



Implications of HBsAg from Integrated DNA for Clinical Trial Design

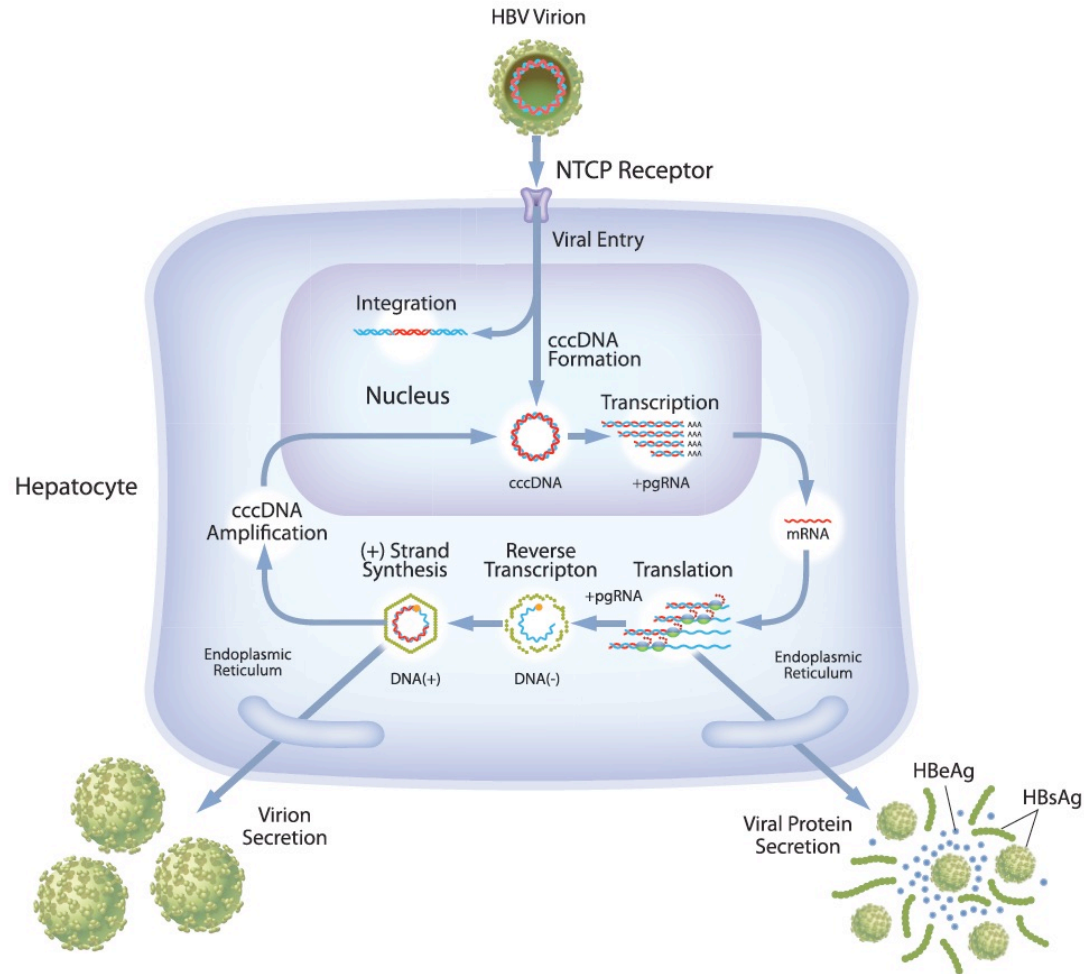
Bruce D. Given, MD
HBV Forum 3, October 24, 2017



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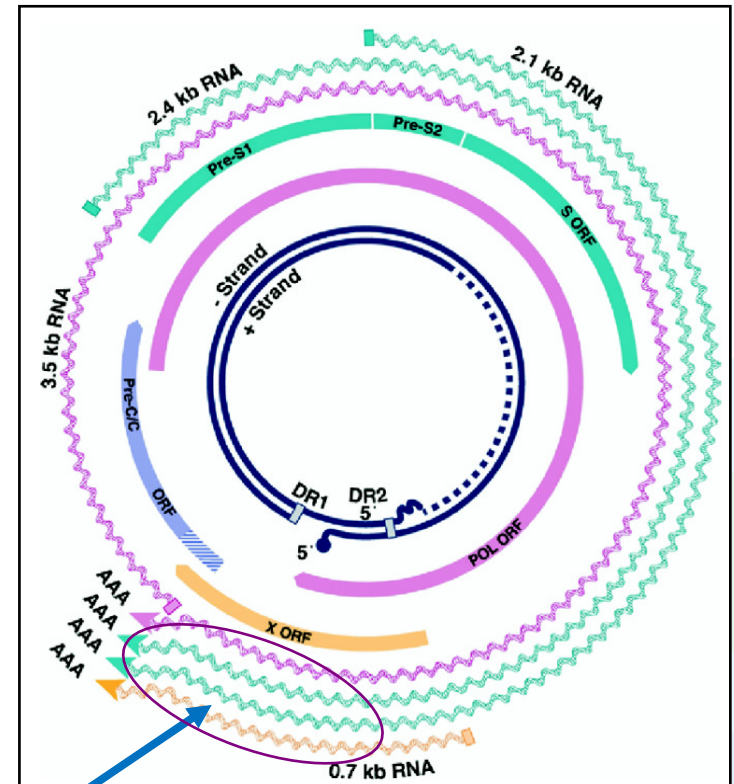
Hepatitis B Virus Life Cycle



All HBV RNA derived from cccDNA can be targeted with one siRNA

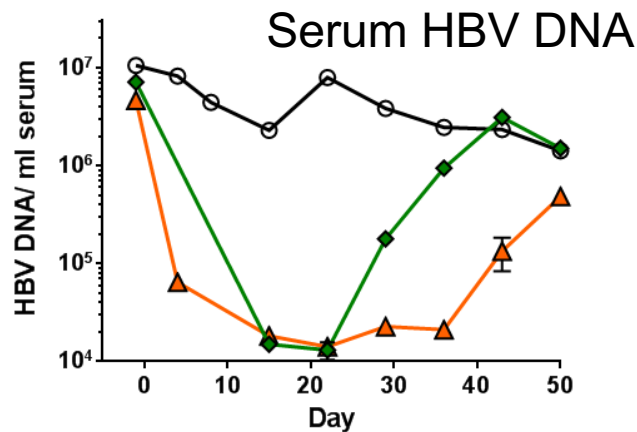
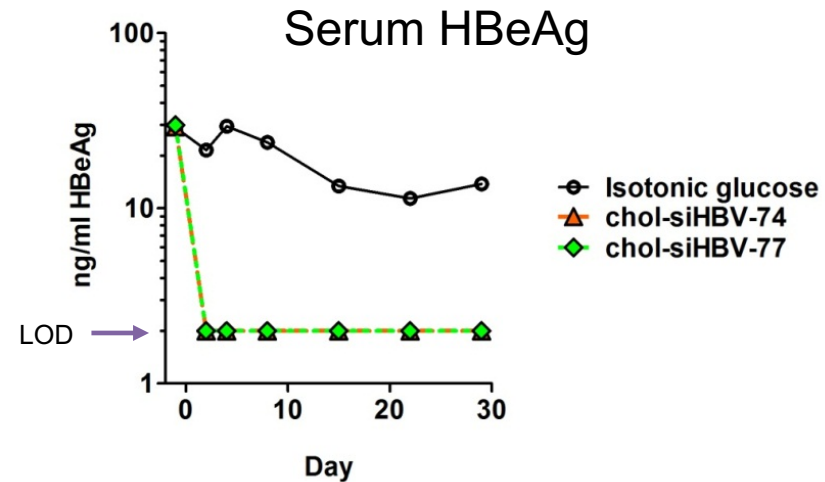
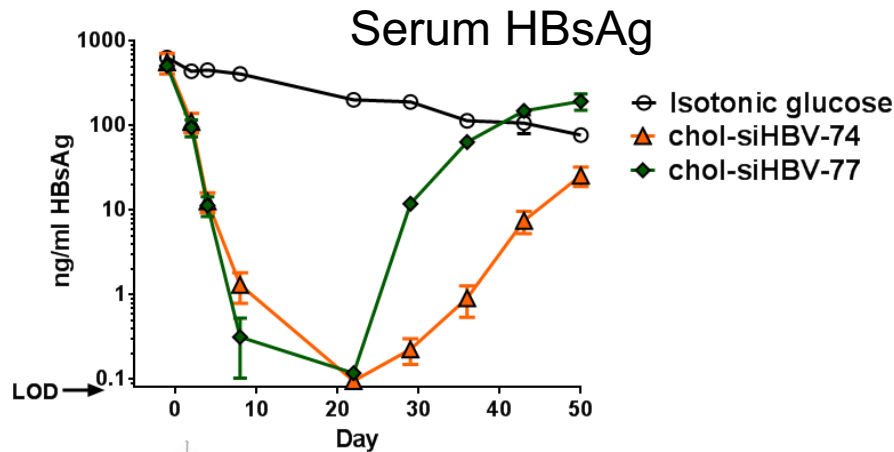
- All HBV transcripts, including pregenomic RNA, have common sequence and terminate with the same polyadenylation signal.

HBV Transcript Map



Single siRNA can reduce all HBV proteins

Co-injection of chol-siHBVs with NAG-MLP in HBV mouse model



Strong reduction of serum viral markers using either chol-siHBV-74 or -77 with NAG-MLP after a single dose

Decreased HBsAg

- 3-4 log reduction with both chol-siHBVs
- > 2 log reduction for 1 month

Decreased HBeAg to LOD

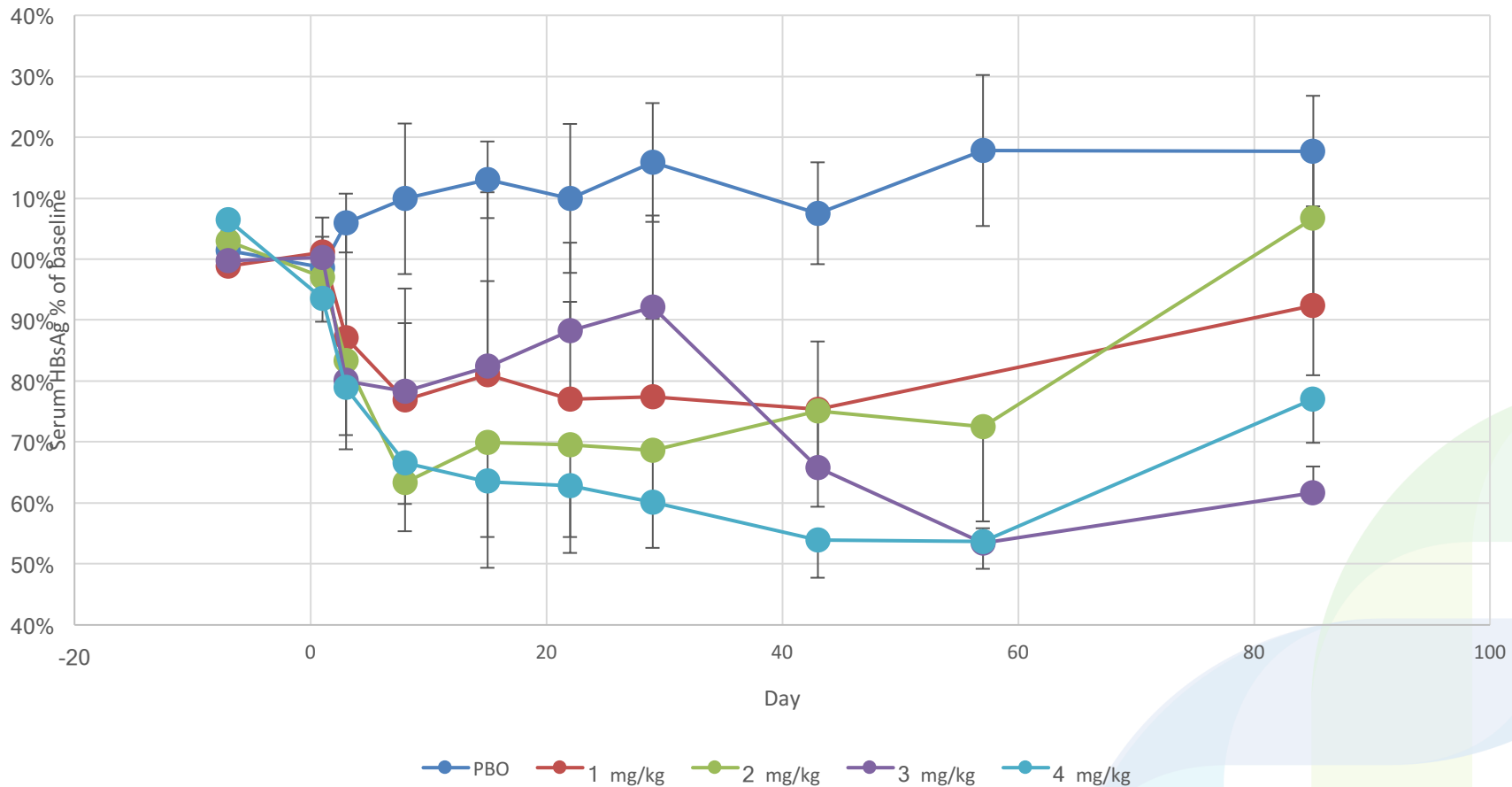
Decreased HBV DNA

- ~ 3 log reduction of HBV DNA for ~ 1 month

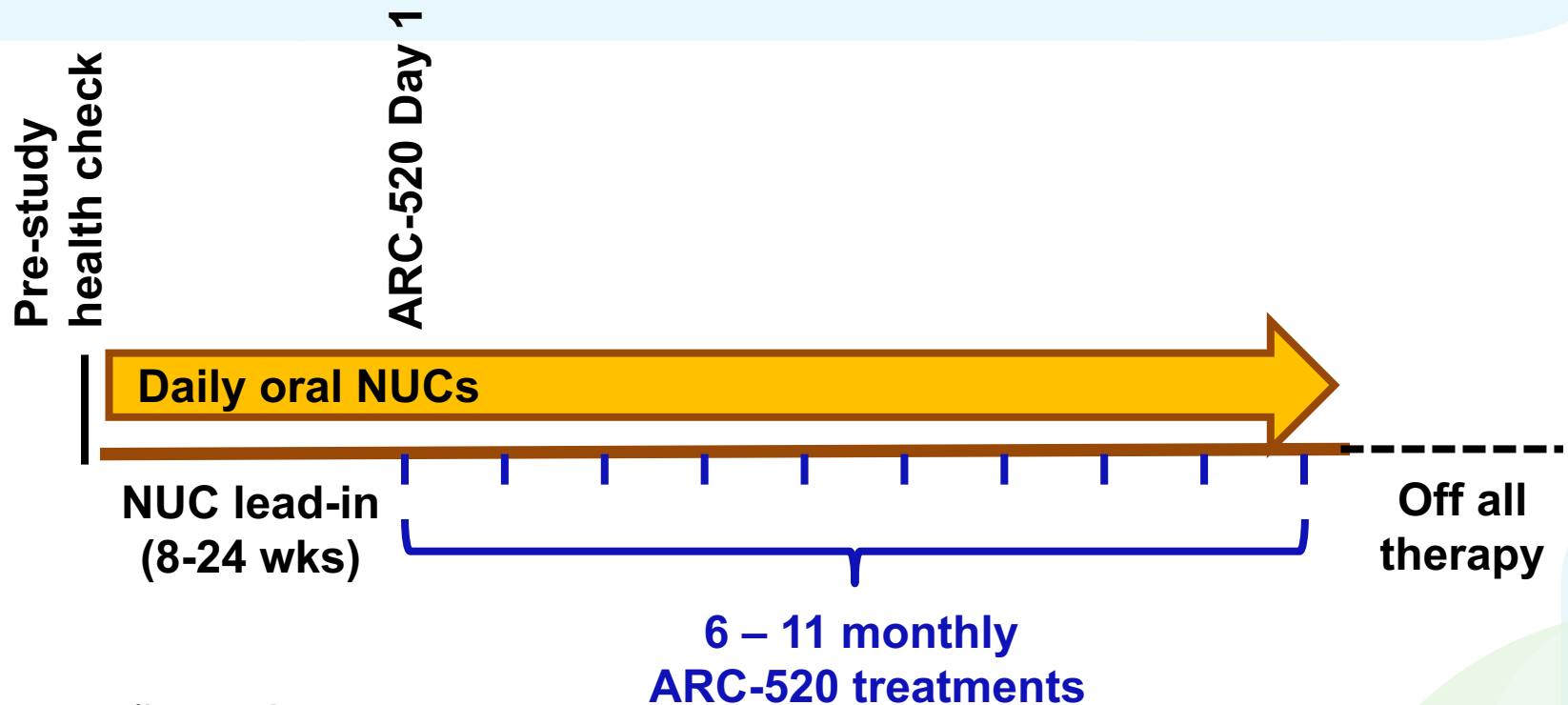
6 mg/kg NAG-MLP + 6 mg/kg chol-siRNA
Wooddell et al, Mol Ther 2013 May; 21(5) 973-85

HBsAg data in NUC- experienced HBeAg neg patients show less than expected activity

Batch analyzed Cohorts 1-4 with ARC-520/placebo

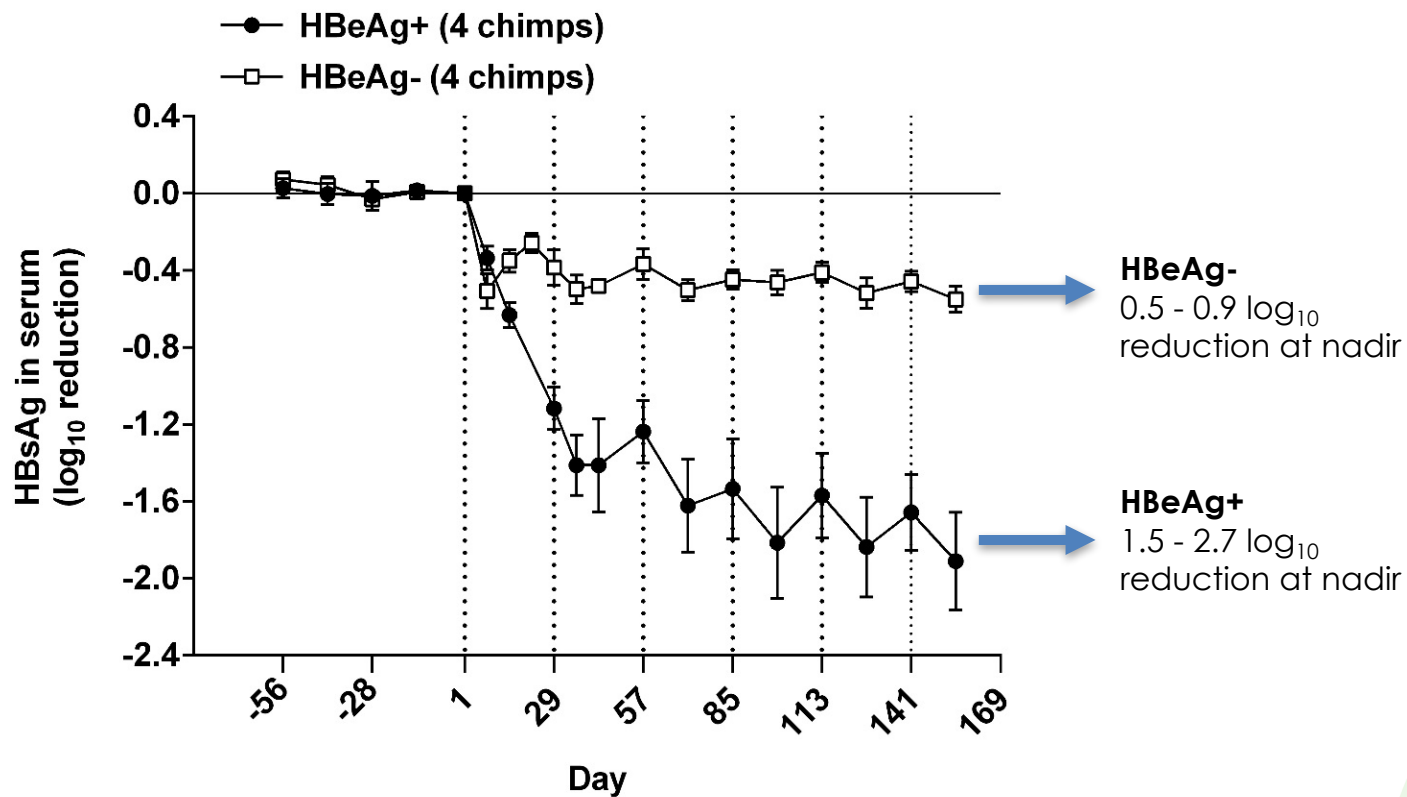


Chimp dosing and sampling timeline



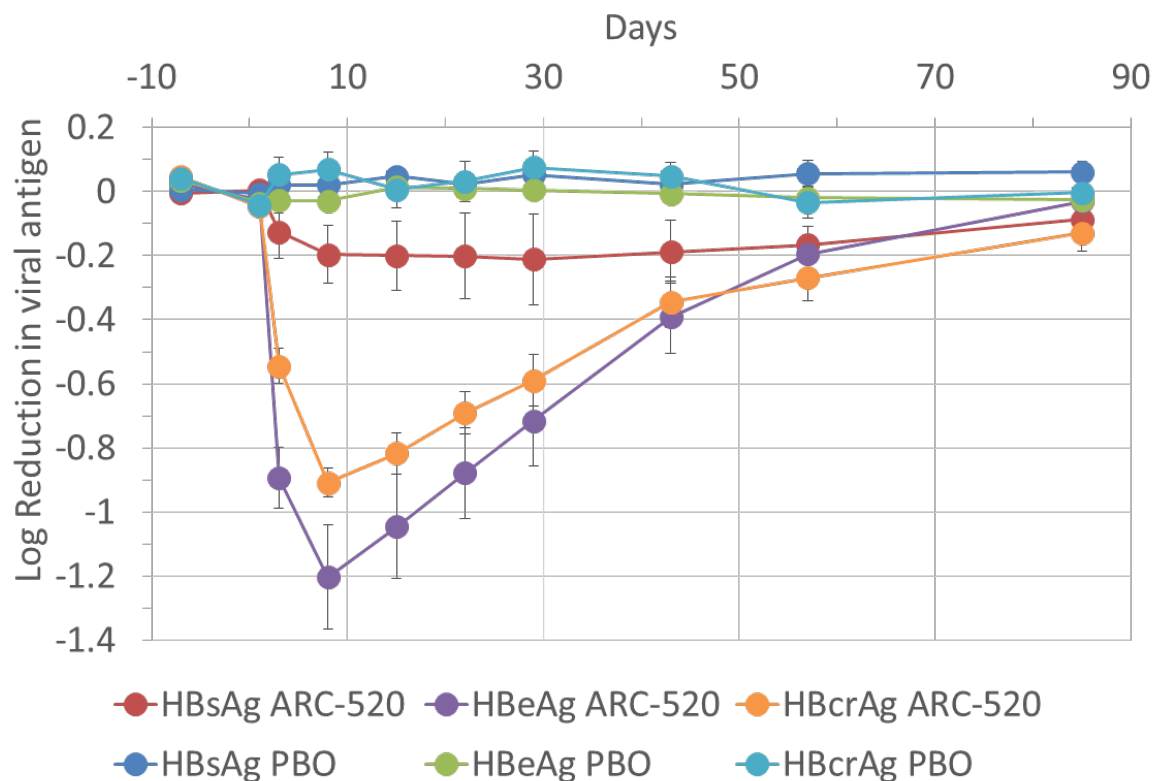
- Daily NUCs:
 - 0.5 or 1.0 mg entecavir (ETV)
 - 300 mg tenofovir added at week 15 for chimp Michele
- Monitor safety and efficacy
 - Blood collection performed regularly throughout study
 - Periodic liver needle biopsies

Differential HBsAg Reduction Observed in Chimpanzees with ARC-520



HBeAg positive responded better than HBeAg negative chimps

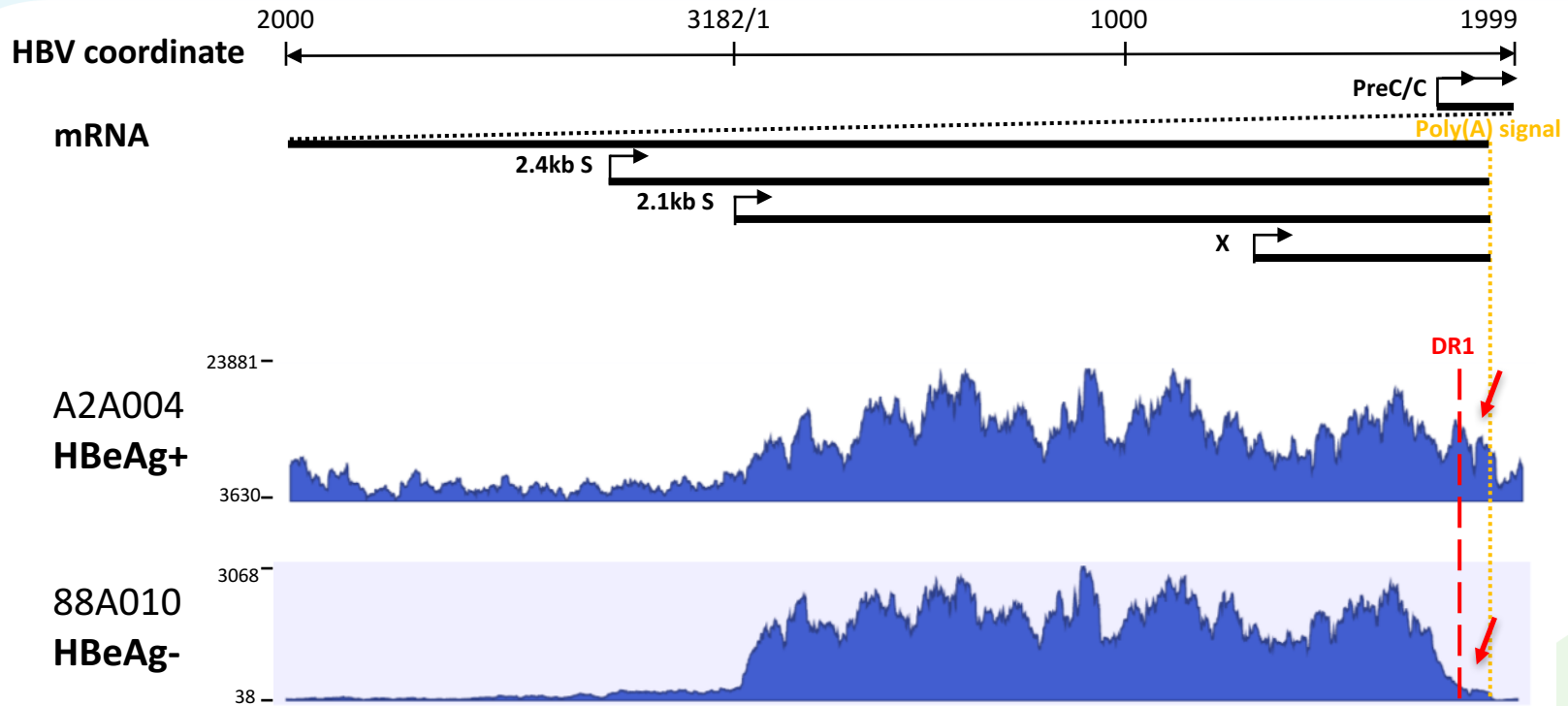
Response to ARC-520 in NUC-experienced, HBeAg positive patients



- High level KD of HBcrAg and HBeAg (cccDNA derived)
- Lower KD of HBsAg

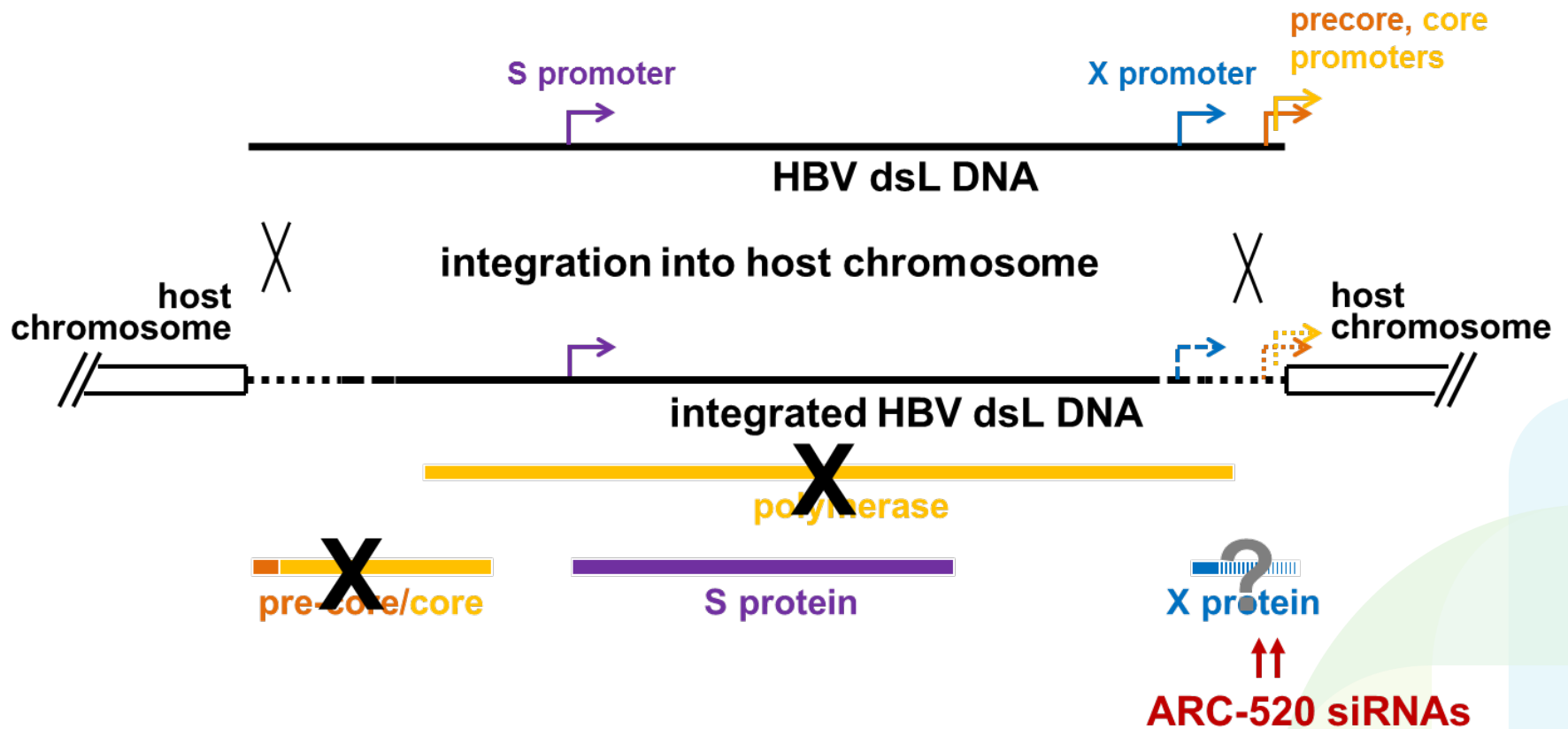
4 mg/kg ARC-520

Representative HBV transcript profiles in HBeAg+ and HBeAg- chimps (Illumina RNA-seq analysis)

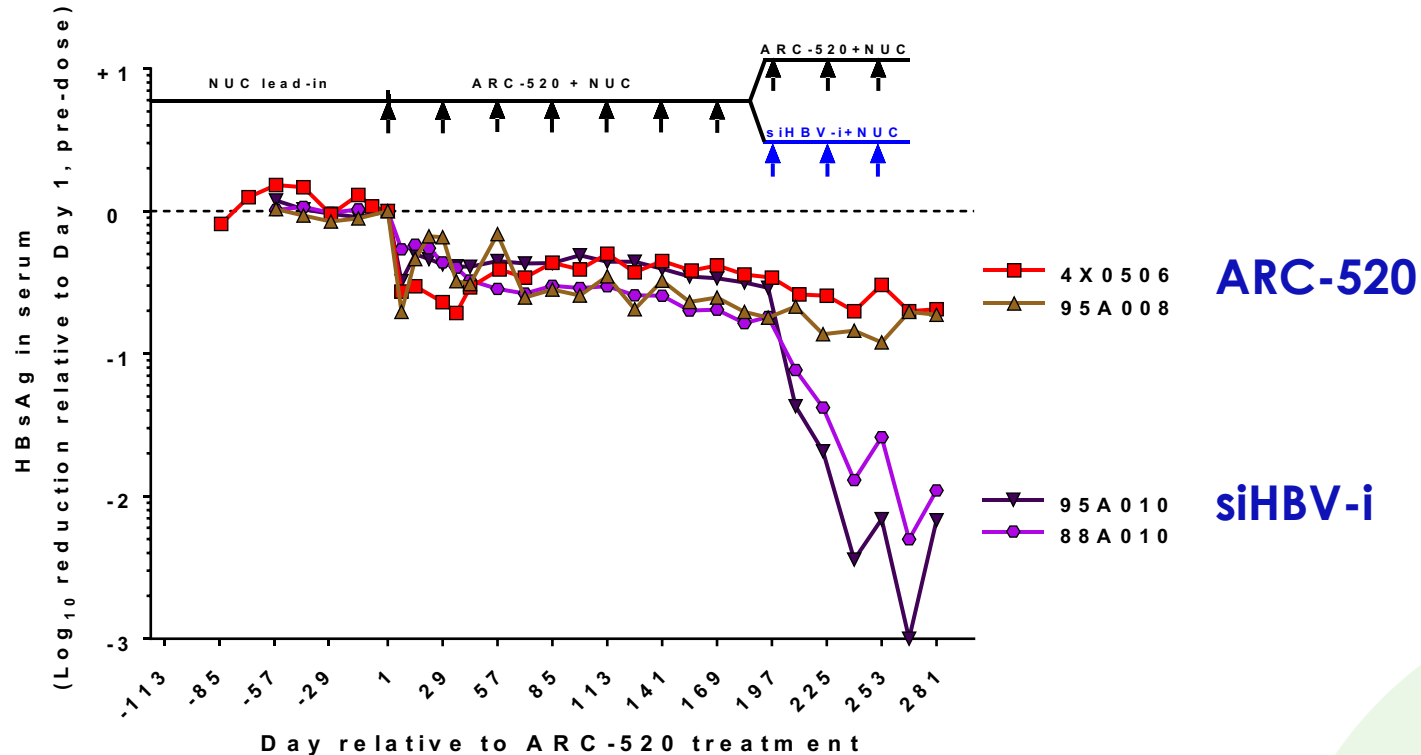


- Fewer transcripts with HBV poly(A) signal in HBeAg- vs HBeAg+ chimps
- In HBeAg- chimps, frequency of reads is reduced in region near DR1 : known for high frequency integration
- *Are these transcripts coming from integrated HBV DNA?*

Process of HBV dsL DNA integration and theoretical production of HBsAg



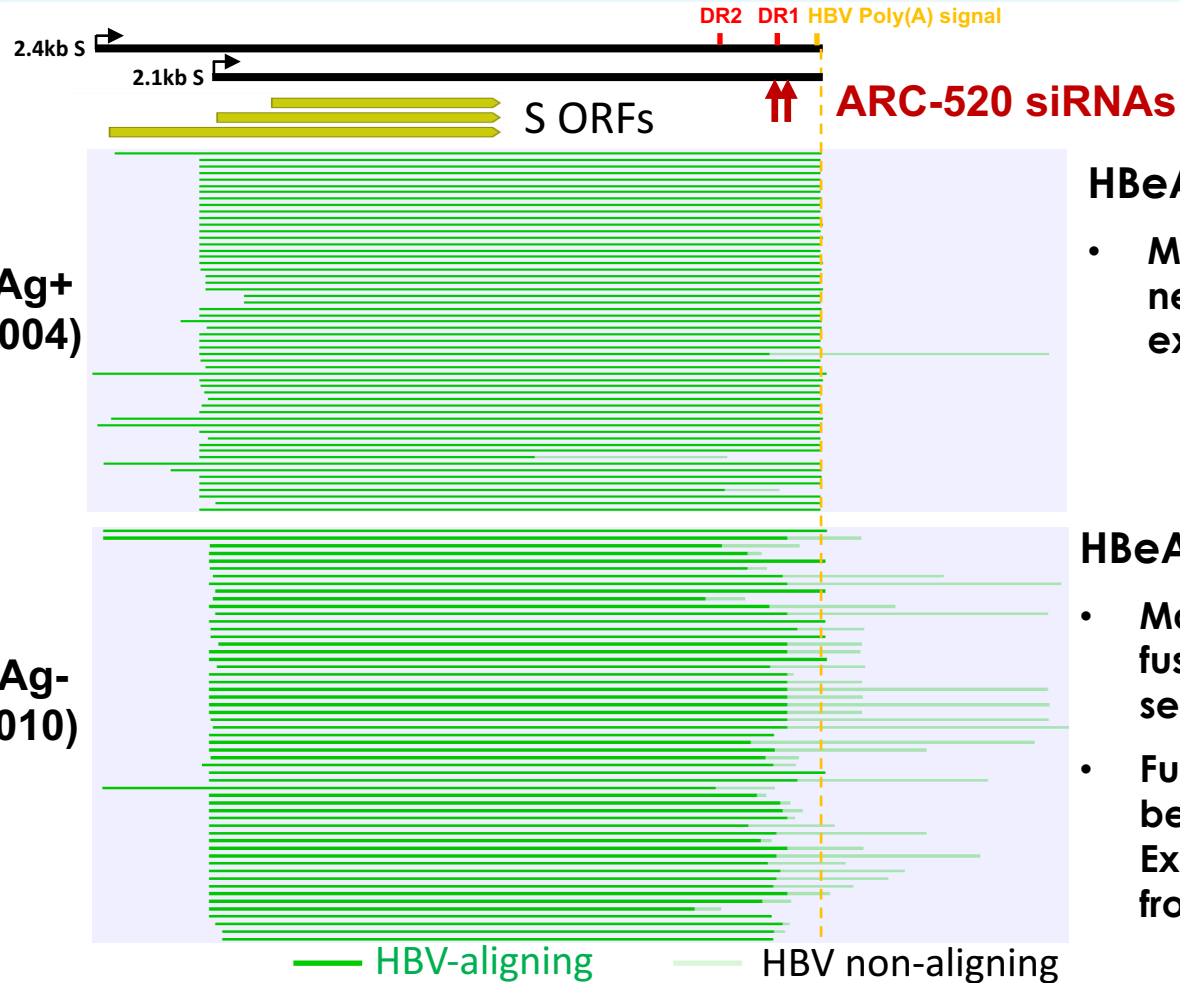
siRNA Designed to Target RNA Derived From HBV Integration Products in HBeAg- Chimps



- 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

HBV Transcripts in HBeAg+ vs. HBeAg- Chimps

PacBio Single Molecule Real-Time (SMRT) Sequencing



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

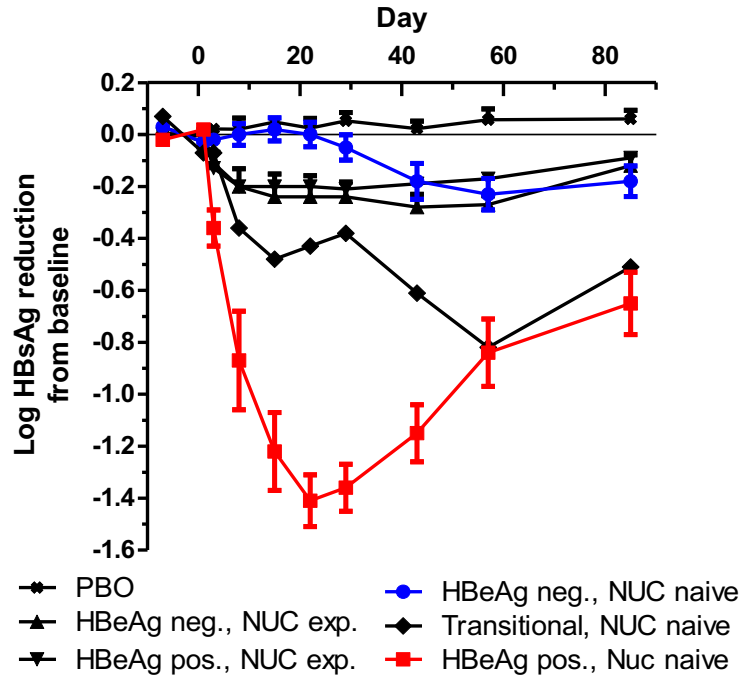
ARC-520 Phase2a explored 4 HBV groups

**Think of the groups as quadrants
Defined by HBeAg status and NUC experience**

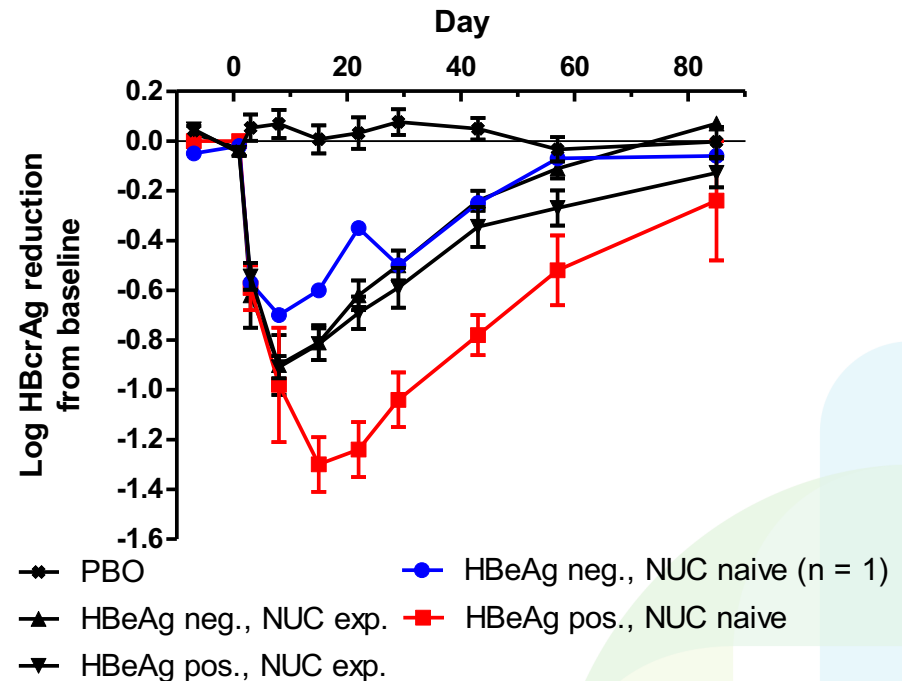
NUC Naïve	Naïve HBeAg+	Naïve HBeAg-
NUC Experienced	Experienced HBeAg+	Experienced HBeAg-
	HBeAg+	HBeAg-

ARC-520 Results Lead To New Understanding of Role of Integrated HBV DNA

HBsAg reduction after 4 mg/kg ARC-520 dose

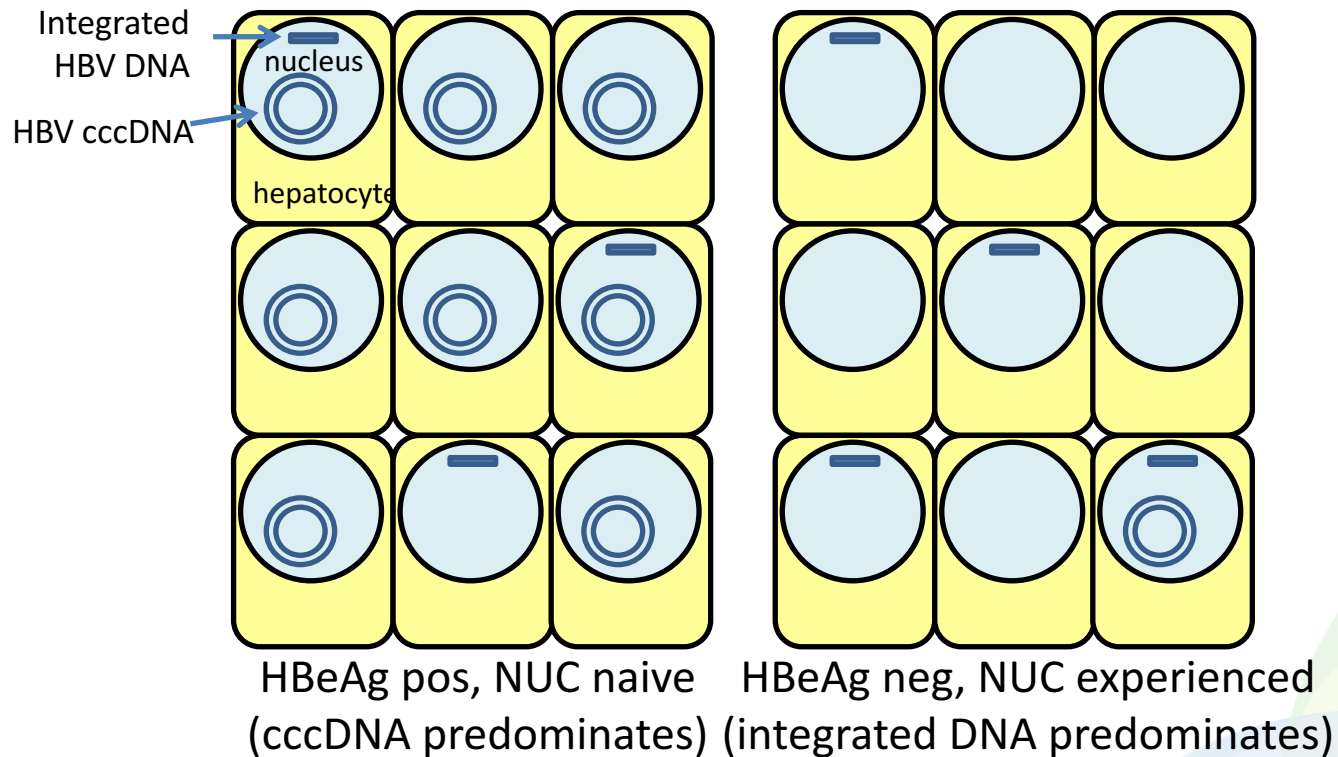


HBcrAg reduction after 4 mg/kg ARC-520 dose



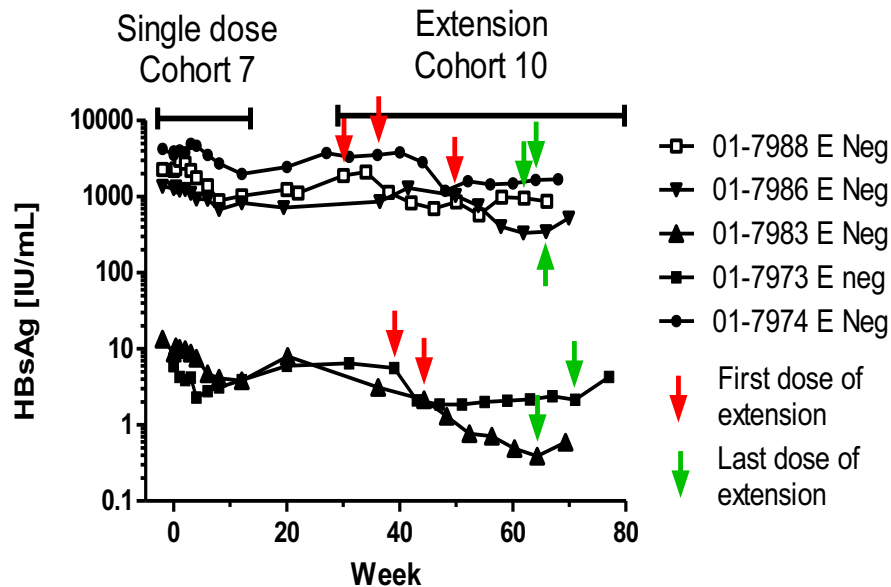
- HBeAg status and previous NUC affect HBsAg response
- HBcrAg data confirms potent antigen reduction in all patients

HBV DNA in hepatocytes of HBeAg pos and HBeAg neg

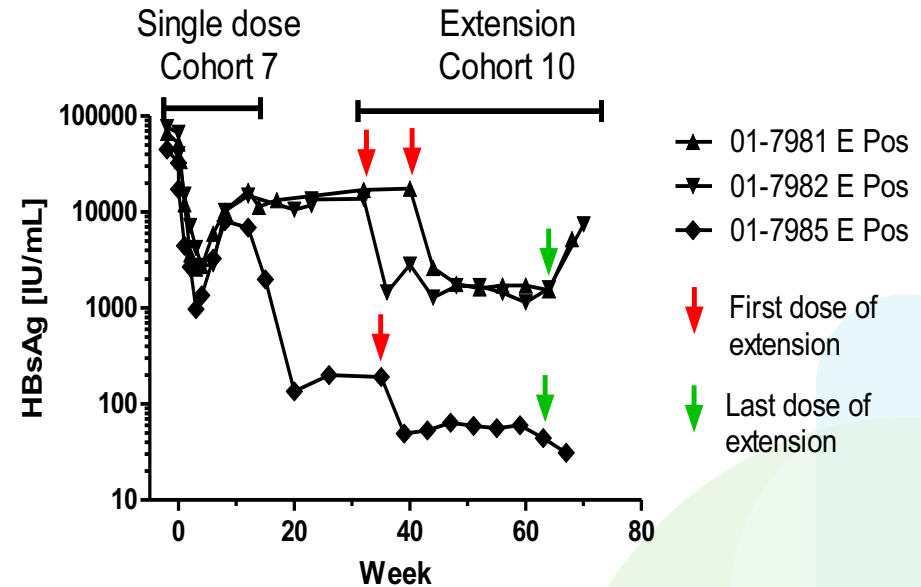


HBsAg reduction in HBeAg negative patients

HBeAg neg



HBeAg pos



- Even with undetectable circulating HBV DNA, HBV RNA, HBcrAg and HBeAg significant amounts of HBsAg persist

Where we believe this leaves us

- Integration has been shown to occur as early as acute infection
 - ~10% of circulating virions contain dsL DNA, instead of RC DNA
 - Largely studied as a means of assessing clonality and for possible oncogenic effects
 - Has been mostly viewed as a result of “failed” reverse transcription
 - Generally hasn’t been considered as transcriptionally active
- These results should make us ask if this isn’t instead an effective viral response to host immunological pressure
- If so, even with complete loss of cccDNA activity, HBsAg may persist if the host can’t also control transcription from integrants or eliminate cells with active transcription from integrants
 - **A question for the field: Is this what we historically have referred to as the “inactive carrier” state?**

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