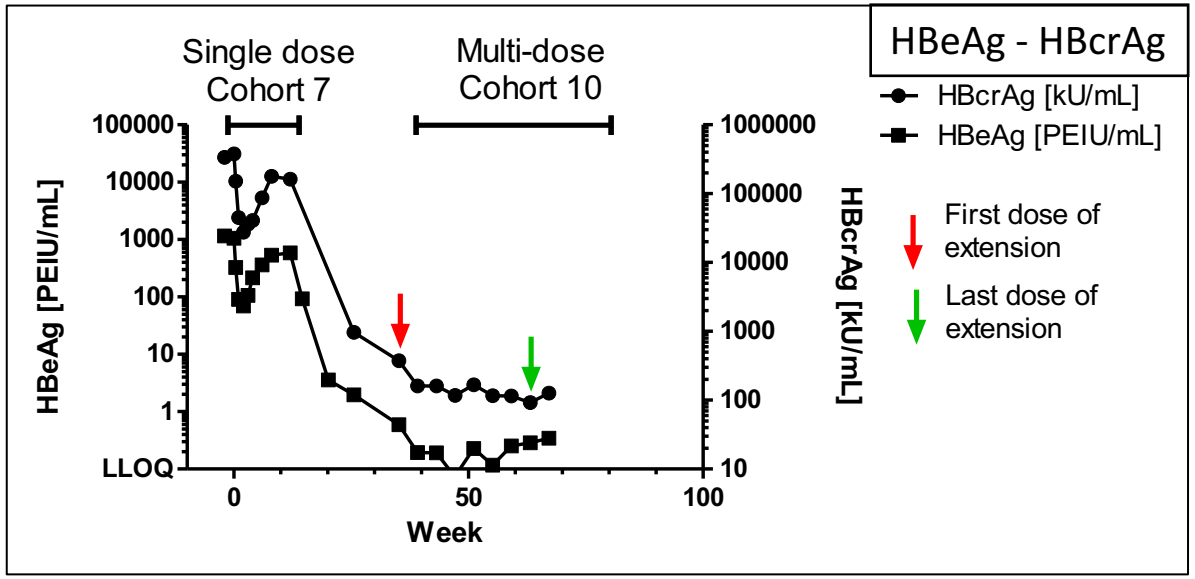


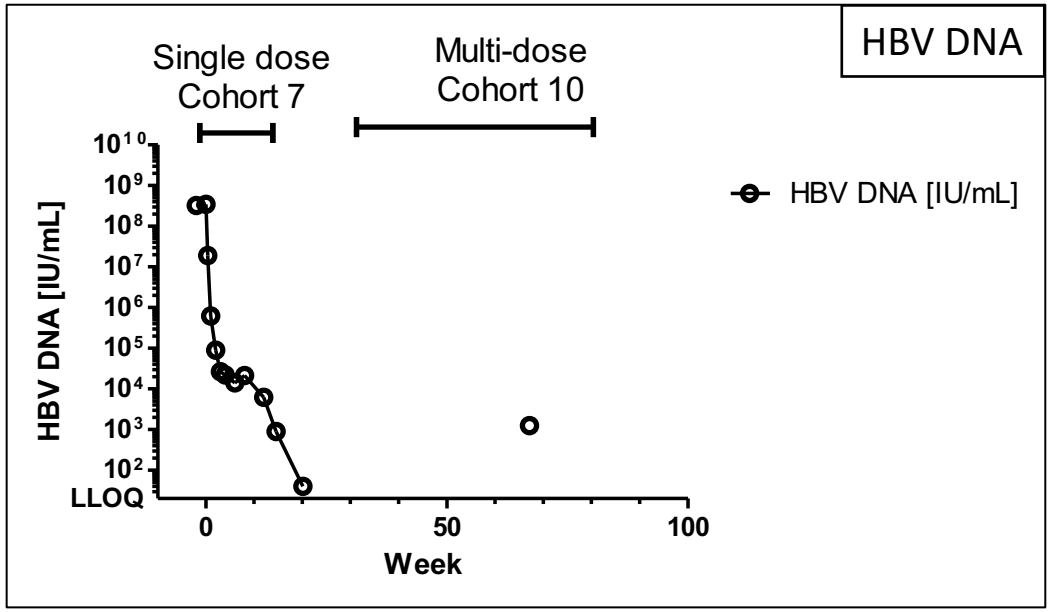
- Multi-dose re-challenge further reduced HBsAg in all patients
- HBeAg neg patients showed delayed reductions in HBsAg
- HBeAg neg patients showed lower reductions in HBsAg
  - Mean max -0.7 Log10
  - Max observed -1.4 Log10

- Lower HBsAg response consistent with findings of a higher fraction of HBsAg from integrated DNA in HBeAg negative patients

Case study 1: HBeAg positive patient

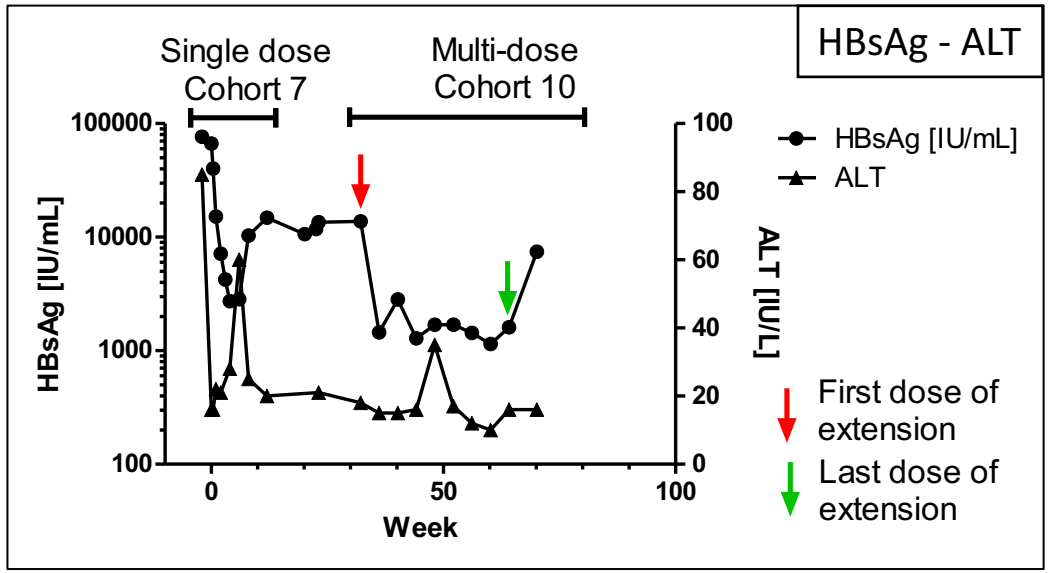


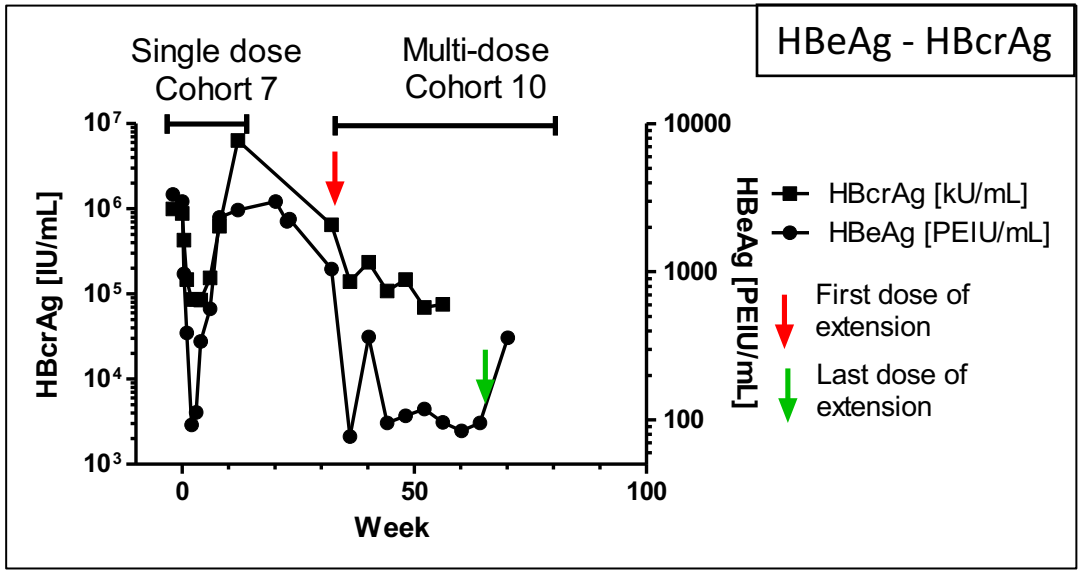


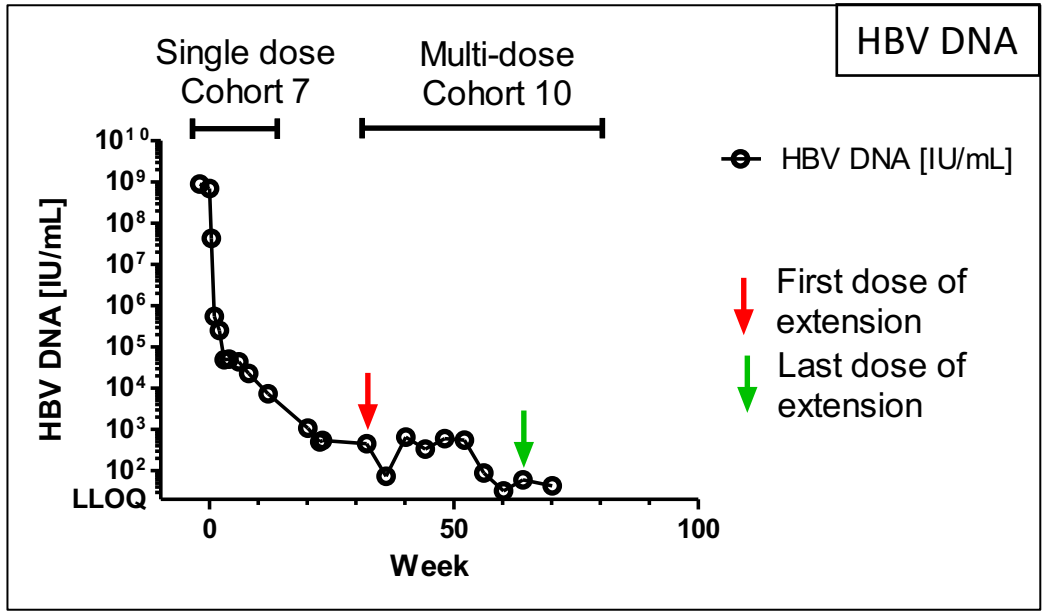


- 3.1 Log10 HBsAg reduction from baseline
- 3.6 Log10 HBcrAg and 4.2 Log10 HBeAg reduction
- Rapid reduction of HBV DNA to BLOQ
- ALT elevation after initial antigen reductions
- Antigen decrease during ARC-520 treatment holiday consistent with increased immune control of HBV virus

Case study 2: HBeAg positive patient

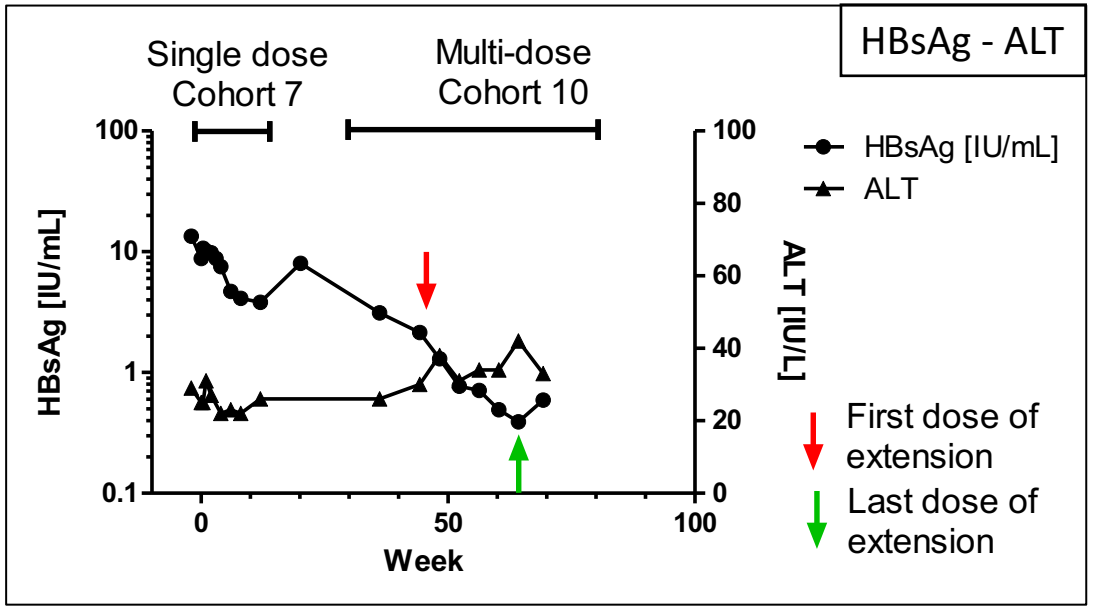


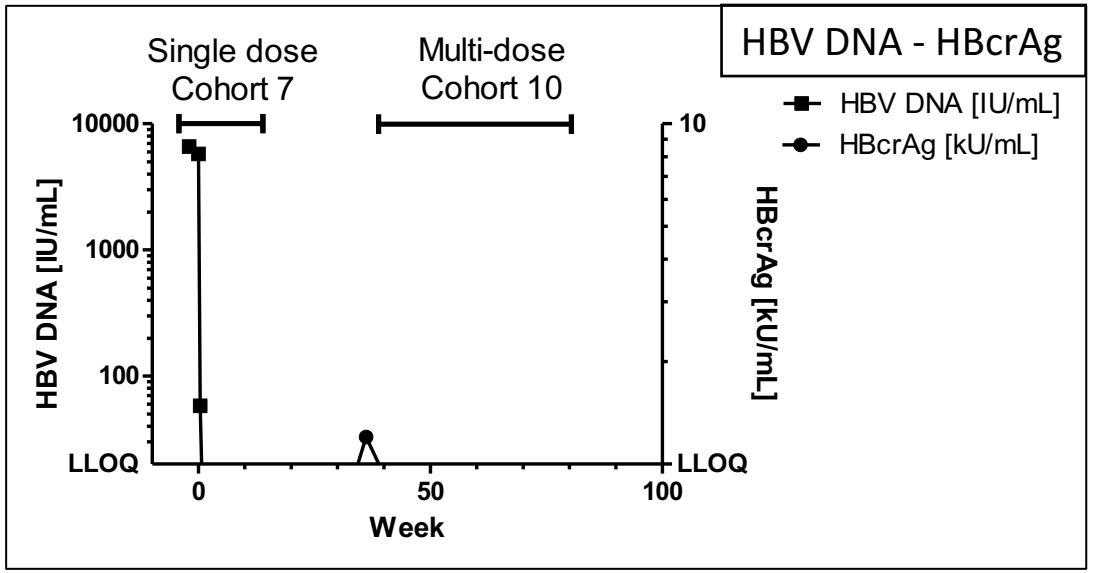




- 1.8 Log10 HBsAg reduction from baseline
- 1.1 Log10 HBcrAg and 1.6 Log10 HBeAg reduction
- Biphasic reduction of HBV DNA by 7.4 Log10
- ALT elevations coinciding with antigen and DNA reductions
- HBsAg and HBeAg did not return to baseline after single dose ARC-520, consistent with increased immune control of HBV virus

Case study 3: HBeAg negative patient





- 1.4 Log10 HBsAg reduction from baseline to less than 1 IU/mL
- Delayed HBsAg response
- HBcrAg BLOQ throughout the study
- Rapid reduction of HBV DNA to undetectable levels with ARC-520 plus entecavir
- Antigen decrease during treatment holiday consistent with increased immune control of HBV virus

Summary

- ARC-520 was well tolerated
- ARC-520 + ETV were effective at rapidly suppressing HBV DNA
- A single dose of ARC-520 together with ETV reduced HBsAg for up to 44 weeks
- Multiple doses of ARC-520 resulted in additional HBsAg reductions in all patients, as much as 3.1 logs
- HBeAg positive patients showed larger, multi-log reductions in HBsAg, while HBeAg negative patients showed lower reductions with delayed onset, consistent with previously reported results in chimpanzees
- All HBeAg positive and some HBeAg negative patients showed ALT elevations coincident with antigen reductions that may indicate increased immune control of the HBV virus

Conclusions

- RNA interference as a mechanism can rapidly and deeply reduce all viral antigens for which we currently have assays and, as previously shown in mice, RNAi appears to synergize with NUCs to rapidly lower serum levels of HBV DNA

- RNAi is a strong candidate to synergize with other DAAs acting on viral substrates and serve as a cornerstone of combination therapies for HBV

Acknowledgments

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