9TH ANNUAL
DIGESTIVE DISEASES: NEW ADVANCES

September 16–17, 2022

W Hotel
Philadelphia, PA

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Hepatitis B Cure
New Drugs, Novel Strategies

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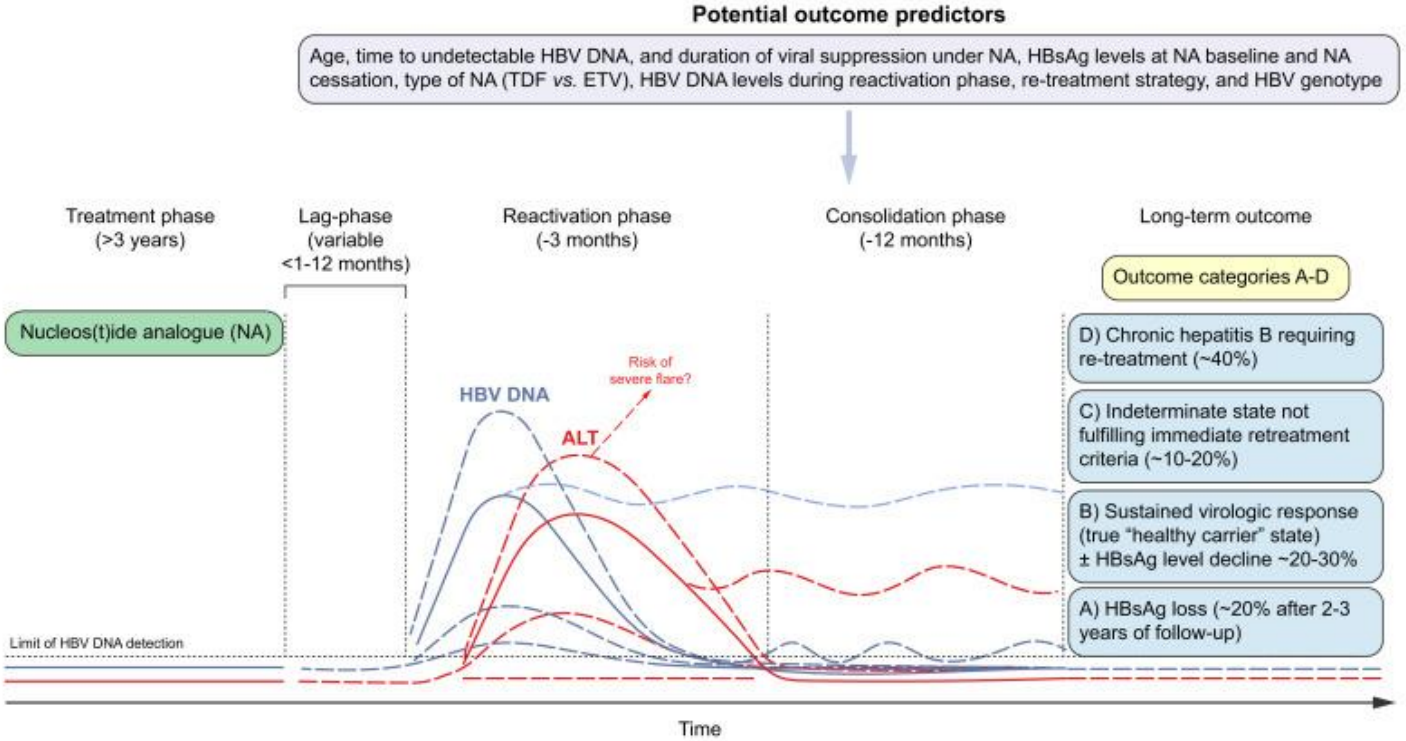
Disclosures

- **Jordan J. Feld MD, MPH**
  - **Consulting:** AbbVie, GlaxoSmithKline, Janssen, Roche, Eiger, Enanta, Antios, Arbutus, and Bluejay
  - **Research:** AbbVie, Gilead, GlaxoSmithKline, Janssen, Roche, Eiger, and Enanta

Outline

- **Stopping Nucs**
- **New Treatment for HBV & HDV**
  - Virological targets
  - Immunological targets
  - Combinations

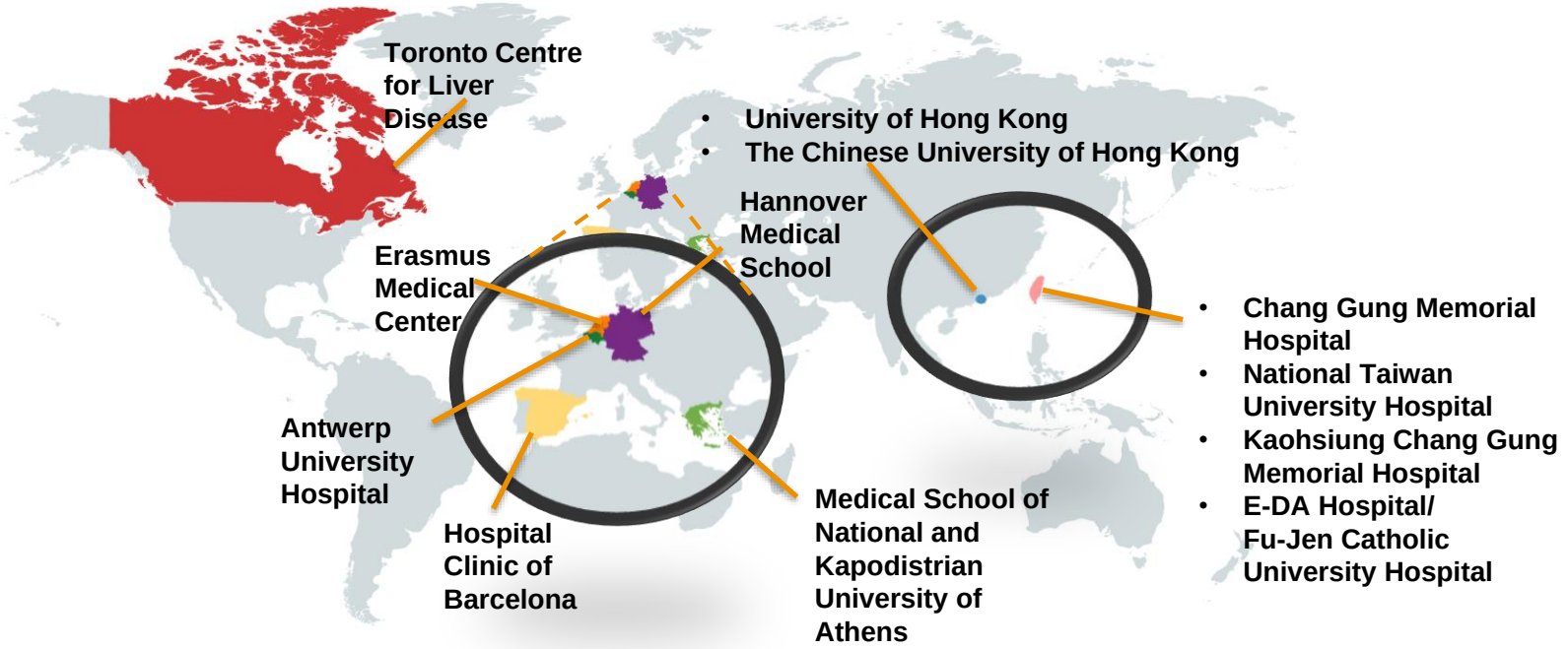
Increasing Interest in Stopping Nucs



Lampertico & Berg. *Hepatology*. 2018.

RETRACT-B

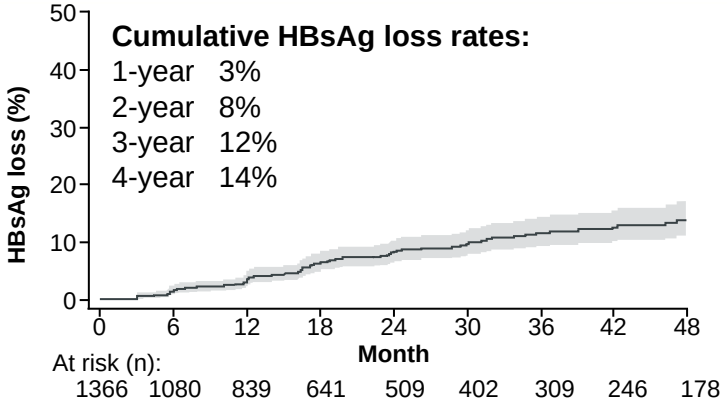
International collaborative effort to outcomes of NA withdrawal

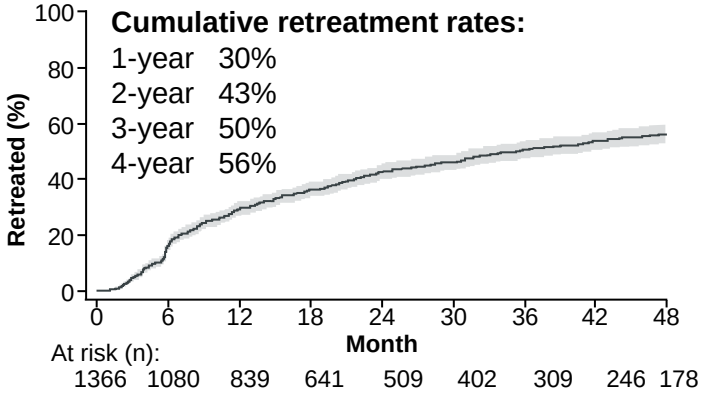


Hirode. *Gastro*. 2022.

Large International Cohort – NA Withdrawal

Baseline demographics	n (%), unless stated
Total (N)	**1541**
Age at baseline, years, mean ±SD	53 ± 11
Male	1117 (73)
Race: Asian/White/other	**1359 (88)**/ 152 (10)/ 30 (2)
HBV genotype: A/B/C/D	7 (0.5)/ 669 (43)/ 172 (11)/ 23 (2)
NUC type prior to cessation: ETV/TDF/other	927 (60)/ 443 (29)/ 171 (11)
NUC duration, years, median (IQR)	3.0 (2.8–3.8)
At baseline (time of NA cessation)	
Cirrhosis	70 (5)
HBsAg, Log_{10} IU/mL, mean ± SD	2.6 ± 0.8
ALT x ULN, median (IQR)	0.6 (0.4–0.8)



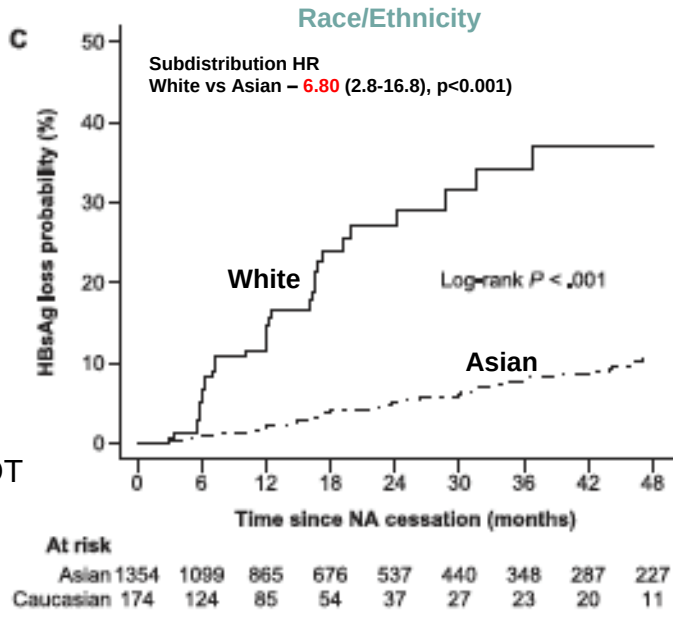


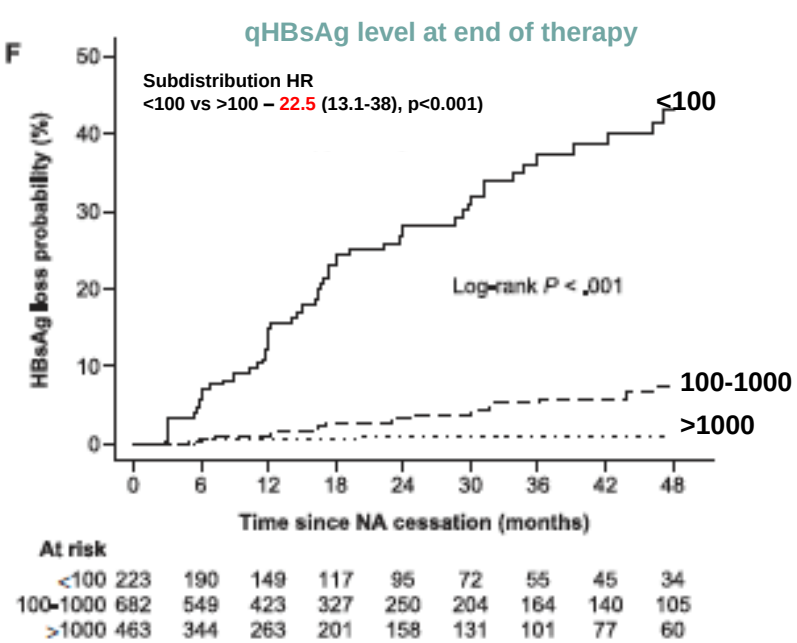
Hirode. *Gastro*. 2022.

Predictors of HBsAg loss

Predictors UV analysis
- Asian
- HBsAg<100
- Age > 50
- TDF vs ETV
- Prior IFN therapy

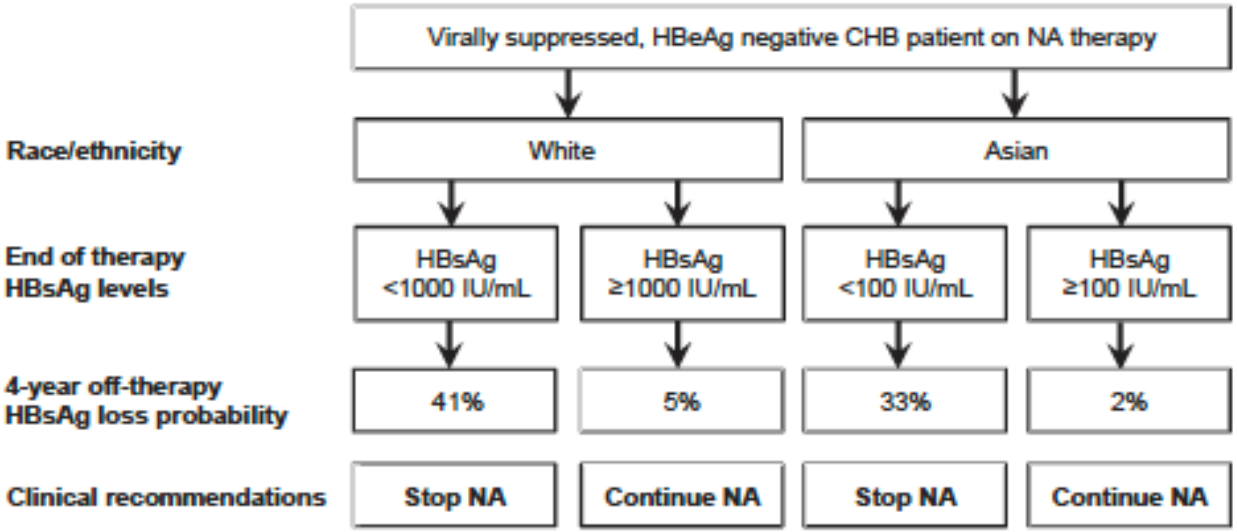
No effect of:
- Sex
- HBeAg at baseline
- ALT at baseline or EOT





Hirode. *Gastro*. 2022.

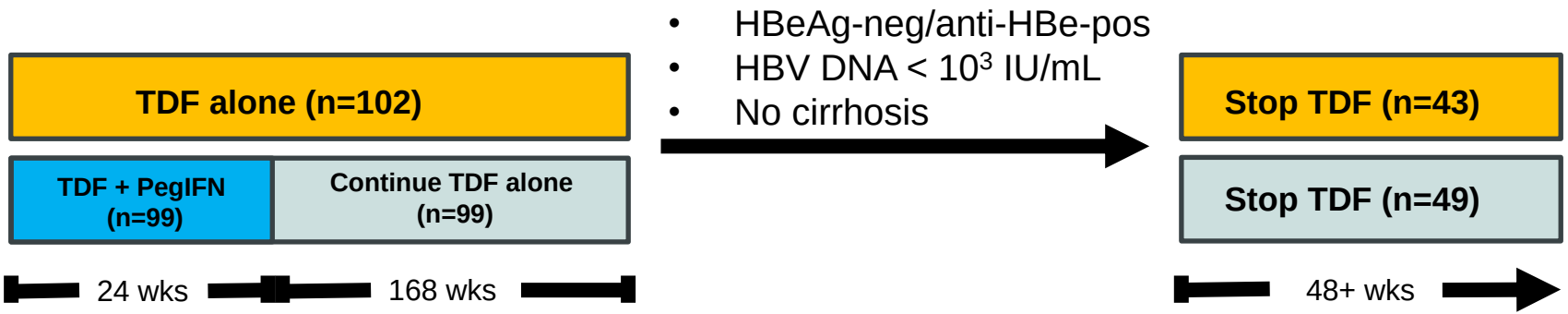
Practical Approach



Different HBsAg thresholds for withdrawal: White 1000 IU/mL
Asian 100 IU/mL

Are Post-Withdrawal Flares Beneficial?

NIH-Sponsored Hepatitis B Research Network (HBRN)
Prospective evaluation of NA withdrawal after 4 years of therapy



- HBsAg decline/loss
- Outcomes: ALT elevations (Grade 1 1-2x ULN, 2 2-5x ULN, 3 5-10x ULN, 4 >10x ULN)
- Active disease at end of f/u (ALT > 2x ULN with HBV DNA > 10^5 IU/mL

Feld. AASLD. 2021.

Withdrawal Population

Variable	TDF alone (n=43)	TDF + PegIFN (n=49)	P-value
	n (%)/ med (IQR)	n (%)/ med (IQR)	
Male Sex, n (%)	30 (69.8)	32 (65.3)	0.67
Age (study entry), yrs	45.9 (39-56)	43.4 (37-53)	0.16
Race, n (%)	n=42	n=49	0.92
Asian	34 (81.0)	41 (83.7)	
White	3 (7.1)	4 (8.2)	
Black	5 (11.9)	4 (8.2)	
HBV genotype			0.32
A1	4 (9.3)	3 (6.1)	
A2	3 (7.0)	2 (4.1)	
B	19 (44.2)	24 (49.0)	
C	9 (20.9)	17 (34.7)	
D	5 (12)	1 (2)	
E	3 (7)	2 (4)	

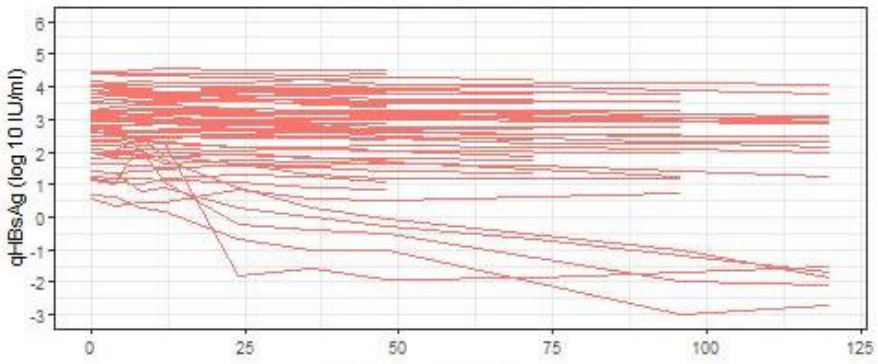
Variable	TDF alone (n=43)	TDF + PegIFN (n=49)	P-value
	n (%)/ med (IQR)	n (%)/ med (IQR)	
At study entry			
HBeAg-positive	8 (18.6)	13 (26.5)	0.46
HBV DNA (log IU/mL)	5.6 (4.9:6.4)	57 (4.5:6.6)	0.82
qHBsAg (log IU/mL)	3.2 (2.9:4.0)	3.1 (2.8:3.9)	0.24
qHBsAg<100	0	2 (4.1)	0.50
ALT x ULN	2.7 (1.9:5.1)	2.9(1.9:4.3)	0.83
At Withdrawal (Wk 192)			
HBeAg-positive* / anti-HBe-positive	0 / 38 (92.7)	0 / 46 (95.8)	0.79
HBV DNA (log IU/mL)	0.7 (0.0:1.0)	0.9 (0.6:1.1)	0.07
qHBsAg (log IU/mL)	3.2 (2.6:3.6)	2.7 (2.0:3.3)	0.08
qHBsAg<100	4 (9.3)	14 (28.6)	0.035
ALT x ULN	1.1 (0.8:1.5)	1.0 (0.8:1.3)	0.29

Feld. AASLD. 2021.

Did ALT Flares Lead to HBsAg Decline?

Trajectory of qHBsAg after TDF withdrawal by ALT flare (5x ULN)

Without Grade 3 flare (> 5x ULN)

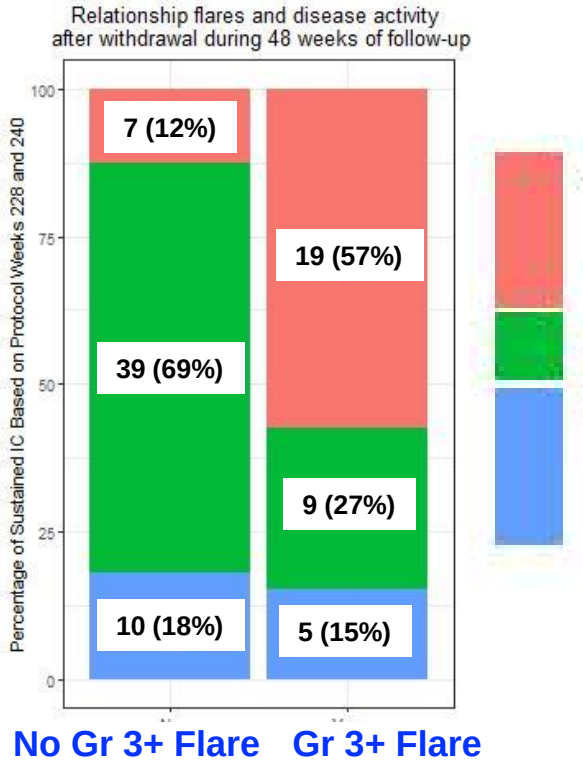


With Grade 3 flare (> 5x ULN)

Greater HBsAg decline seen in those ***without*** ALT flares

Feld. AASLD. 2021.

Do Flares Predict Future Disease Activity?



Sustained phenotype
(≥ 2 visits) at end of follow-up

Active:
HBV DNA > 2,000 IU/mL and
ALT > 2x ULN or started treatment

Indeterminant

Inactive Carrier or Immune Control:
HBV DNA < 1,000 IU/mL and
ALT < 1x ULN or lost HBsAg

Feld. AASLD. 2021.

Factors Associated With ALT Flares (>5x ULN)

- **Baseline**
  - **Age** - OR 1.05 (95% CI 1.01-1.09)
  - **HBV DNA** (log) – OR 1.50 (1.12-2.01)
- **At end of treatment**
  - **No factors!**
  - **ALT, DNA, HBsAg not predictive!**
- **At flare visit**
  - **HBV DNA** – OR 2.79 (2.23-3.49)
  - **qHBsAg** - OR 9.58 (2.36-38.9)
- **At visit prior to flare**
  - **HBV DNA** – OR 3.02 (2.28-4.02)
  - **HBV DNA > 4 log** - OR 29.9 (12.3-72.3)

ALT flares can be predicted…***and prevented***

Feld. AASLD. 2021.

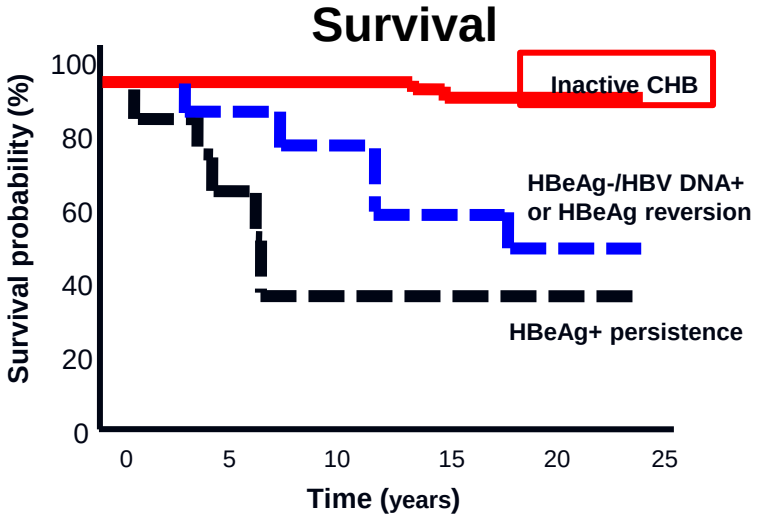
Conclusions on nuc Withdrawal

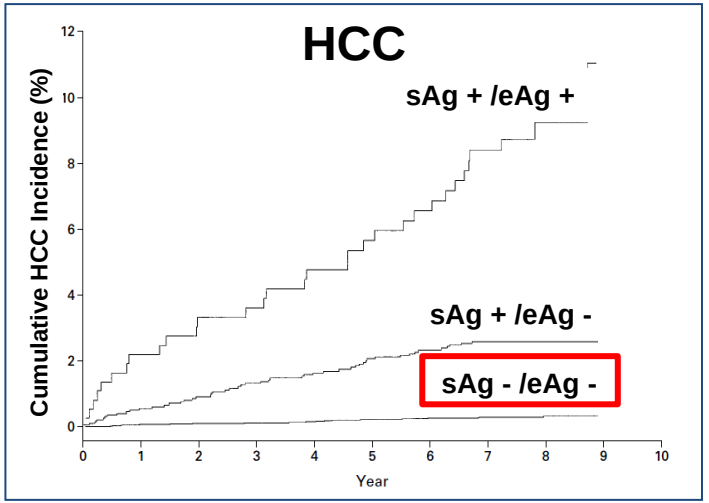
- HBsAg loss/sustained inactive disease after NA withdrawal infrequent in Asians
- ALT flares not required for HBsAg loss/decline…***questions concept of 'therapeutic flare'***
- High HBV DNA (>4 log IU/mL) predicts flare → trigger to restart Nuc
- Bad outcomes if cirrhosis, HBeAg+ or even anti-HBeAg-neg

If you consider this → key considerations:

1. **Non-cirrhotic, HBeAg-neg/anti-HBe-pos**
2. **Reliable follow-up!**
3. **Asians: qHbsAg<100, White qHbsAg<1000**
4. **Follow closely – if HBV DNA > 4log – restart – don't wait for the flare**

What Are the Goals of New HBV Therapy?
Learning From Natural History





- Very inactive disease and ideally HBsAg loss associated with excellent long-term and cancer-free survival
- ***A good goal for therapy***

Fattocvich. *Gut*. 2008; Yang. *NEJM*. 2002.

Goals of Therapy

- **Cure the infection**
  - True cure = all traces of HBV gone from the liver (ie. like HCV)
  - This is **VERY** difficult (if not impossible) → cccDNA + integrated HBV DNA
- **Functional cure**
  - Use the markers of excellent natural history…

1. HBsAg loss (ideally with anti-HBs)
2. Possibly…sustained off treatment inactive disease without HBsAg loss (HBeAg –ve, DNA undetectable, normal ALT, normal histology) (some call this '**partial cure**')

Is There Consensus?

88% of attendees at EASL/ASSLD HBV Endpoints conference chose Functional Cure as the preferred goal for future therapies

Sustained Virological Response
(sAg +ve, DNA negative, off therapy)
An advance but not enough of one

Functional Cure
(sAg loss with undetectable DNA & Normal ALT)
Challenging but achievable goal

Sterilizing cure
(cccDNA loss)
Too hard to achieve

EASL/AASLD Endpoints Meeting Take 2 – 2019.

Is There Consensus Changing?

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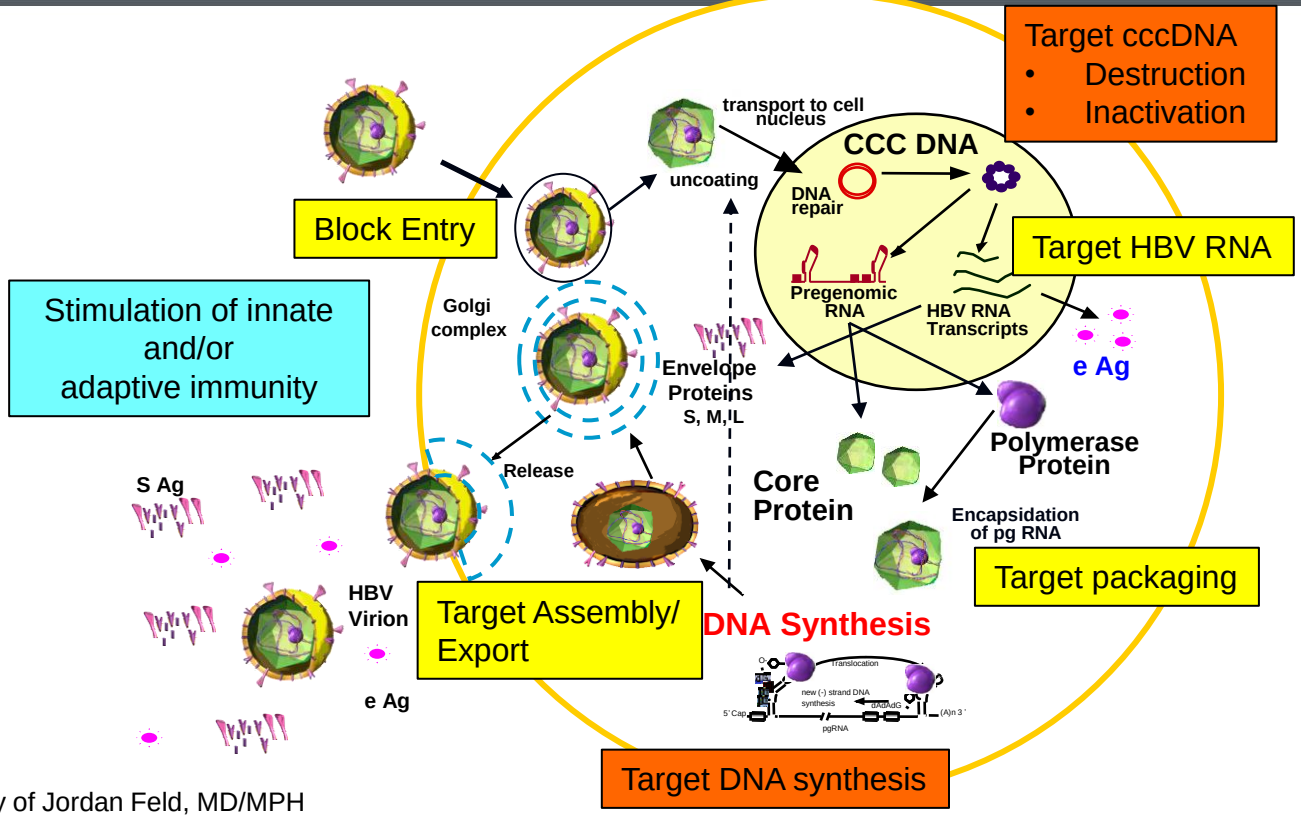
(sAg loss with undetectable DNA & Normal ALT)
Challenging but achievable goal

Partial cure endorsed by many
- **HBsAg + but low level**
  - **<100? <10?**
- **HBV DNA low vs undetectable**
- **?HBV RNA or HBcrAg negative?**

Sterilizing cure
(cccDNA loss)
Too hard to achieve

EASL/AASLD Endpoints Meeting Take 3 – 2022.

Potential Targets in the Lifecycle



Slide courtesy of Jordan Feld, MD/MPH

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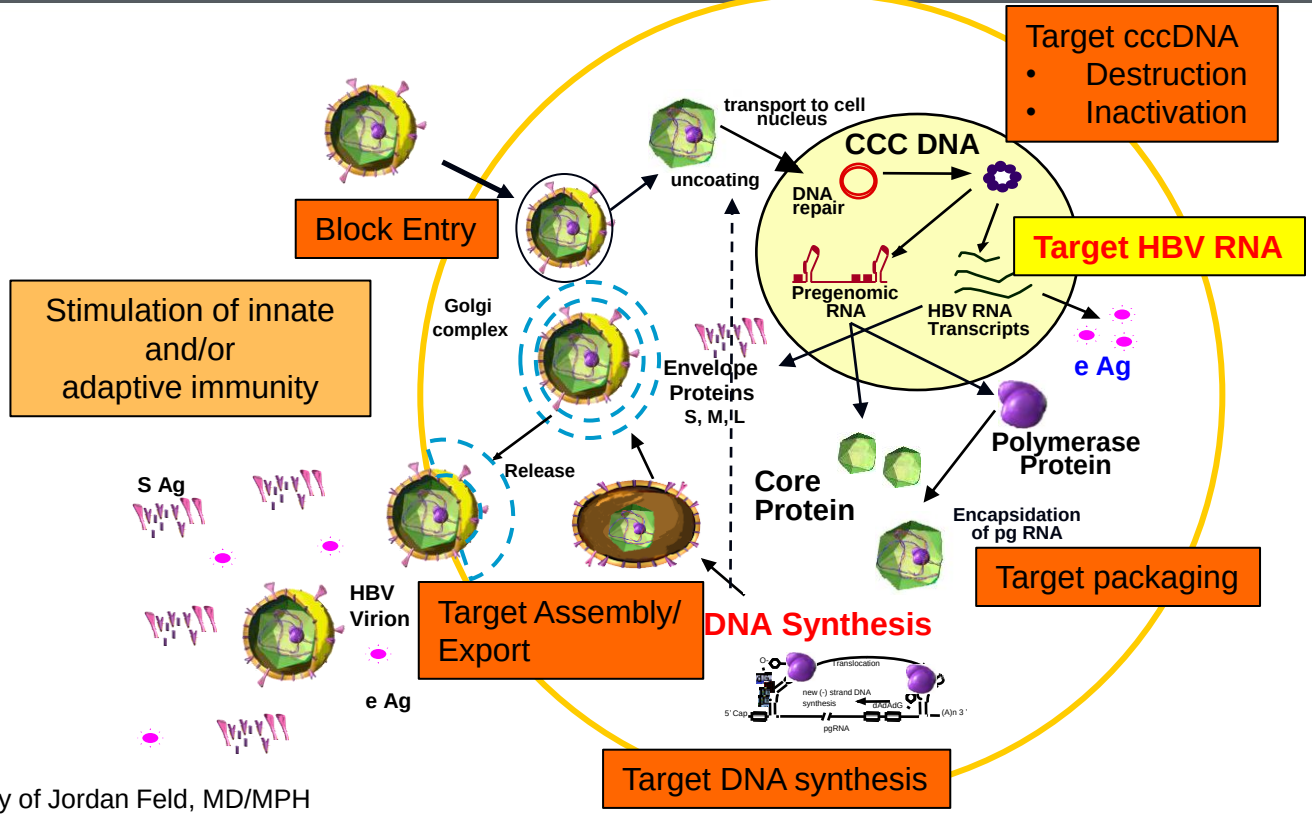

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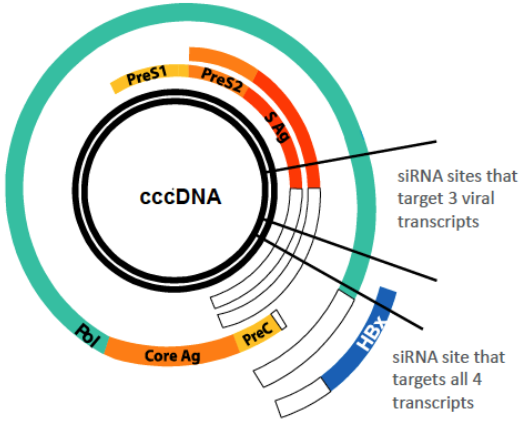
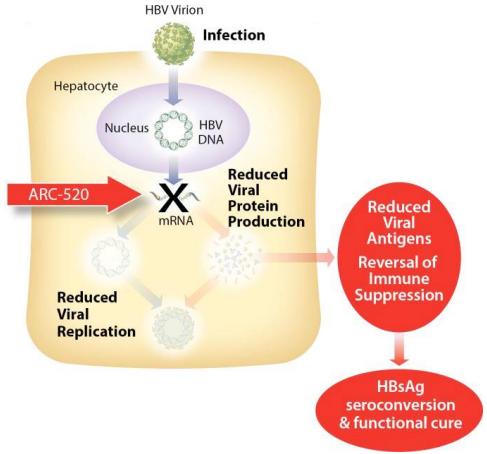
Target RNA – siRNA



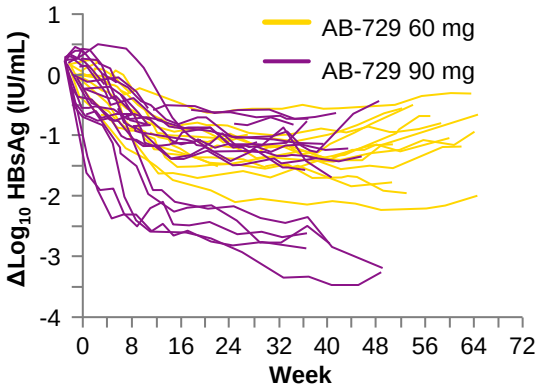


- Overlapping reading frames = conserved regions
- siRNA targeting can eliminate ***all*** HBV gene products
  - Antigen reduction (sAg, pol, core) → **restore immune function**
  - pgRNA → **block replication**

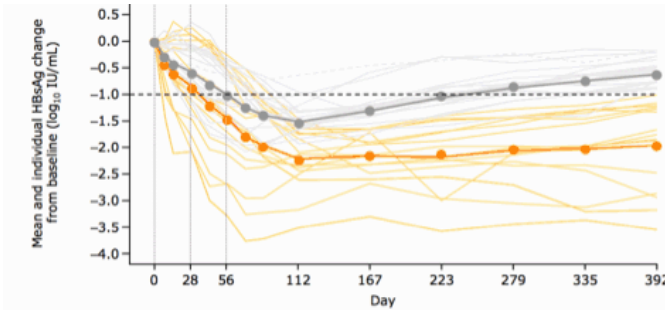
Woodell. *Mol Ther*. 2013.

RNA Inhibitor – siRNA

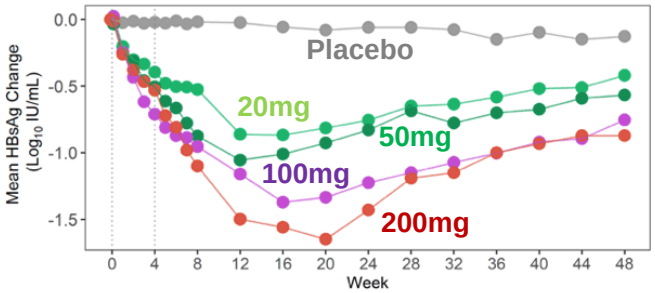
AB-729 (60/90 mg) + Nuc



JNJ-3989 (ARO-HBV) + Nuc



VIR 2218 + Nuc

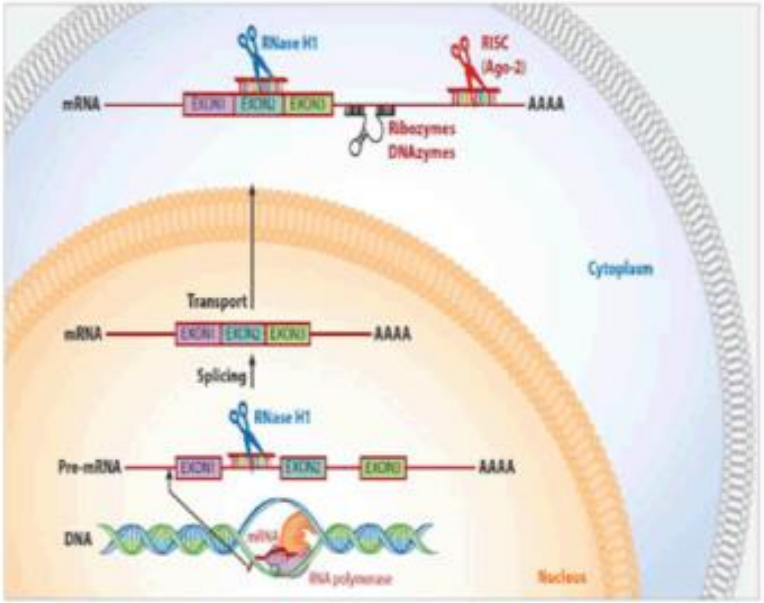


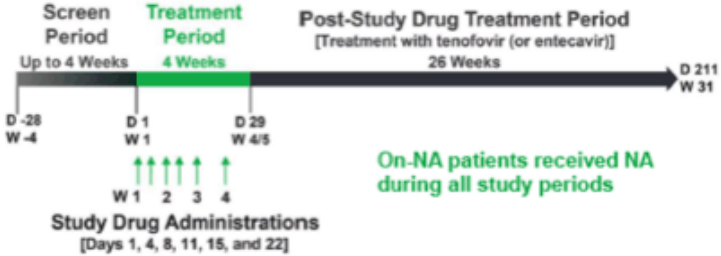
- Fairly consistent results – initial decline → **plateau – why?**
- Off-treatment – sustained response ~40% - what does this mean? Immune control?
- Infrequent dosing, minimal toxicity & resistance

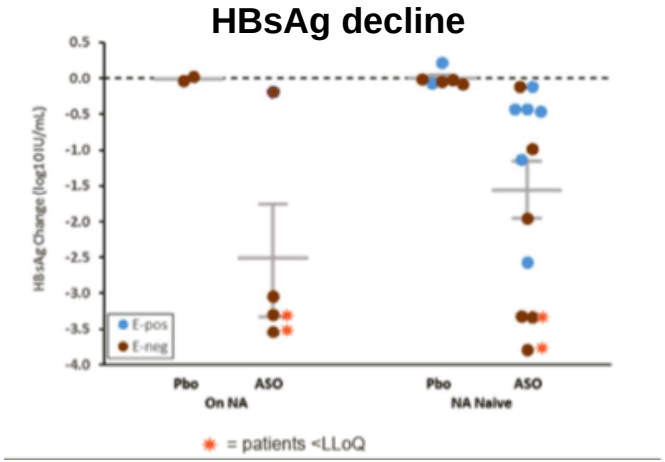
Gane et al. EASL. 2020; MF Yuen. AASLD. 2021; MF Yuen. AASLD. 2021.

Antisense Oligonucleotide – GSK 836

- Similar concept to RNAi
- ASO binds HBV RNA species and degraded by RNase H rather than Ago



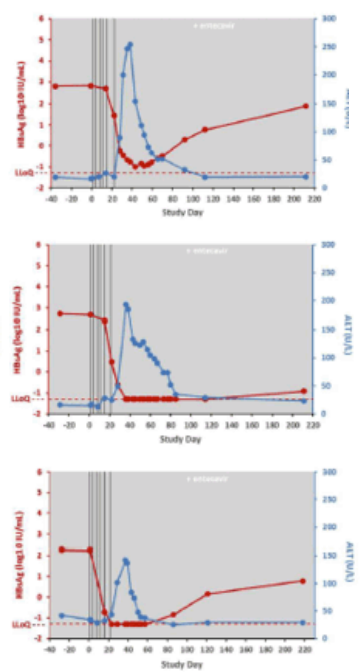


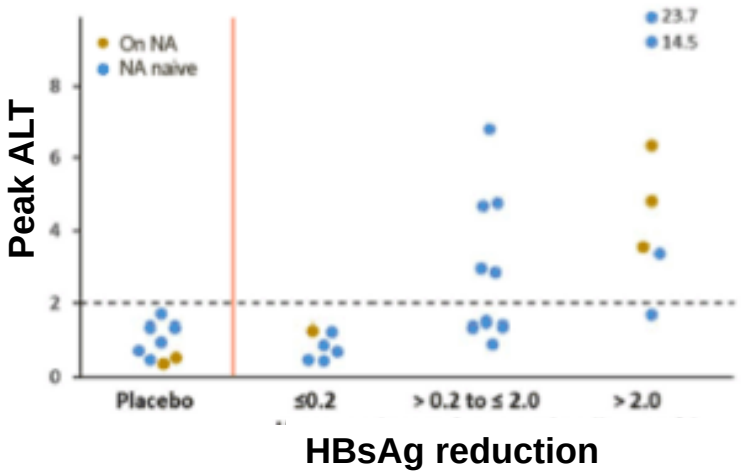


MF Yuen. *Nat Med*. 2021.

RNAi – Antisense Oligonucleotide

Nuc suppressed patients





- ALT flare with HBsAg decline – similar with and without NA
- Marked HBsAg decline in NA-suppressed
- Non-GalNac targeting more effective! Possibly TLR8 related…
- Are these immune restoration, toxicity or something else entirely?

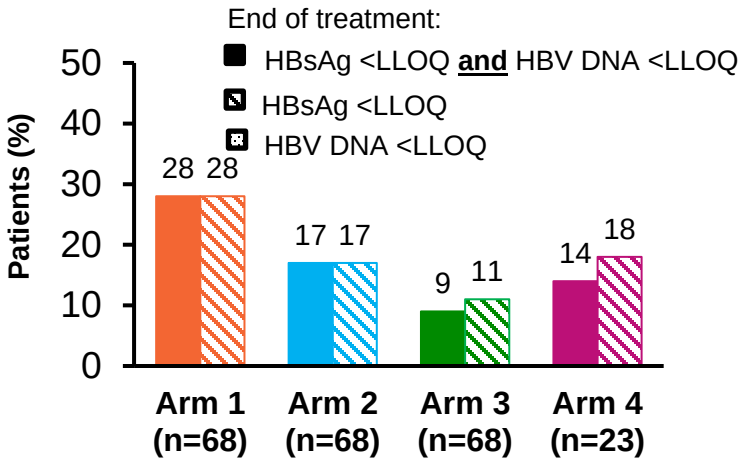
MF Yuen. *Nat Med*. 2021.

B-Clear: Phase 2 of ASO (Bepirovirsen) +/- NA

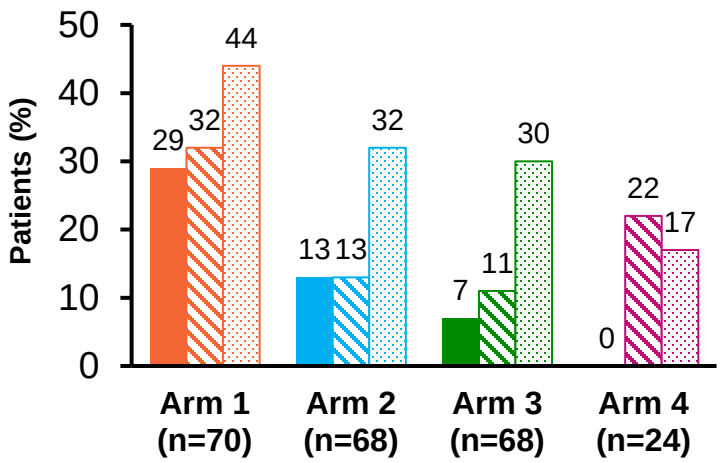
Patients With HBsAg <LLOQ and/or HBV DNA <LLOQ at End of Treatment

BPV 300 mg w/ LD x24wk
BPV 300 mg w/ LD x12wk + PBO x12wk
BPV 300 mg w/ LD x12wk + BPV 150 mg x12wk
PBO x12wk + 300 mg w/o LD x12wk

Patients receiving NUCs



Patients not receiving NUCs



- Most effective with lower HBsAg levels - **~30% HBsAg loss with 24 weeks of therapy!**
- Moving to Phase 3 in HBeAg-negative patients on NA – 300 mg x 24 weeks – simple trial

Yuen MF et al. EASL 2022. #LB004A/4B.

Summary – RNAi & ASO

	RNAi	Antisense Oligonucleotide
Mechanism	• mRNA processing – RISC	• RNase H complex

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HBsAg loss	• Rare	• **30% in low HBsAg levels**

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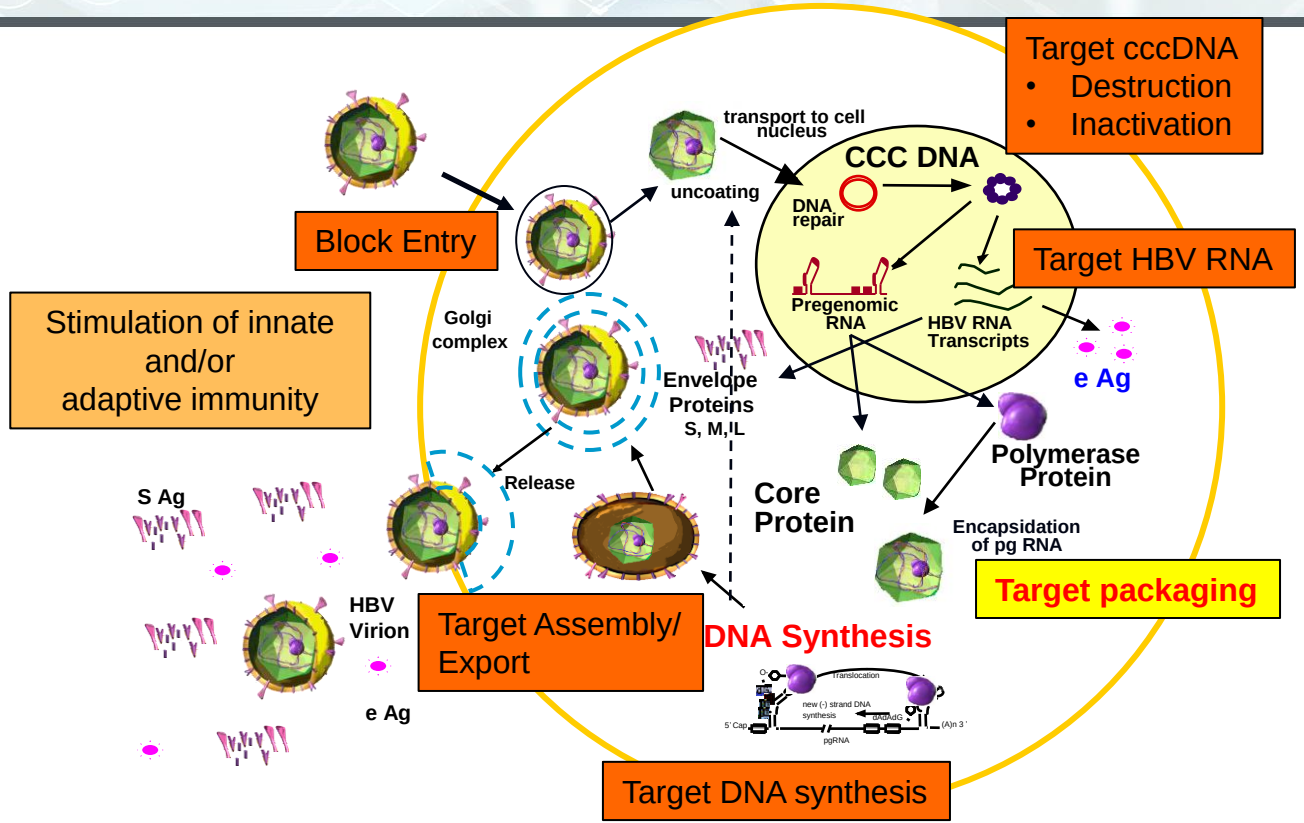
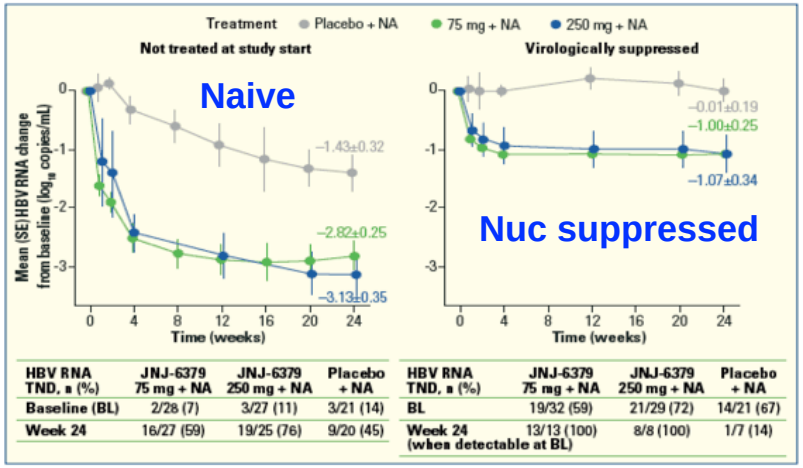


Slide courtesy of Jordan Feld, MD/MPH

Capsid Assembly Modulators (CAMs)

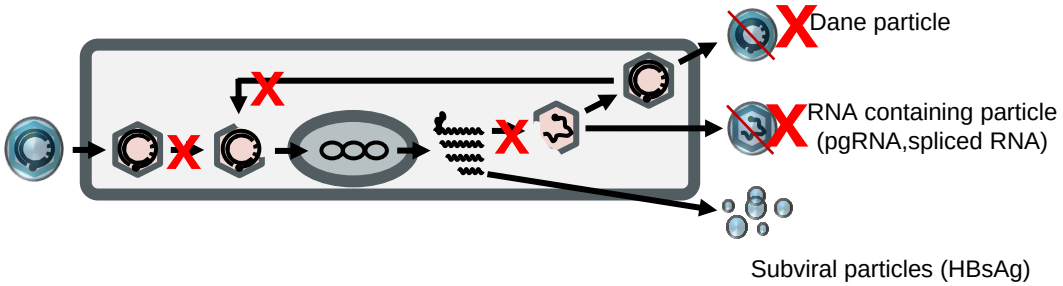
JNJ-6379 PO OD x 24 w in non-cirrhotic naïve/nuc-suppressed CHB

HBV RNA



HBV RNA TND, n (%)	JNJ-6379 75 mg + NA	JNJ-6379 250 mg + NA	Placebo + NA
Baseline (BL)	2/28 (7)	3/27 (11)	3/21 (14)
Week 24	16/27 (59)	19/25 (76)	9/20 (45)

HBV RNA TND, n (%)	JNJ-6379 75 mg + NA	JNJ-6379 250 mg + NA	Placebo + NA
BL	19/32 (59)	21/29 (72)	14/21 (67)
Week 24 (whea detectable at BL)	13/13 (100)	8/8 (100)	1/7 (14)



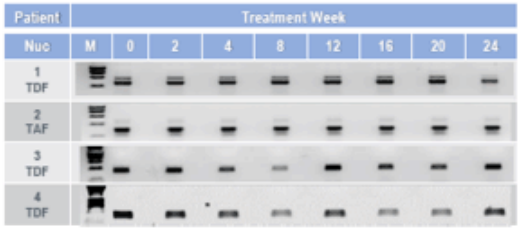
- **Minimal or no effect on HBeAg HBsAg levels**
- **Resistance risk if monotherapy**

- Well tolerated
- Potent HBV DNA suppression with ***limited dose response at higher dose***
- Higher dose may be required for ***disruption of formed capsids to prevent cccDNA replenishment***
- **Many others in development**

Janssen. EASL. 2020.

Will Potent Suppression Allow for Stopping?

Nuc monotherapy

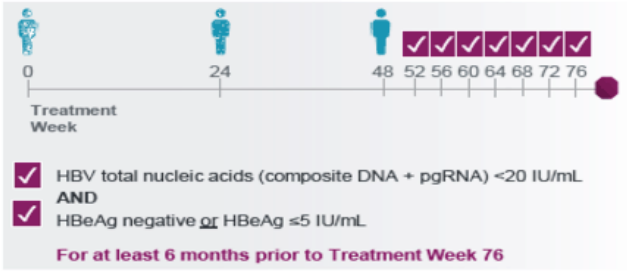


Residual low-level viremia

Addition of CAM

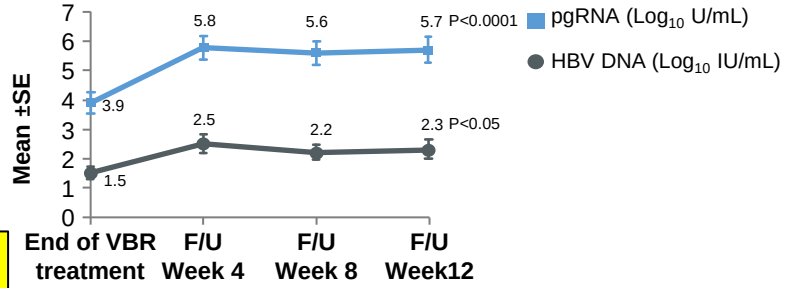
Low-level viremia decline

Is this enough to let them stop?



HBV DNA and pgRNA

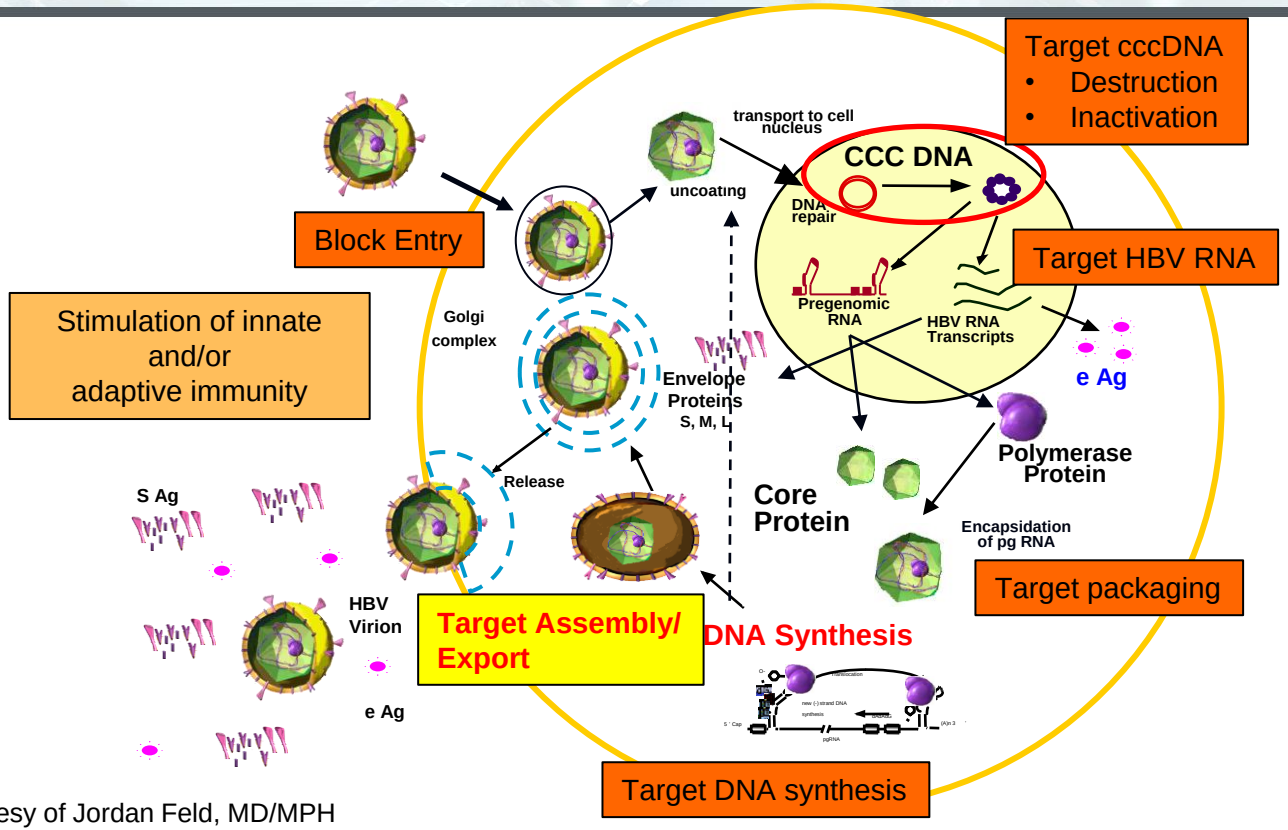
Treatment-naive



- Unfortunately stopping was not effective – 100% rebound
- Would longer therapy have worked? Would a more potent CAM be more effective?

Lalezari. EASL. 2019; Yuen MF. EASL. 2020; Fung. EASL. 2020; Yuen MF. AASLD. 2021.

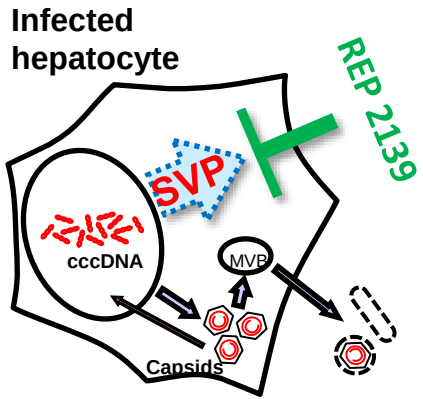
Potential Targets in the Lifecycle

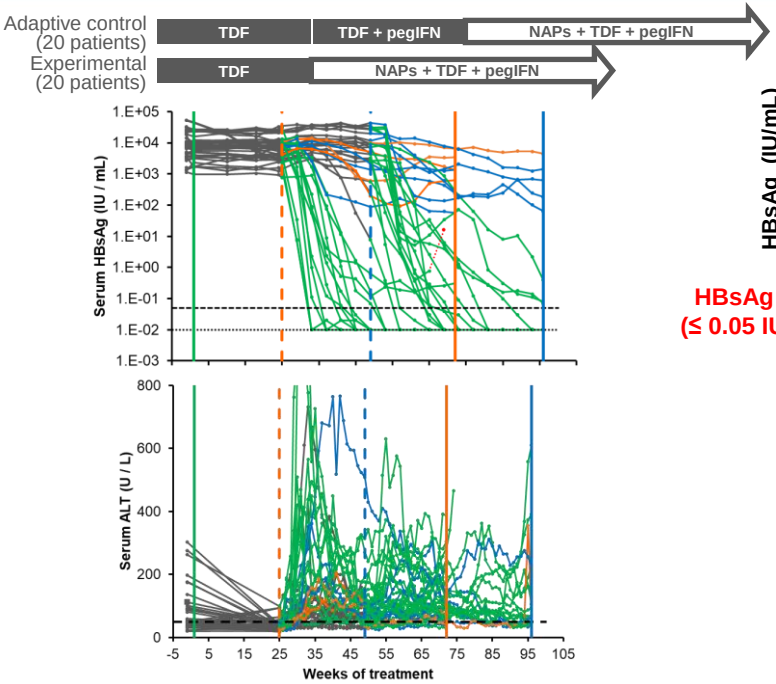


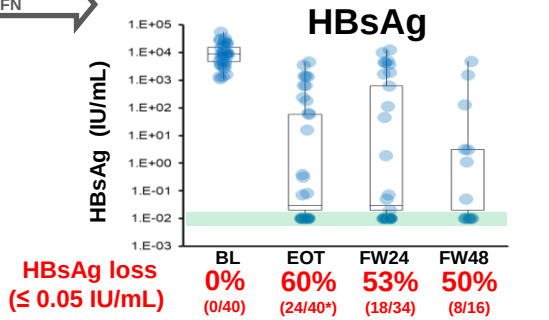
Slide courtesy of Jordan Feld, MD/MPH

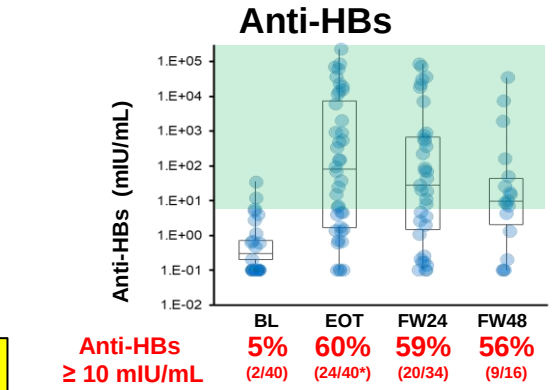
Nucleic Acid Polymers (NAPs) – Reducing HBsAg

- NAPs block assembly/release of **subviral particles**
- Aim to restore immune response → viral control





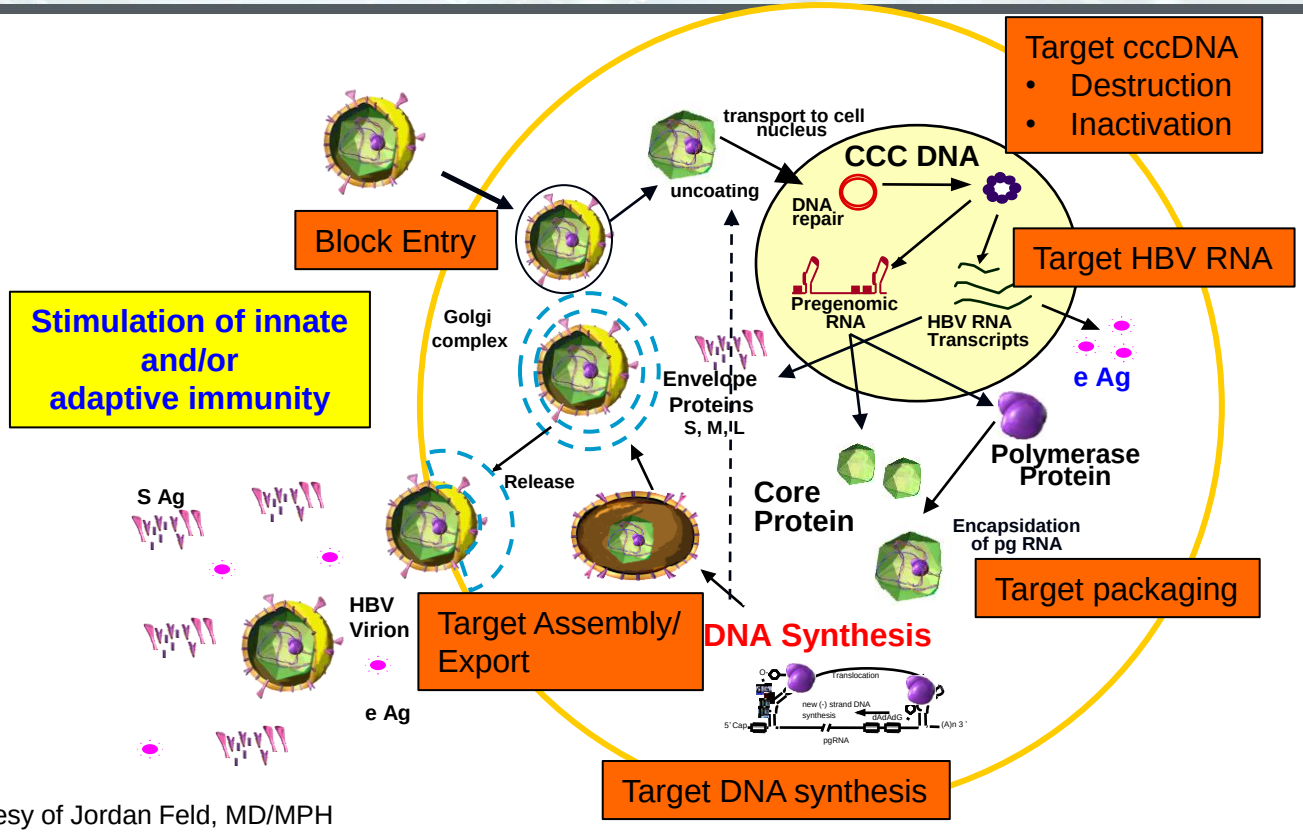




- Marked and seemingly durable HBsAg loss & gain of anti-HBs for CHB & HDV – ***impressive HBsAg loss***
- Interesting…need to confirm ALT flares due to immune activation, new data on mechanism evolving

Bazinet. *Gastro*. 2020.

Potential Targets in the Lifecycle



Slide courtesy of Jordan Feld, MD/MPH

Immunotherapies

Innate

- Cytokine therapy
  - IFN
- TLR agonists
  - TLR7, TLR8
- RIG-I agonists

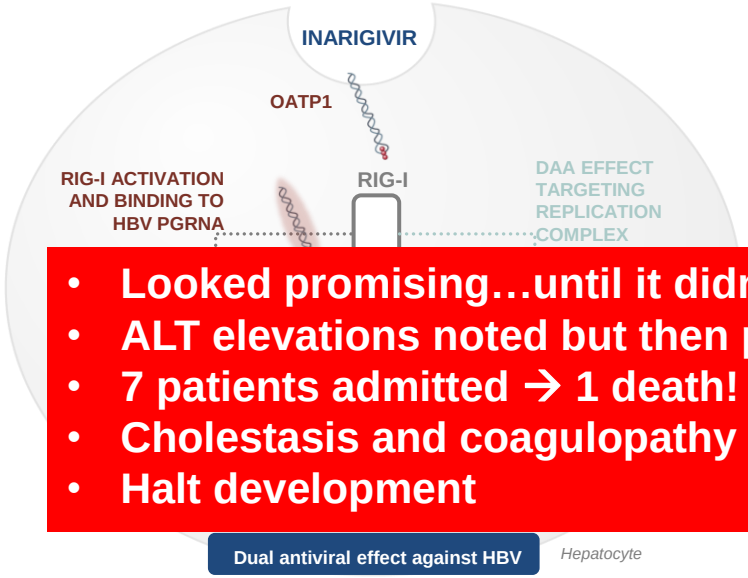
Adaptive

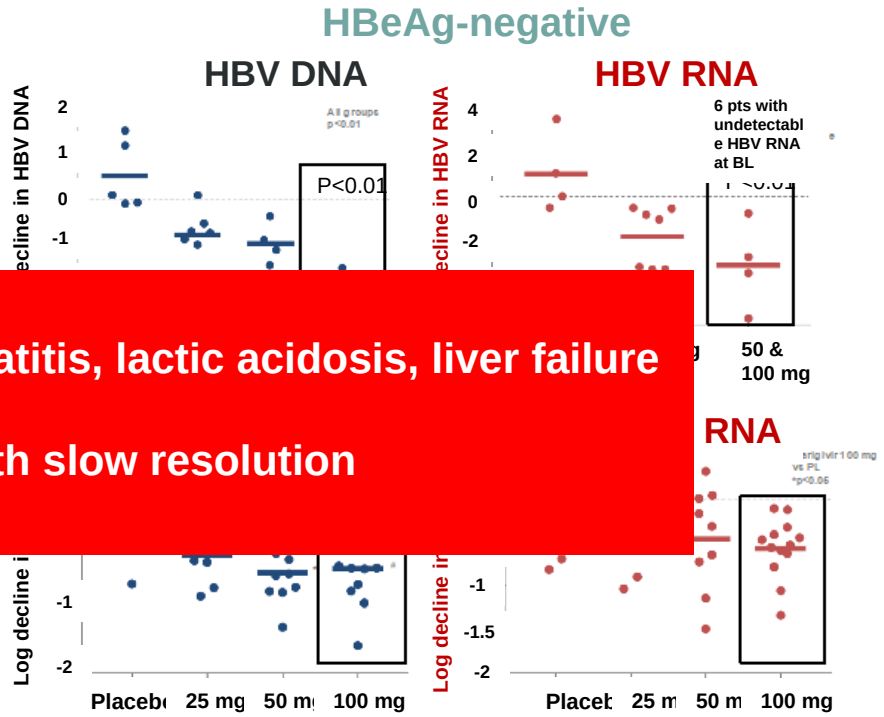
- Therapeutic vaccine
- Checkpoint inhibitors
  - PD-1
  - PD-L1

Immune restoration through inhibition of viral antigens

Attractive but a little bit stressful…flares can be good but flares can scary!

Inarigivir – A Novel Approach With Dual Antiviral Activity





- **Looked promising…until it didn't…**
- **ALT elevations noted but then pancreatitis, lactic acidosis, liver failure**
- **7 patients admitted → 1 death!**
- **Cholestasis and coagulopathy in 2 with slow resolution**
- **Halt development**

- Dose-dependent decline in HBV DNA & HBV RNA **> in HBeAg-neg patients and those with low qHBsAg levels**
- HBV RNA effects persisted after cross-over to tenofovir – 'new set-point'? ***Interesting proof-of-concept***

Yuen et al. AASLD. 2018, Abstract 75; Agarwal. *HBV Forum*. 2020.

Attractive Combinations

HBV DNA suppression

+

Viral Protein Depletion (s, x, core)

Nuc

+/- [illegible]

[illegible]cleic Acid Polymers

cccDNAi

TLR/RIG-I agonist

αPD1/PDL1

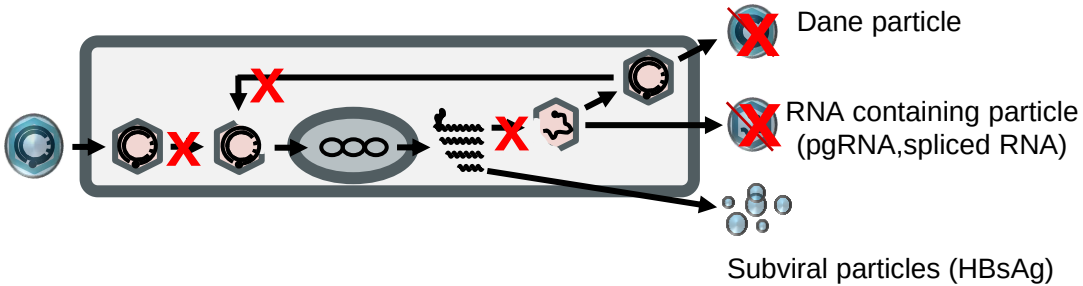
Therapeutic vaccine

Lots of potential combinations

Mix and match…complicated matrix!

The First Combination

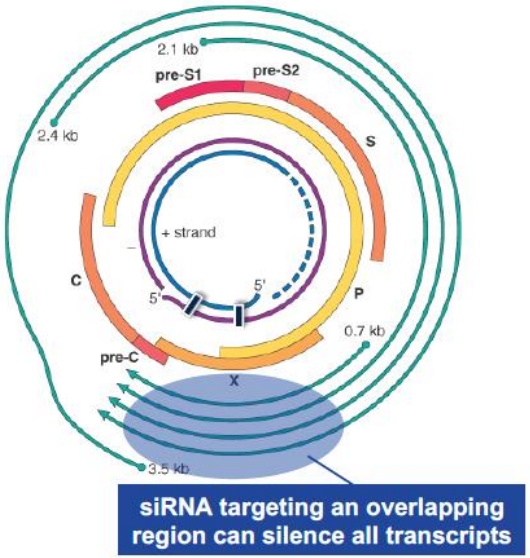
Core Assembly Modulators



2 mechanisms:

1. Block encapsidation – decrease HBV DNA & RNA
2. Block cccDNA formation

siRNA



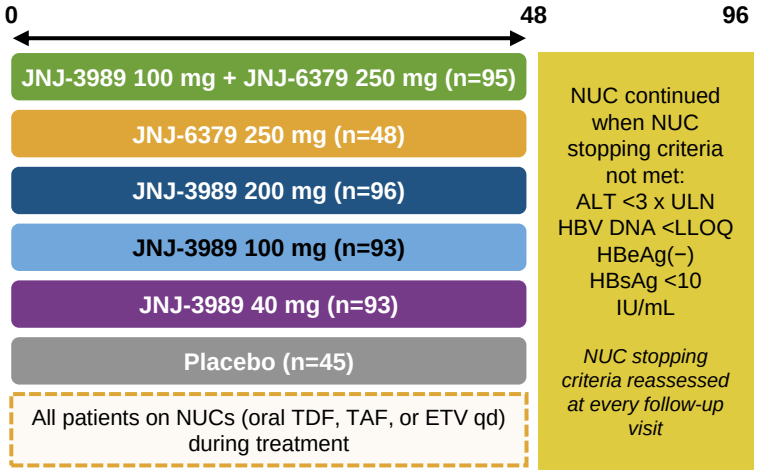
2 mechanisms

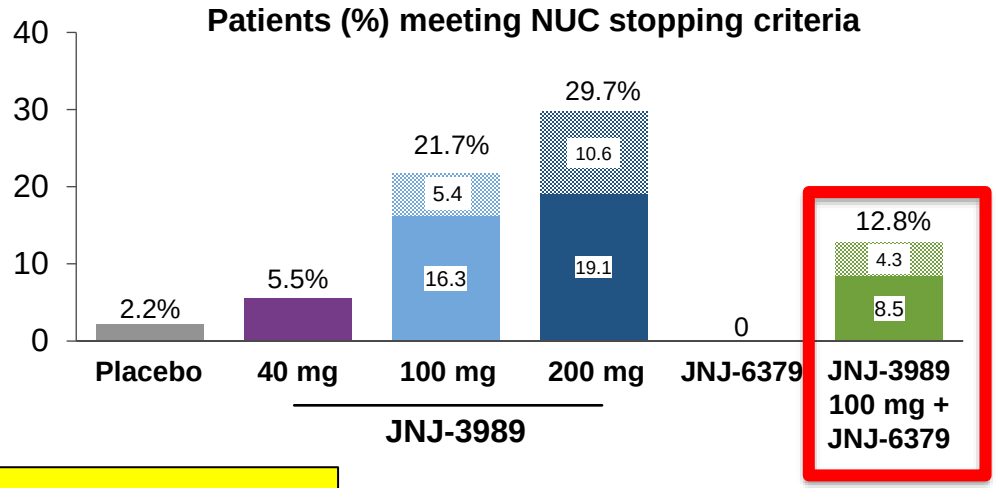
1. Block viral replication – pgRNA
2. Block Ag production – restore immunity

Slide courtesy of Jordan Feld, MD/MPH

REEF-1: siRNA + CAM

siRNA (3989) (40, 100 or 200) vs (6379) vs combination (siRNA + CAM) x 48 wks + 24 wks f/U
Non-cirrhotic, nuc suppressed or naïve, HBsAg>100 IU/mL – stratified by HBeAg & treatment

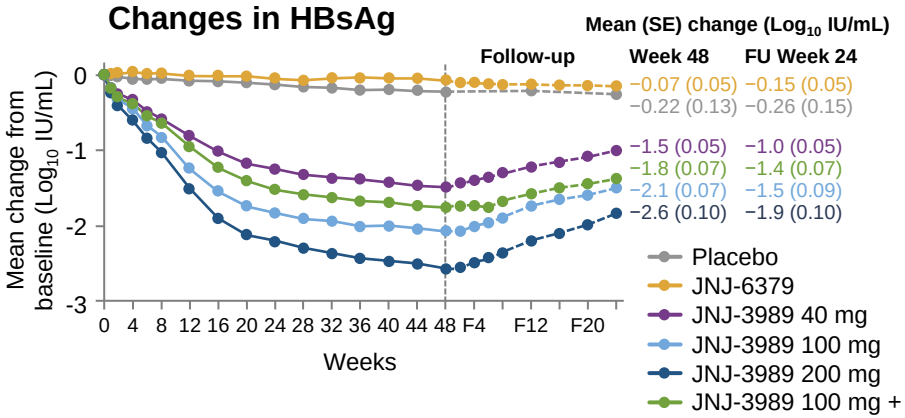


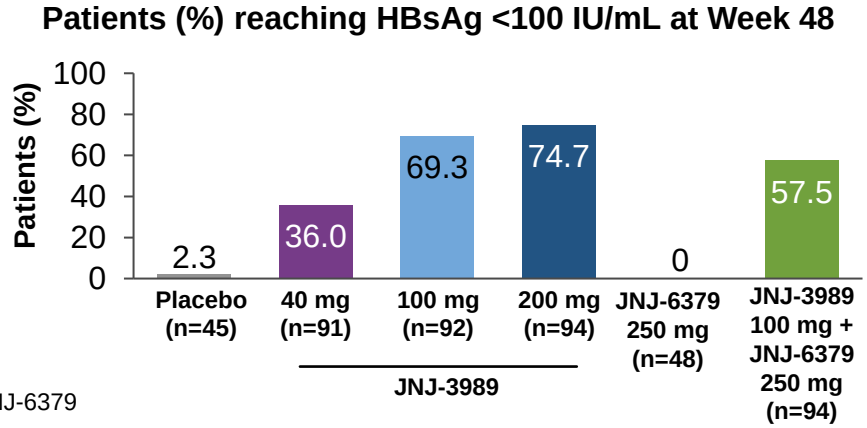


- **Surprisingly combo did worse!**
- siRNA alone at 200 mg most effective…but still not the answer

Yuen MF. AASLD. 2021.

HBsAg Results

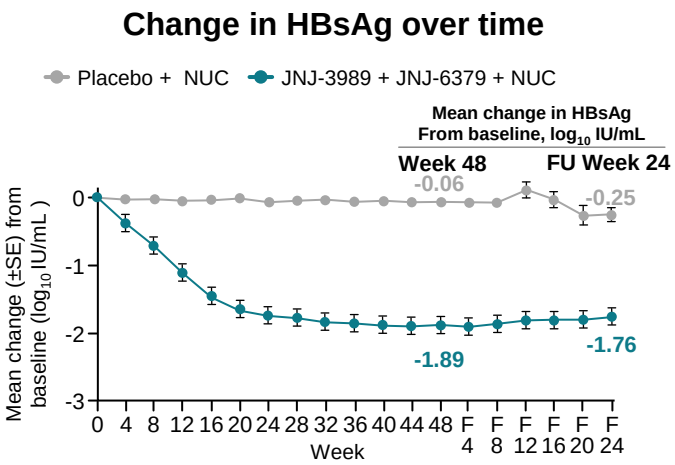




- Initial rapid decline…with plateau after about 24 weeks – why?
- A high proportion achieved HBsAg<100 **but no HBsAg loss!**
- CAM had no effect on HBsAg alone and ?inhibitory effect on siRNA – why?

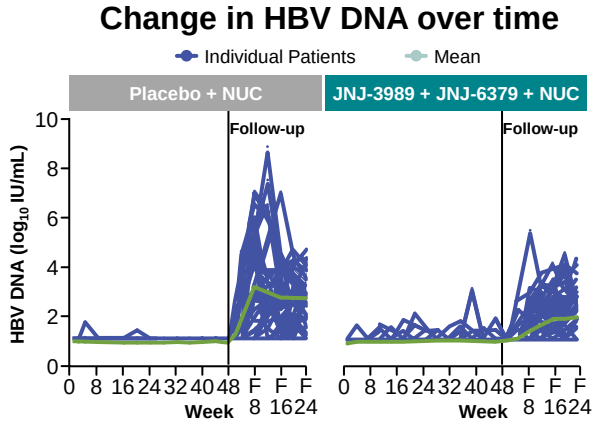
Yuen MF. AASLD. 2021.

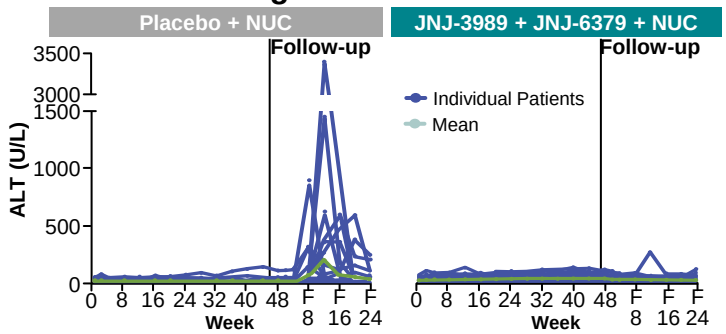
REEF-2 – siRNA + CAM



Change in HBsAg from Week 48 to F/U Week 24

- Despite no HBsAg loss – stable off therapy response
- A bit disappointing…but maybe a new setpoint?
- Could still be useful

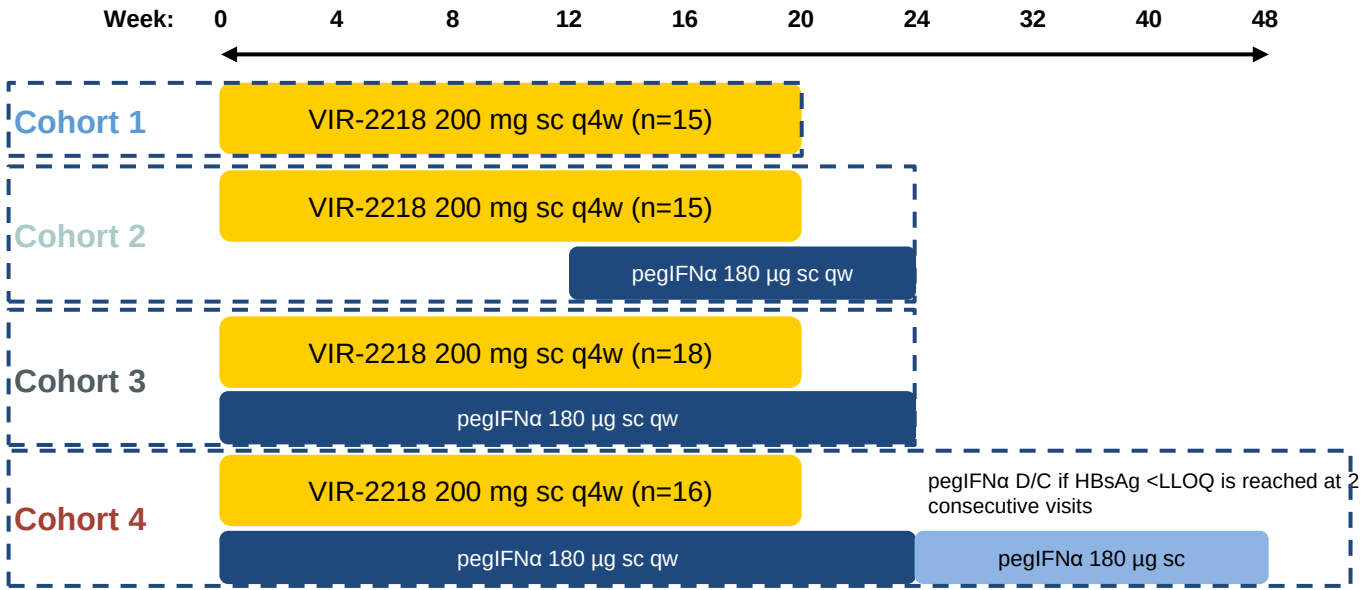




Agarwal K et al. EASL 2022. #GS010.

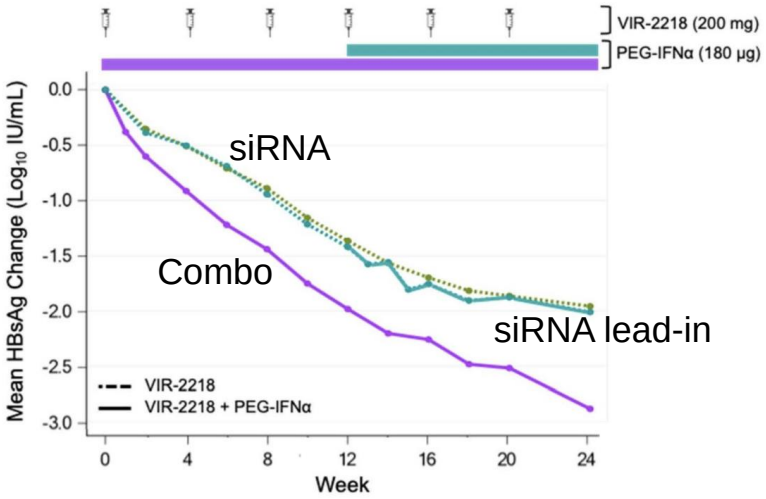
siRNA + PegIFN

siRNA (2218) alone or + PegIFN 180 mcg SC started together or after siRNA lead-in
Non-cirrhotic, nuc suppressed, HBsAg>50 IU/mL



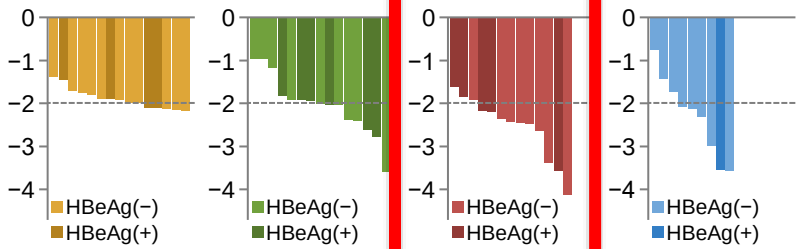
Yuen MF. AASLD. 2021.

siRNA + PegIFN



	Cohort 1 VIR-2218 only	Cohort 2 VIR-2218 lead-in + pegIFNα (12 wk)	Cohort 3 VIR-2218 + pegIFNα (24 wk)	Cohort 4 VIR-2218 + pegIFNα (≤48 wk)
Week 4, n	15	15	17	13
Mean change in HBsAg (Log_{10} IU/mL)	−0.51	−0.51	−0.92	−1.01
Week 12, n	14	15	16	11
Mean change in HBsAg (Log_{10} IU/mL)	−1.39	−1.42	−1.98	−2.05
Week 24, n	15	15	13	9
Mean change in HBsAg (Log_{10} IU/mL)	−1.89	−2.03	−2.55	−2.30

HBsAg change from baseline at Week 24 (Log_{10} IU/mL)



- 3 patients lost HBsAg (started low) and most below 100 IU/mL
- **Combination better but no advantage to 'lead-in' with Ag reduction**
- Perhaps not surprising…Ag reduction may be **more important for adaptive immune response**

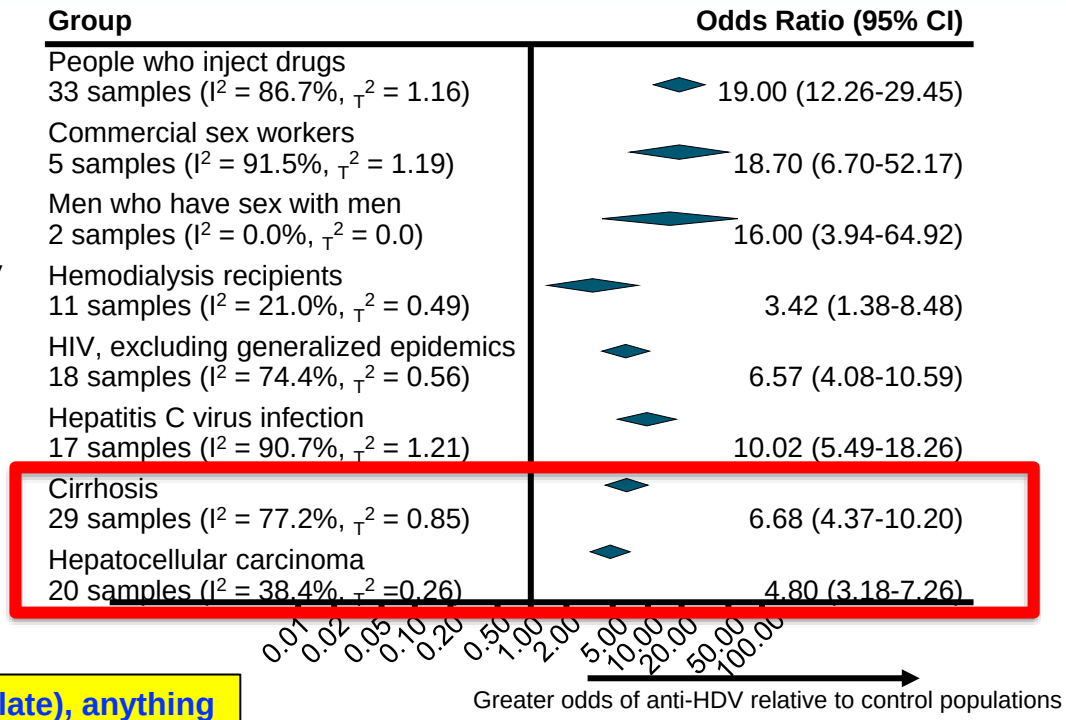
Yuen MF. AASLD. 2021.

It's Not Just Choosing the Right Target/Compound…

- Other MAJOR issues
  1. **Correct population**
     - Highest need?
     - Easiest to show an effect?
     - Immune tolerant/e+/e-/inactive/NA suppressed…
  2. **Correct endpoint**
     - Is sAg loss the same with an NA as with an siRNA?
     - Do we need to look in the liver? Do we need new biomarkers – HBV RNA, HBV crAg others?
  3. **Correct combinations**
     - Lots of possibilities – a huge matrix!!
  4. **Safety!**
     - A major concern…especially with immunotherapies

HDV

- Worst form of viral hepatitis
- Decreasing global prevalence (HBV vaccination & mortality!)
- Population attributable fraction of HBsAg-positive patients suggested HDV accounted for:
  - **18% of cirrhosis**
  - **20% of HCC**
  - Over-represented among all bad outcomes and high risk populations

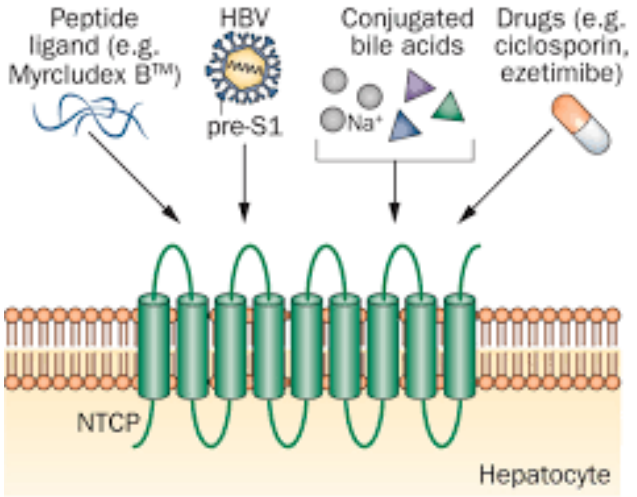


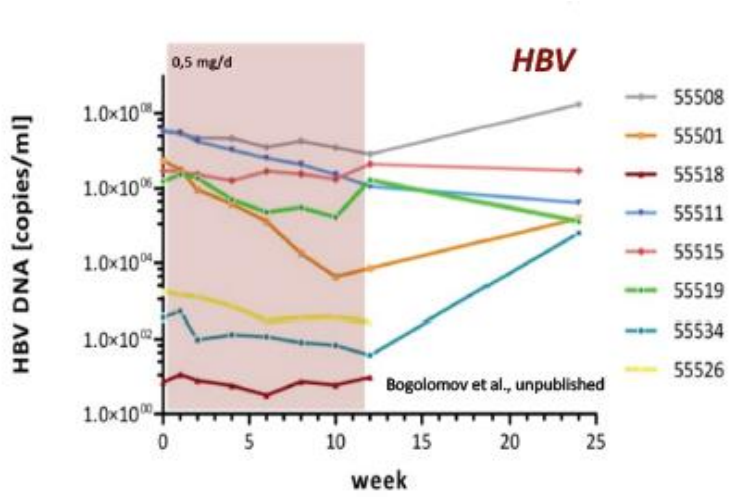
Therapy: Uses on HBsAg – Nucs not helpful (too late), anything that reduces HBsAg may be

Stockdale. *J Hepatol*. 2020

Entry – Bulevirtide (Myrcludex B)

Blocks HBV entry by binding to NTCP receptor



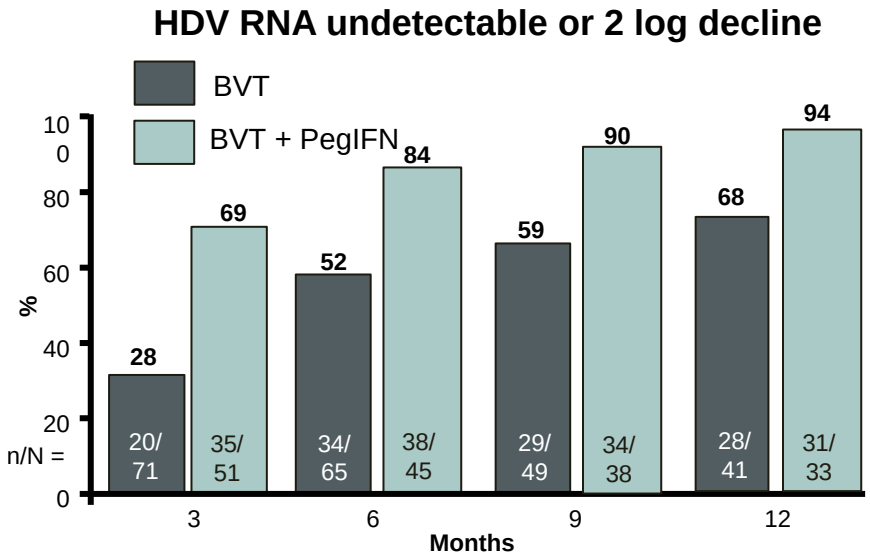


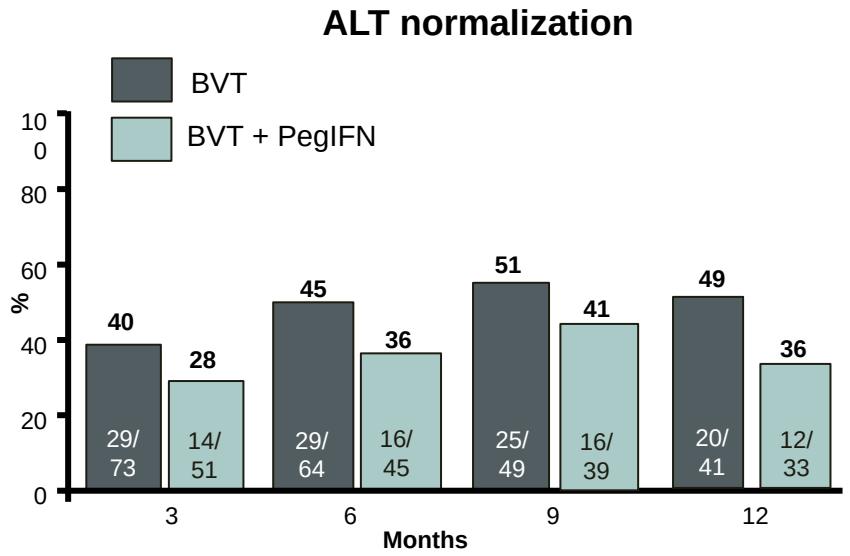
- Modest HBV DNA decline (0.8 log), no effect on HBsAg but ALT normalization (55%) and ***greater effect in HDV***
- **Not likely enough on its own but maybe an adjunct therapy…**

De Ledinghen. AASLD. 2021.

Early Outcomes With HDV

French early access program – bulevirtide 2 mg Sc +/- PegIFN 180 µg/wk - non-randomized





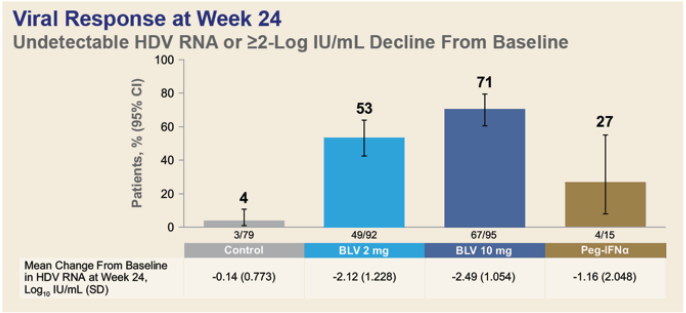
- AEs common but only 2 (BVT) and 3 (BVT + PegIFN D/C for AE
- Bile acid increase in all – no itch

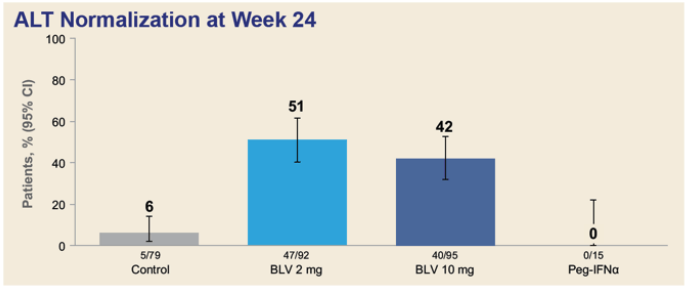
- Promising early data – supportive of combination for virological effect
- ALT normalization even without virological effect

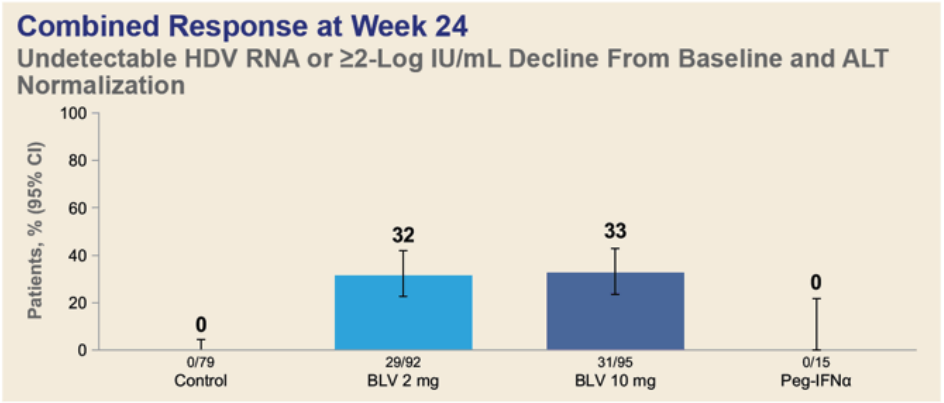
De Ledinghen. AASLD. 2021.

Bulevertide Phase 3 Data

281 with HBV/HDV coinfection randomized: BLV 2 mg, BLV 10 mg, PegIFN or placebo x 24w







Very exciting to have something…still challenges – SC injection daily, long-term, bile acids

Wedemeyer. EASL. 2022.

Summary HDV

- **Underdiagnosis**
  - Screen HBsAg+ or selectively (high ALT but low HBV DNA or PWID or geography)
- **Bulevirtide**
  - Now approved in Europe alone or with PegIFN
  - Early antiviral and biochemical data promising
  - Long-term safety and tolerability require further follow-up
- Other strategies in development
  - **HBsAg-targeting strategies**
    - siRNA/ASO, NAP/STOP and possibly with immunotherapies – **Phase 2**
  - **HDV targeting therapies**
    - lonafarnib (+/- PegIFN–alpha/lambda) – **Phase 3**

Summary for HBV Cure

- **Many virological targets**
  - Entry
  - cccDNA formation/degradation/transcription
  - Protein translation (RNAi/ASO)
  - Capsid
  - Secretion
- **Fewer immunological targets**…but more coming
  - Innate – TLR, ~~RIG-I~~
  - Adaptive – Therapeutic vaccine, checkpoint inhibitors
- **Combination likely required – first attempts underwhelming but very informative**
- **Much more challenging than HCV**…both scientifically and clinically (much higher bar, harder endpoints, more difficult to study)
- Interesting times ahead…