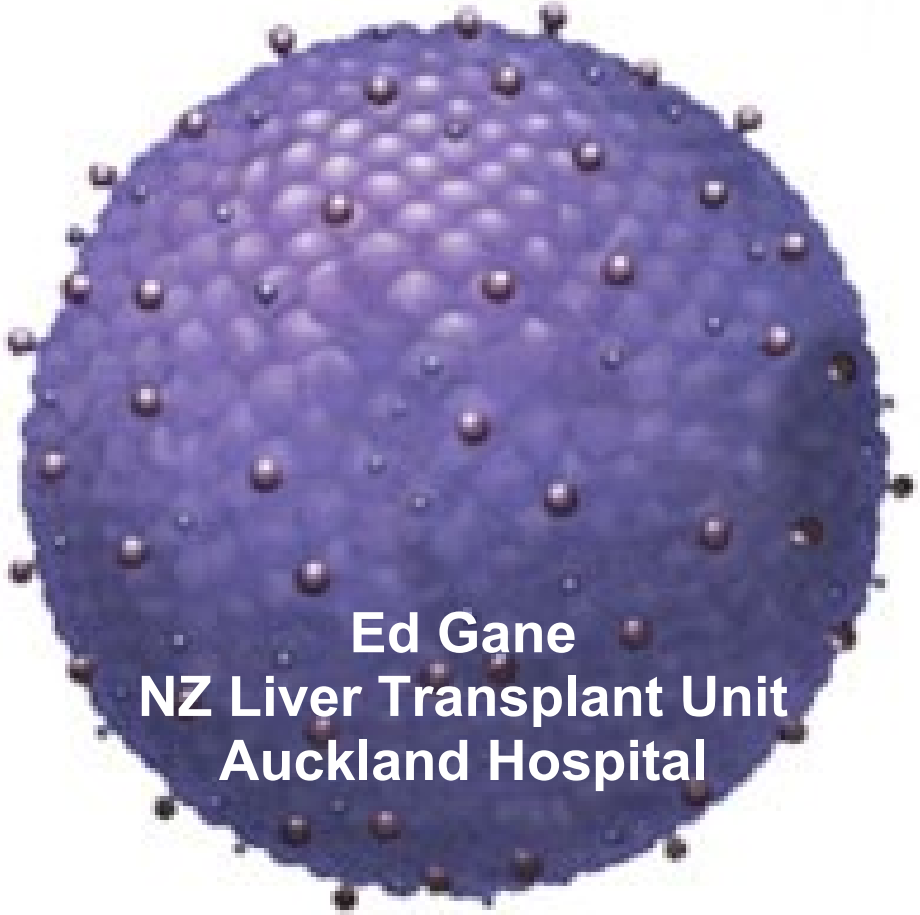
CHRONIC HEPATITIS B

Promising New Treatments



Ed Gane
NZ Liver Transplant Unit
Auckland Hospital

Goals of treatment in CHB: APASL Consensus Statement 2005

"The ultimate long-term goal is prevention of cirrhosis, decompensation and HCC, and prolong survival.

Sustained viral suppression is the key to the reduction or prevention of hepatic injury and disease progression.

Therefore, the primary goal of treatment for chronic hepatitis B is to eliminate or permanently suppress HBV….. "

Liaw YF et al. Liver Int 2005

IFN-α

Lamivudine

Entecavir

Tenofovir

1990s | 1998 | 2002 | 2005 | 2006 | 2008

Thymosin-α
(China, India, Korea, Malaysia, Singapore, Thailand, Vietnam)

Adefovir

PegIFN

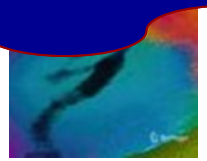
LdT

Clevudine
(Korea)

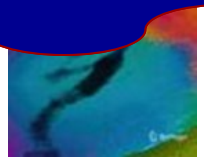
Kick-off March 1999

2003 update
JGH 2003; 18:239–45

2008 update
Hepatol Int 2008; 2:263–83



2015 update
Hepatol Int 2015; In press



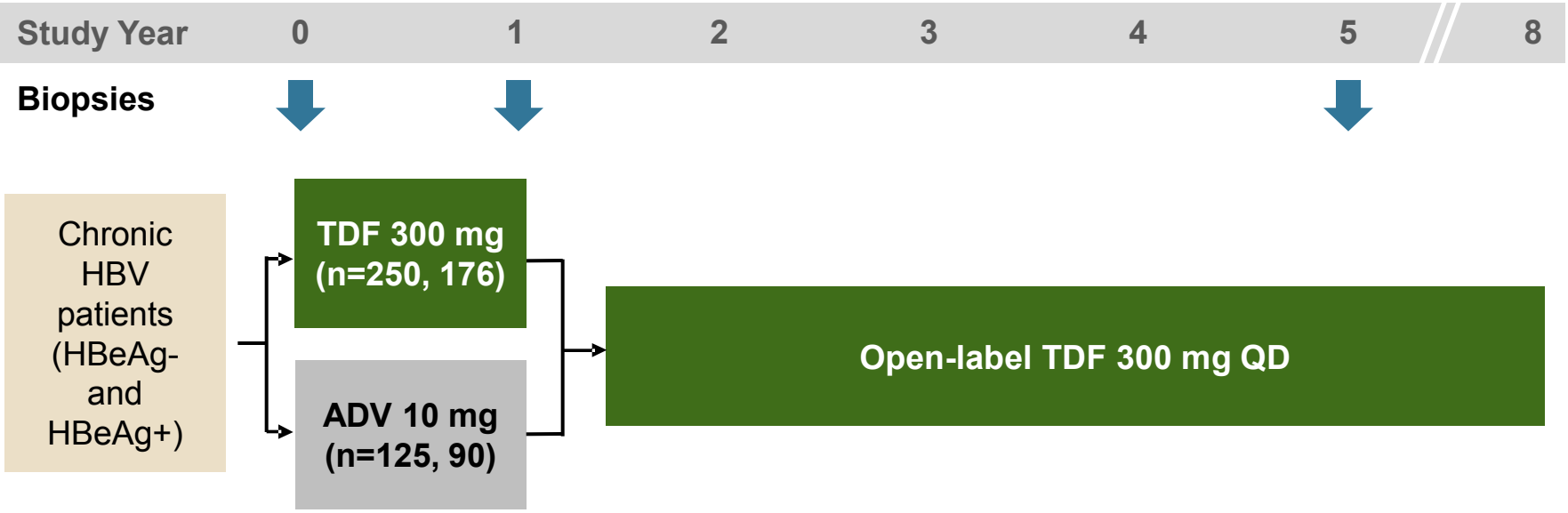
2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015

1st version
JGH 2000; 15:825–41

2005 update
Liver Intl 2005; 25:472–89

20012 update
Hepatol Int 2012; 2:263–83

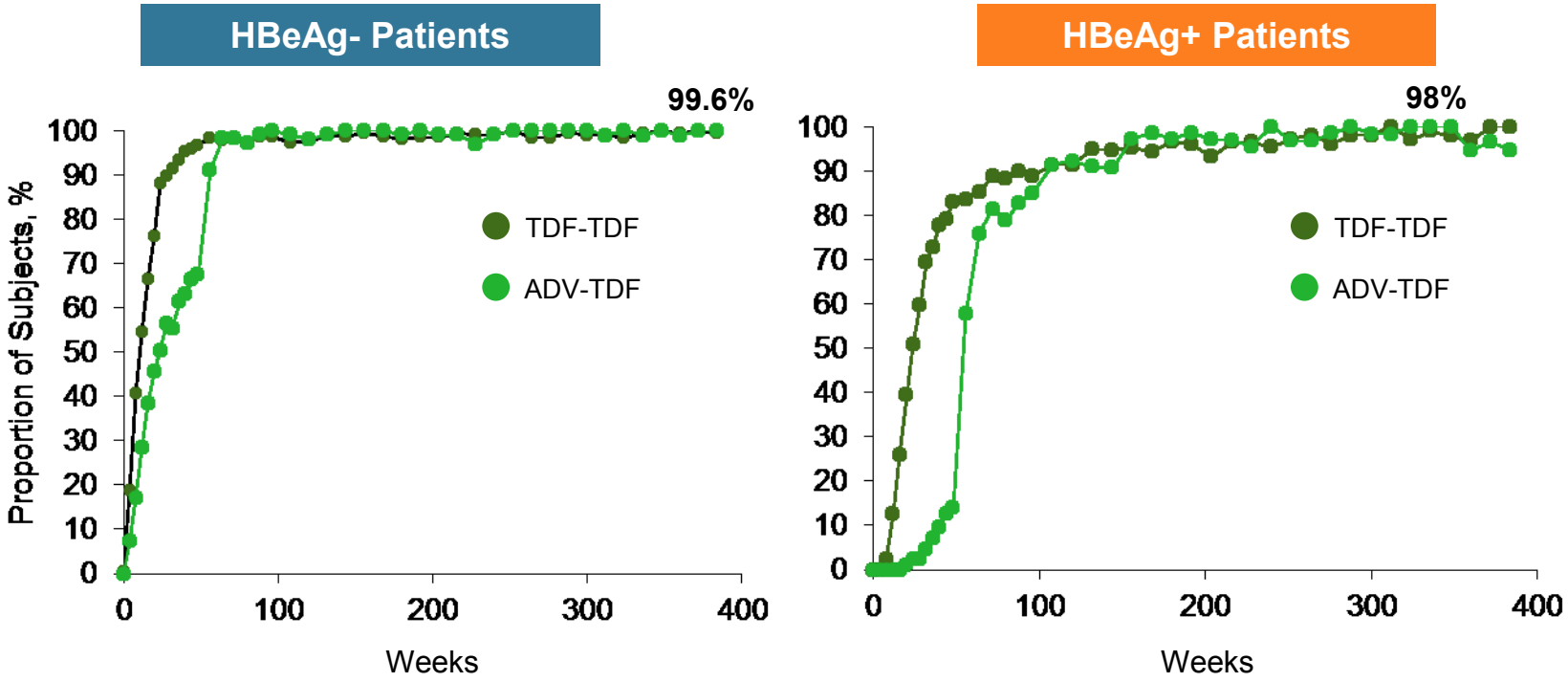
Benefits of Long-term Oral Antiviral Therapy:
Tenofovir in Studies 102 (HBeAg-) and 103 (HBeAg+)



- Two randomized, double-blind, controlled trials in HBeAg- (Study 102) and HBeAg+ (Study 103) CHB [1-3]
  - Rollover to open-label TDF at Week 48
  - FTC allowed after Wk 72 if persistent viremia (DNA ≥69 IU/mL)

1. Marcellin P, et al. J Hepatol. 2014 Jul 18; DOI: 10.1016/j.jhep.2014.07.019 (ePub ahead of print).

Benefits of Long-term Oral Antiviral Therapy: Viral Suppression (Observed)

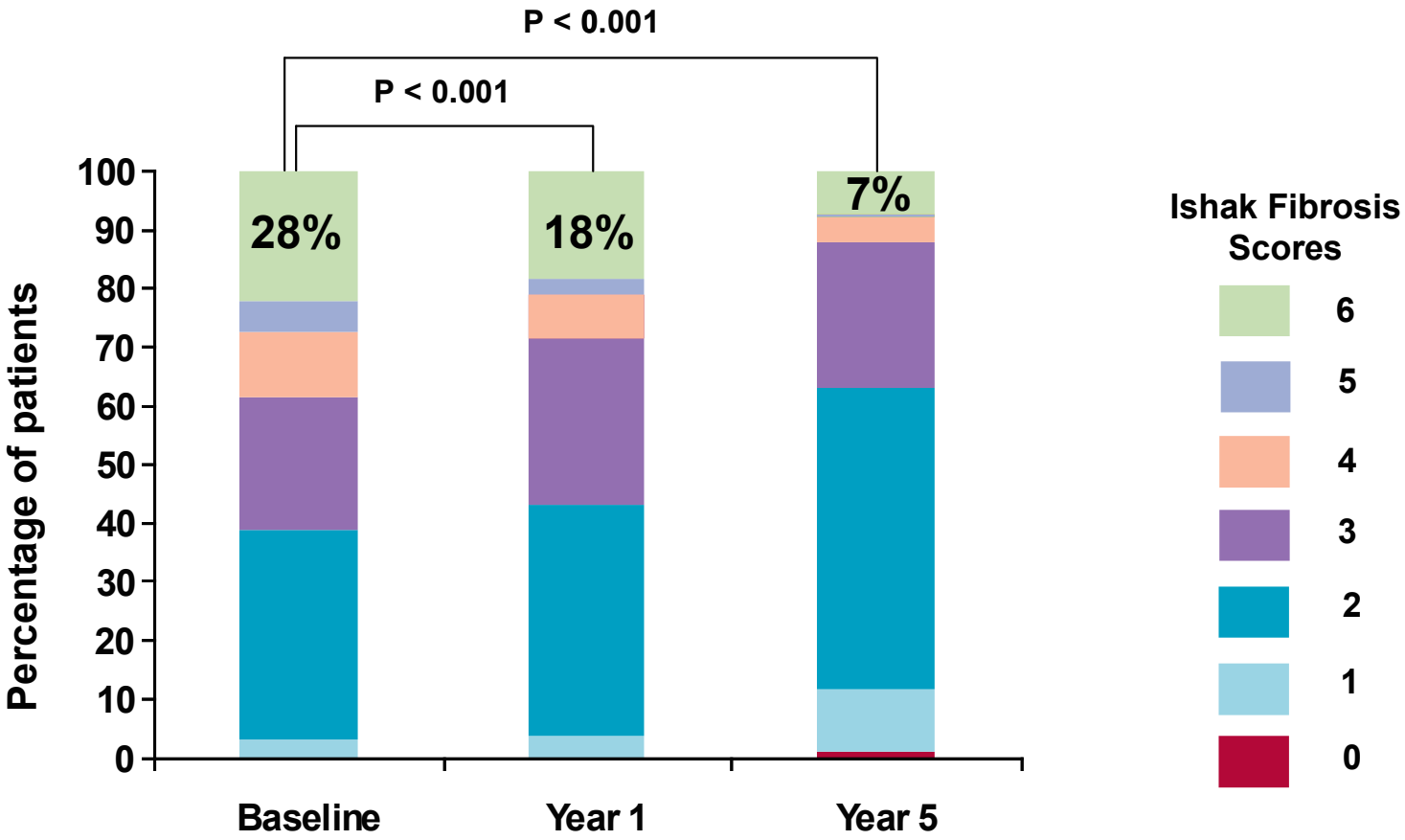


- 99.6% overall response at Year 8
- 98% overall response at Year 8

1. Marcellin P, et al. J Hepatol. 2014 Jul 18; DOI: 10.1016/j.jhep.2014.07.019 (ePub ahead of print).

Benefits of Long-term Oral Antiviral Therapy: Fibrosis Regression over 5 years

- Patients in Long-term Tenofovir Studies 102/103
  - 348 had liver biopsies at baseline, 1 and 5 years

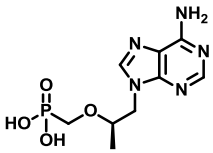


Marcellin P, et al. *The Lancet* 2013; 381(9865): 468-475.

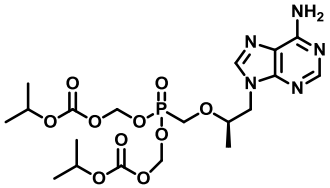
A new Oral Antiviral: Tenofovir Alafenamide (TAF)

Novel Prodrug of Tenofovir

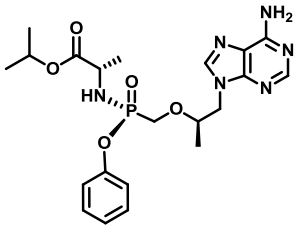
Tenofovir (TFV)

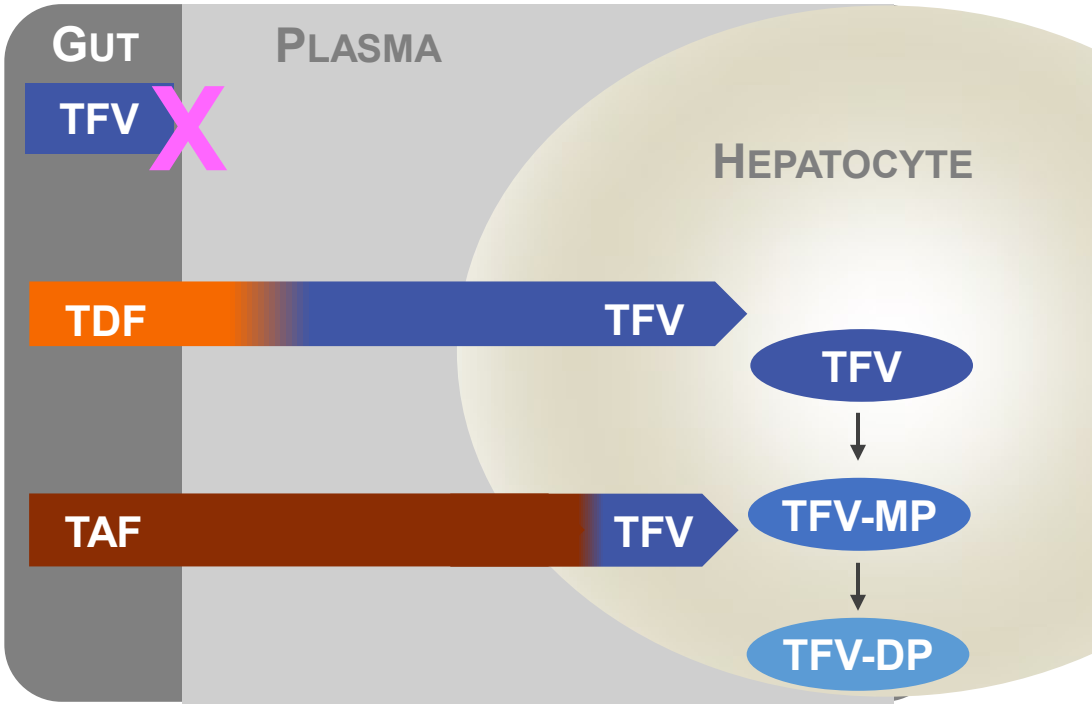


Tenofovir disoproxil fumarate (TDF)



Tenofovir alafenamide (TAF)

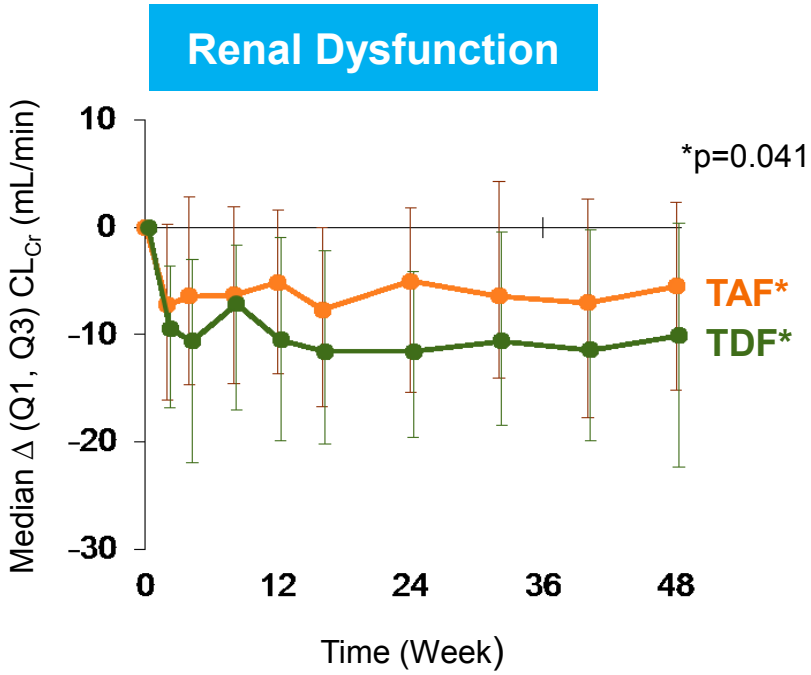


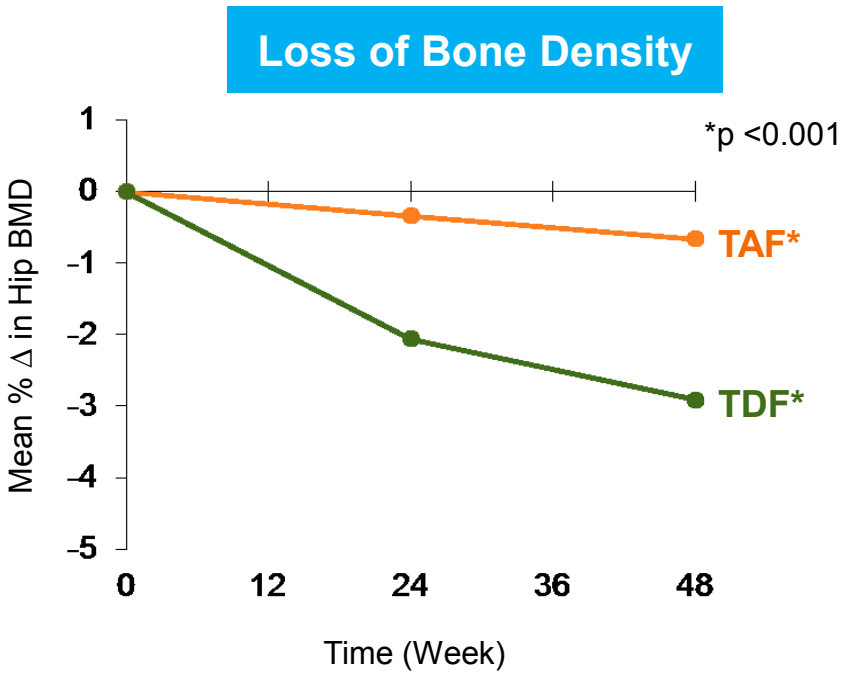


- Enhances delivery of active drug (TFV-DP) to hepatocytes[1]
- Lower dose reduces circulating TFV levels >90% [2,3]
- Lower risk of extrahepatic toxicity

Tenofovir Alafenamide (TAF)

– Improved safety profile vs TDF in HIV patients[4]:

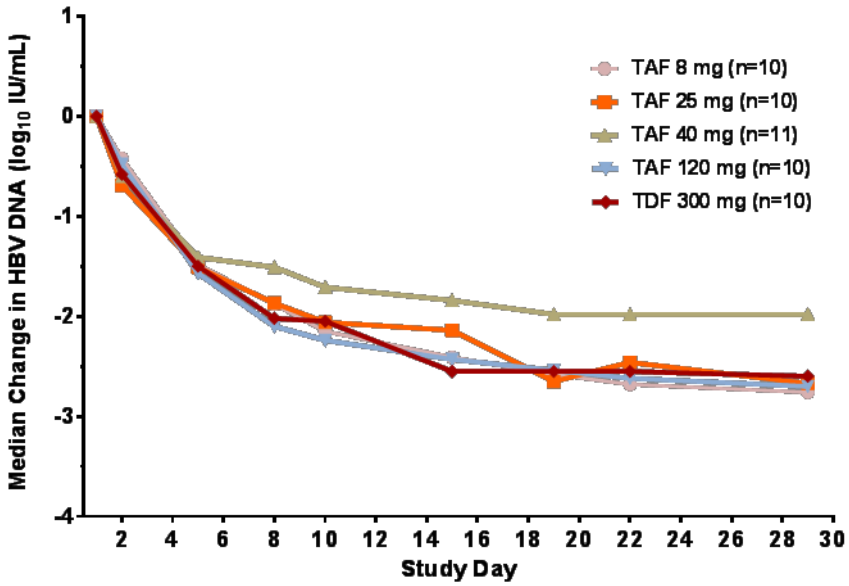




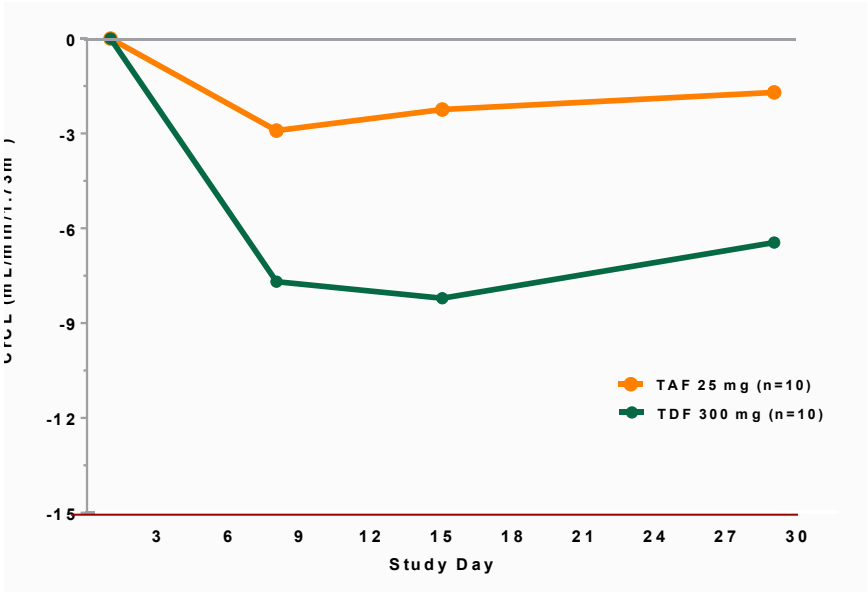
1. Babusis D, et al. Mol Pharmaceutics. 2013;10:459-66; 2. Markowitz M, et al. J Antimicrob Chemother. 2014;69:1362-9 ;
3. Agarwal K et al. J Hepatology 2015;62:533-40; 4. Sax P, et al. JAIDS 2014;67:52-8

TAF Phase 1b in CHB: Key Findings

Viral Suppression



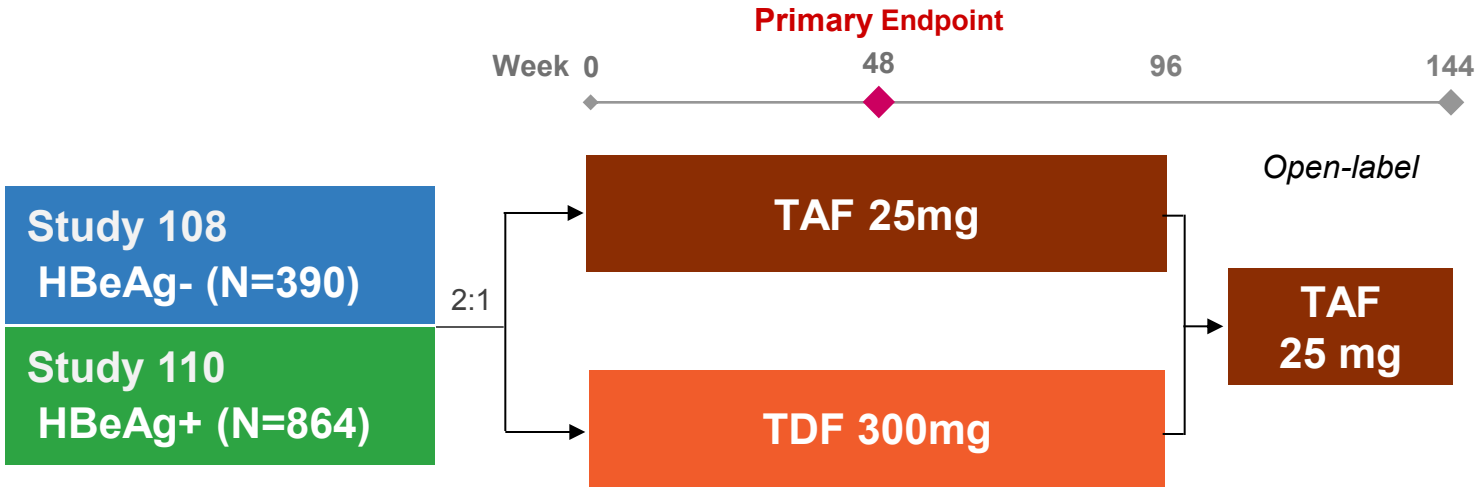
Creatinine Clearance



- TAF 25mg antiviral activity was similar to TDF 300mg
- eGFR (CL_{Cr}) declined less with TAF vs TDF

Agarwal K et al. J Hepatology 2015;62:533-40

TAF HBV Phase IIII Study Design



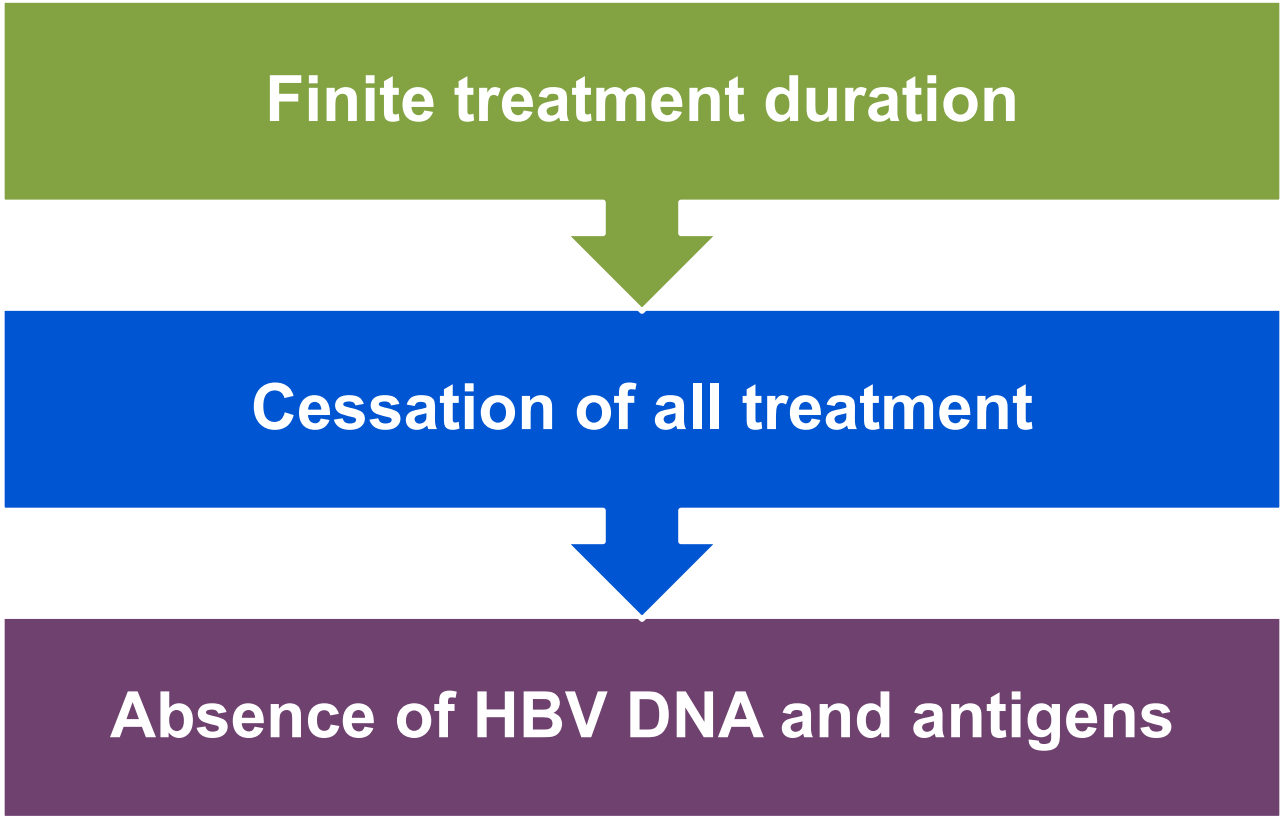
- Two phase 3, randomized, double-blind studies
- Primary endpoint (non-inferiority margin of 10%)
  - HBV DNA < 29 IU/mL at Week 48
- Key secondary safety endpoints
  - Bone mineral density at Week 48
  - Renal parameters at Week 48

Disadvantages of Long-term Oral Antiviral Therapy

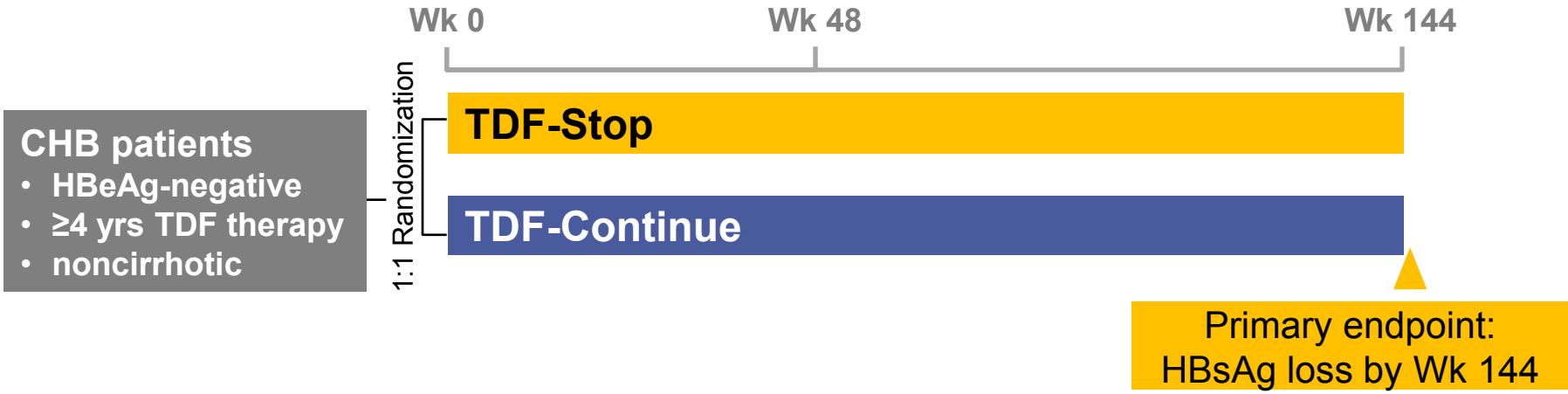
1. **High cost**
2. **Risk of viral rebound ➡ flares ➡ liver failure**
   - Non-adherence
   - Emergence of resistance
3. **Direct toxicity of oral antivirals**
   - Tenofovir➡bone disease, nephrotoxicity
   - Entecavir ➡ risk of mutagenesis?
   - Adefovir/Lamivudine ➡ risk of HCC
     - A181T ➡ truncated S ➡c-Raf-1/MAP kinase pathway

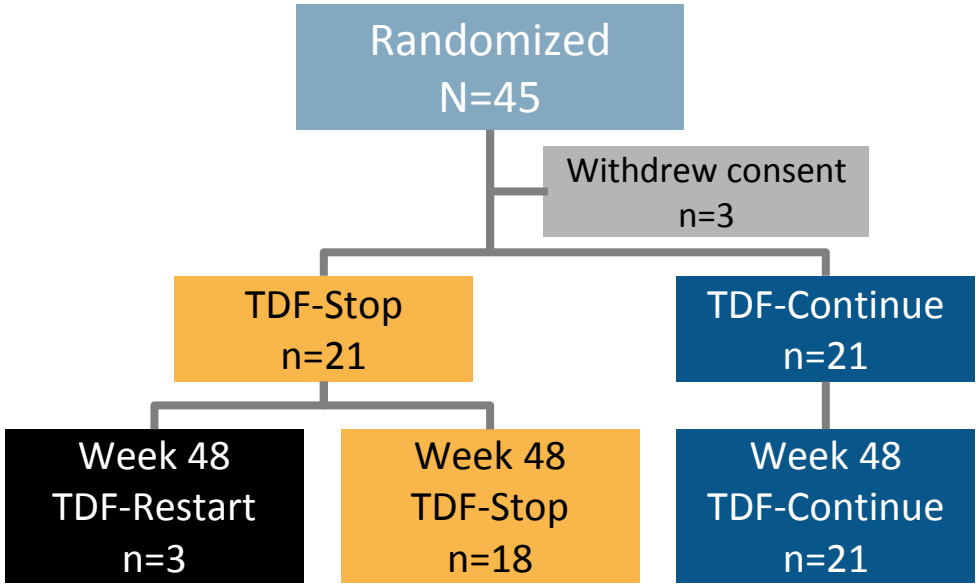
Yeh et al. BMC Cancer 2011, 11:398 -408
Hildt E, et al Recent Results Cancer Res 1998;154:315-29
Warner N, et al. *Hepatology* 2008; 48; 88-98

Therapeutic Goal: Finite course of Therapy



FINITE CHB Study: Stopping TDF treatment after long-term suppression in HBeAg-negative CHB

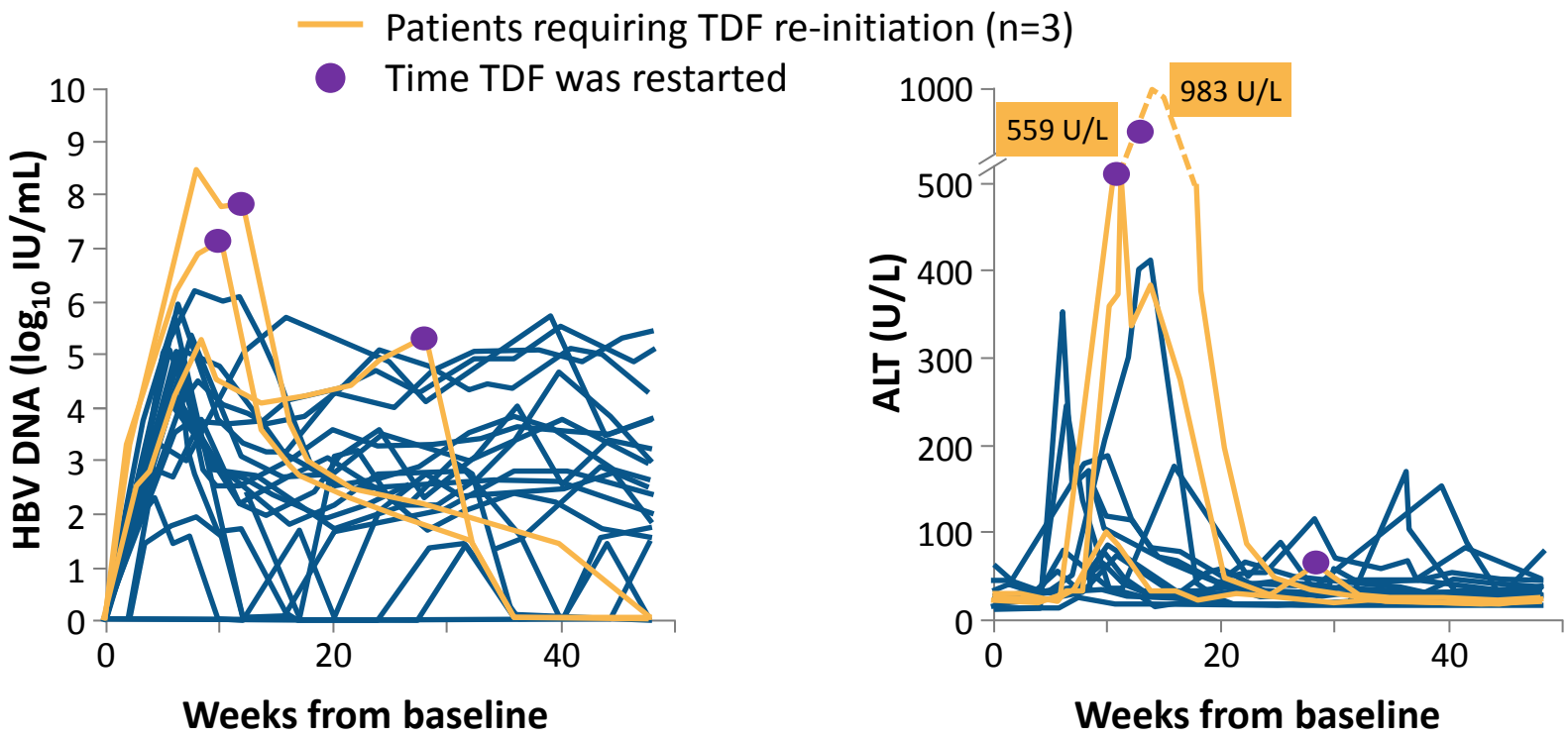




Berg T, et al. EASL 205, Vienna. #O119

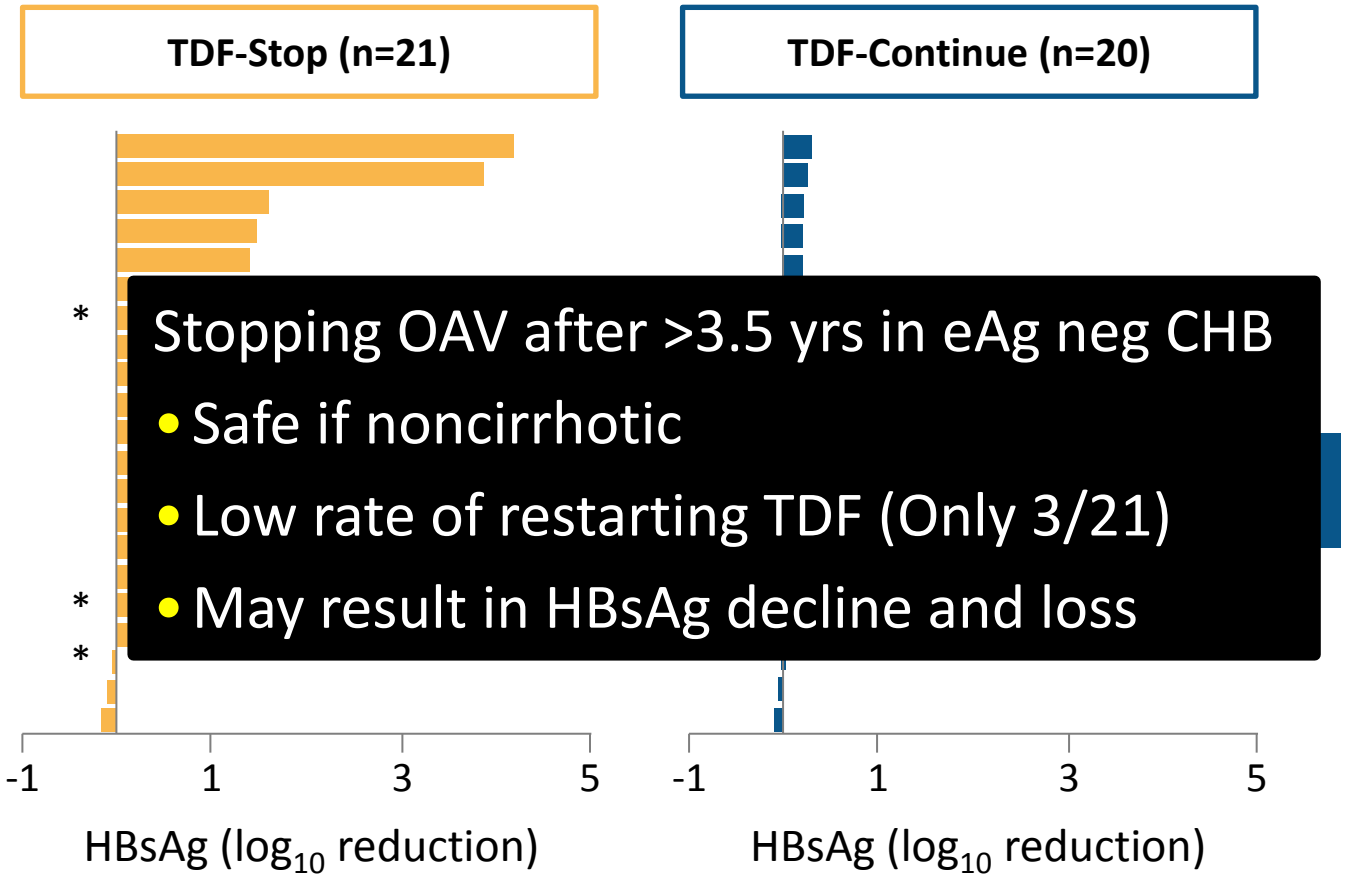
FINITE CHB Study: Stopping TDF treatment after long-term suppression in HBeAg-negative CHB

TDF-Stop (n=21)



Berg T, et al. EASL 2015, Vienna. #O119

FINITE CHB Study: Stopping TDF treatment after long-term suppression in HBeAg-negative CHB



Stopping OAV after >3.5 yrs in eAg neg CHB

- Safe if noncirrhotic
- Low rate of restarting TDF (Only 3/21)
- May result in HBsAg decline and loss

*TDF-Restart

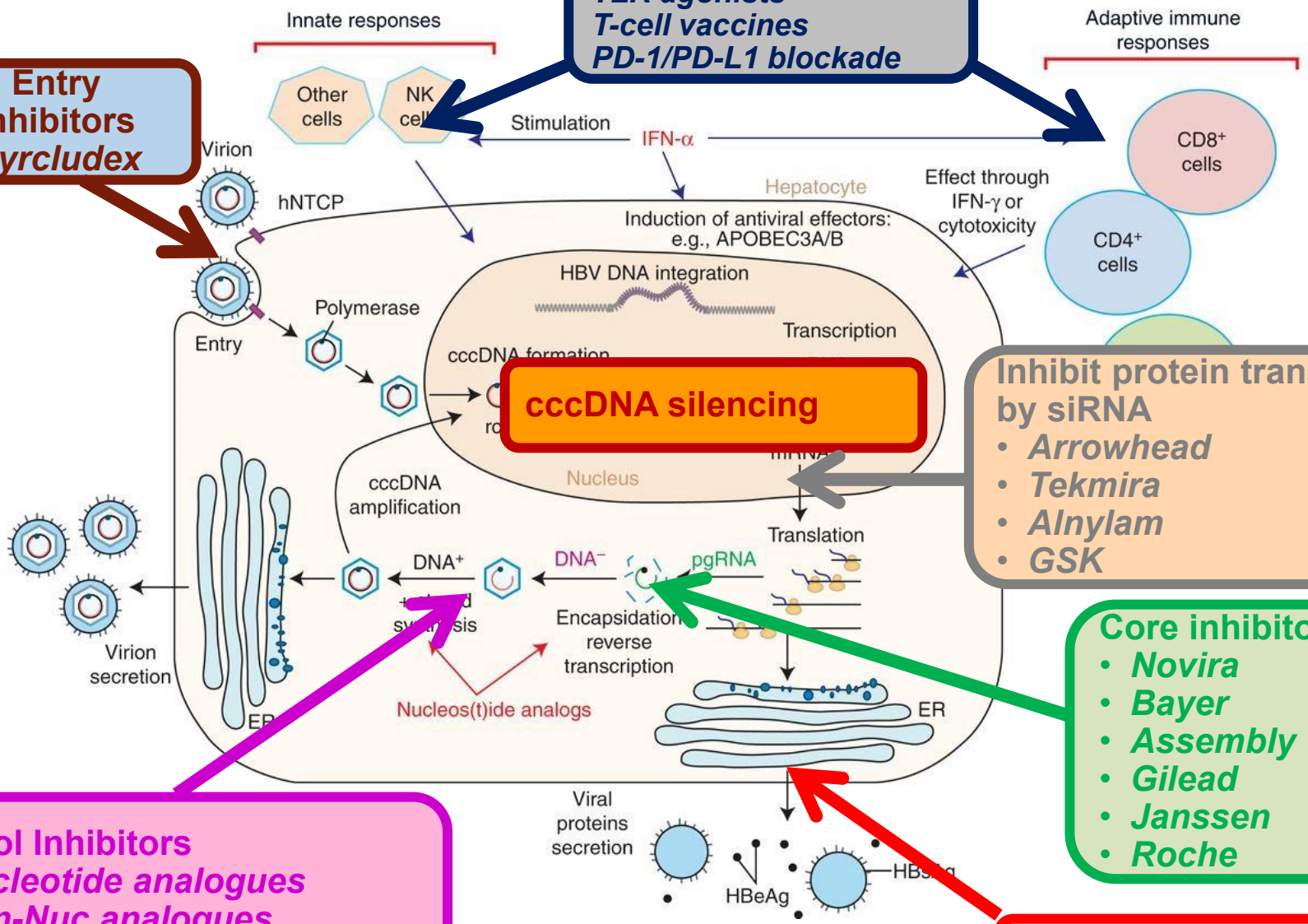
Berg T, et al. EASL 2015, Vienna. #O119

HBV CURE

New Targets for HBV "Cure"

Immunodulators
TLR agonists
T-cell vaccines
PD-1/PD-L1 blockade

Entry Inhibitors
- *Myrcludex*



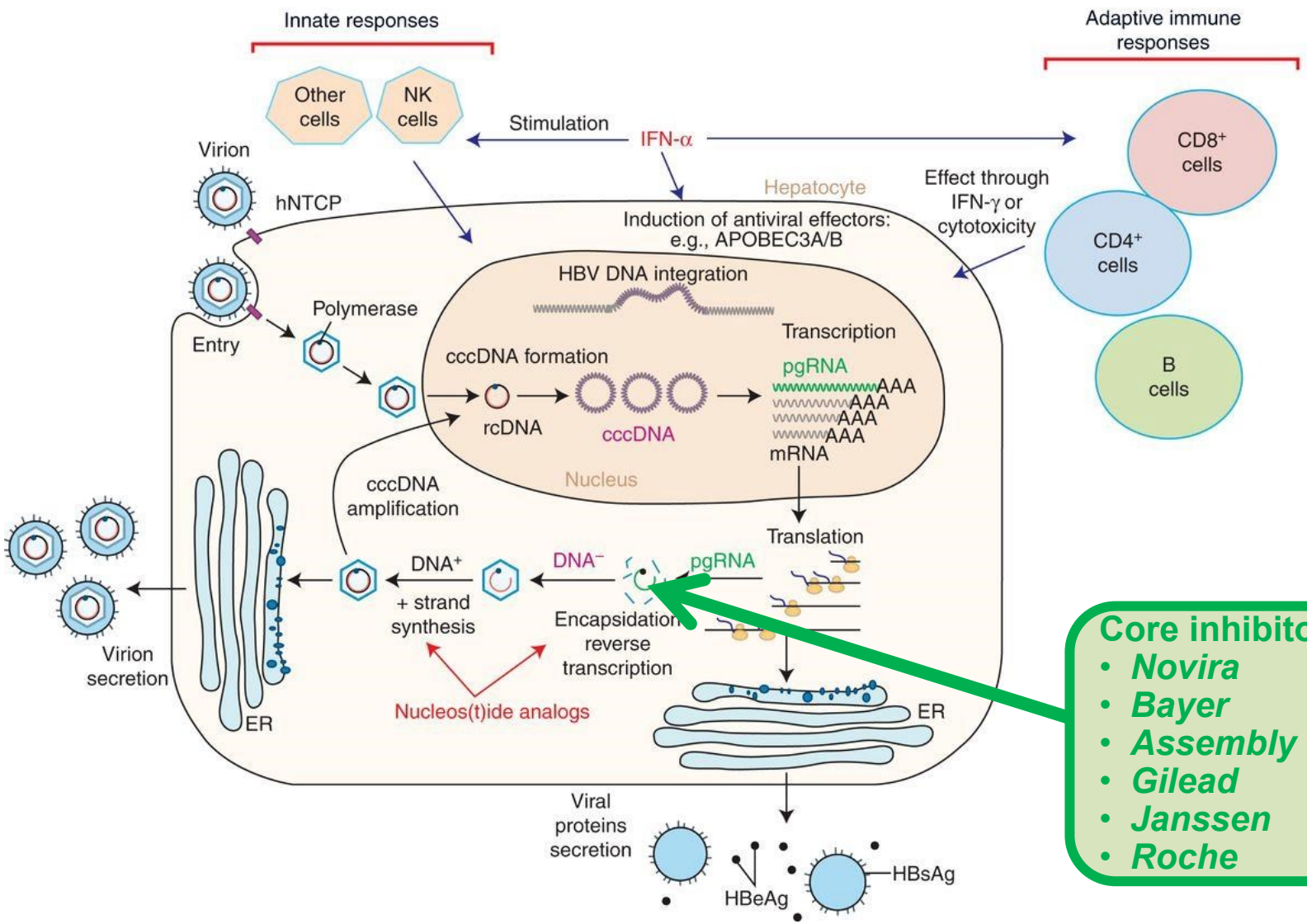
Inhibit protein translation by siRNA
- *Arrowhead*
- *Tekmira*
- *Alnylam*
- *GSK*

Core inhibitors
- *Novira*
- *Bayer*
- *Assembly*
- *Gilead*
- *Janssen*
- *Roche*

RT Pol Inhibitors
- *Nucleotide analogues*
- *Non-Nuc analogues*
- *RNAseH inhibitrs*

HBsAg release Inhibitor
- *NAP*

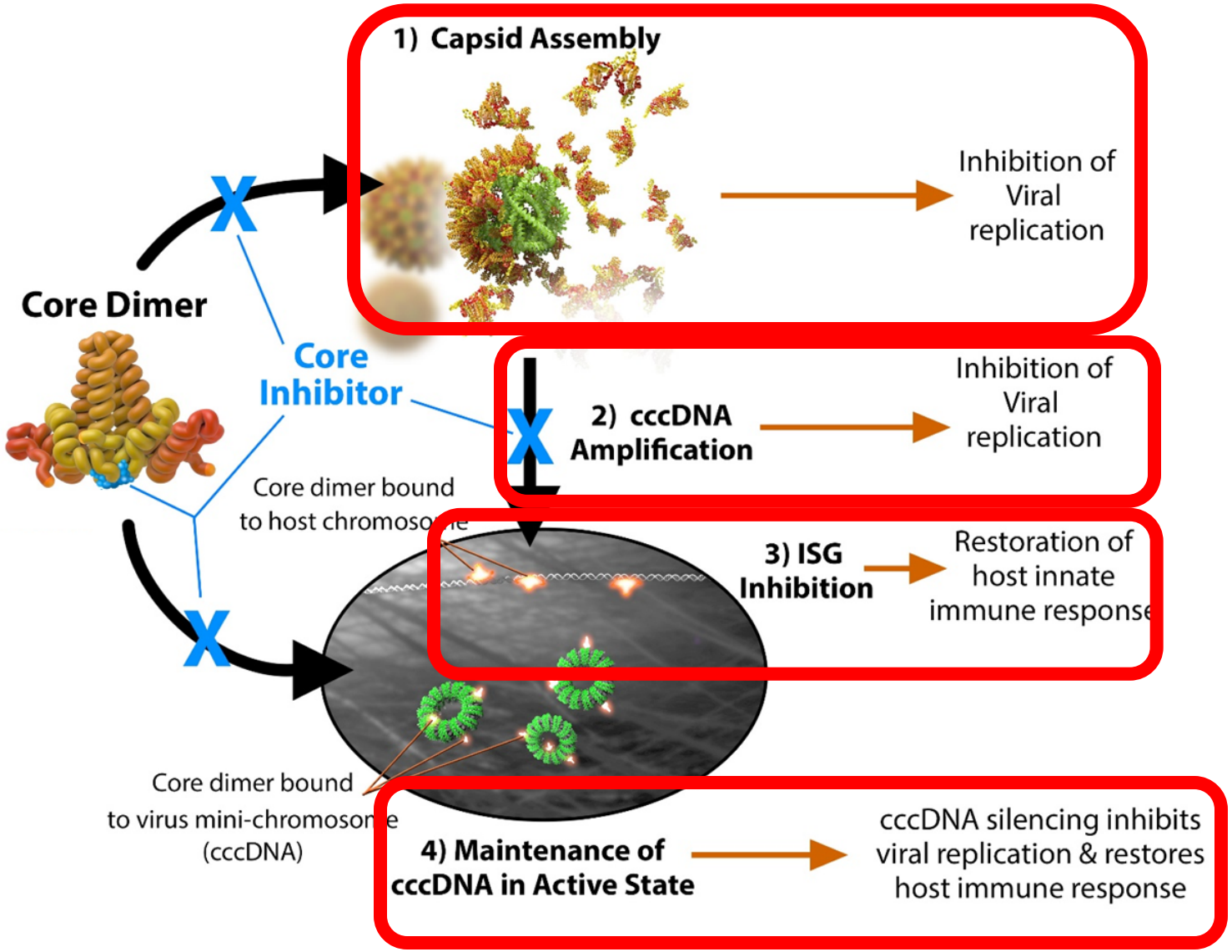
New Targets for HBV "Cure"



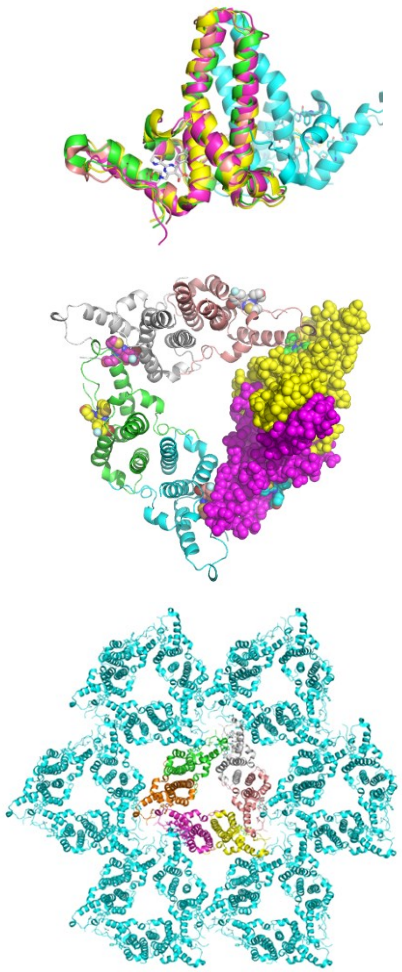
Core inhibitors

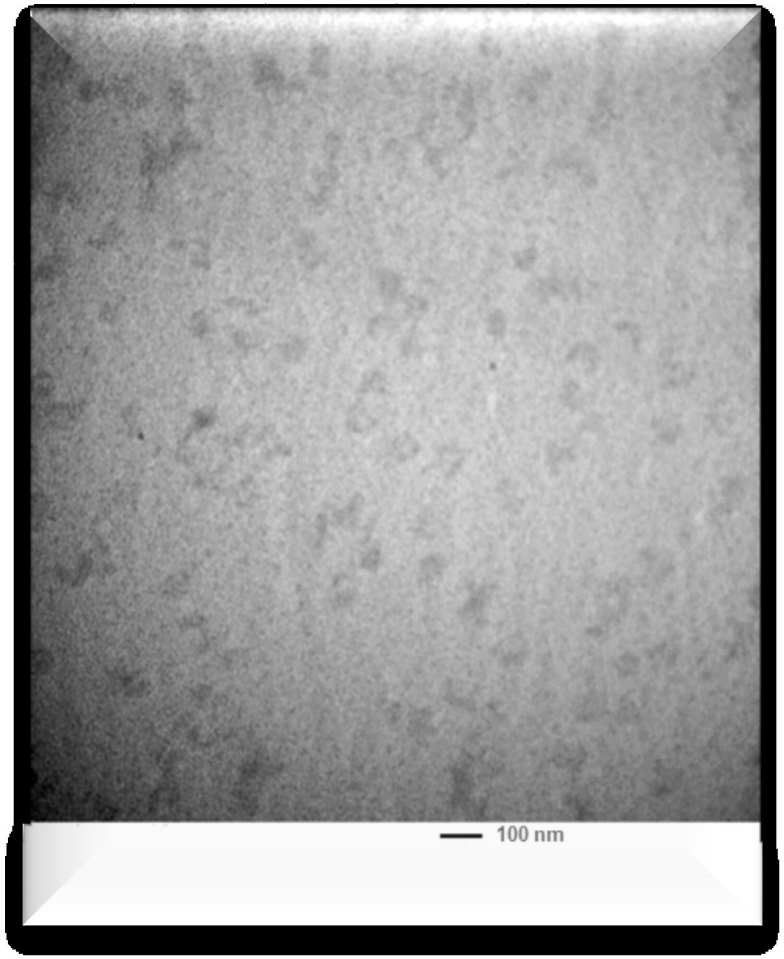
- *Novira*
- *Bayer*
- *Assembly*
- *Gilead*
- *Janssen*
- *Roche*

HBV Core Inhibitors Can Disrupt Multiple Steps Required for HBV Replication and Persistence



NVR 3-778 binds to HBV core & induces formation of abnormal capsids





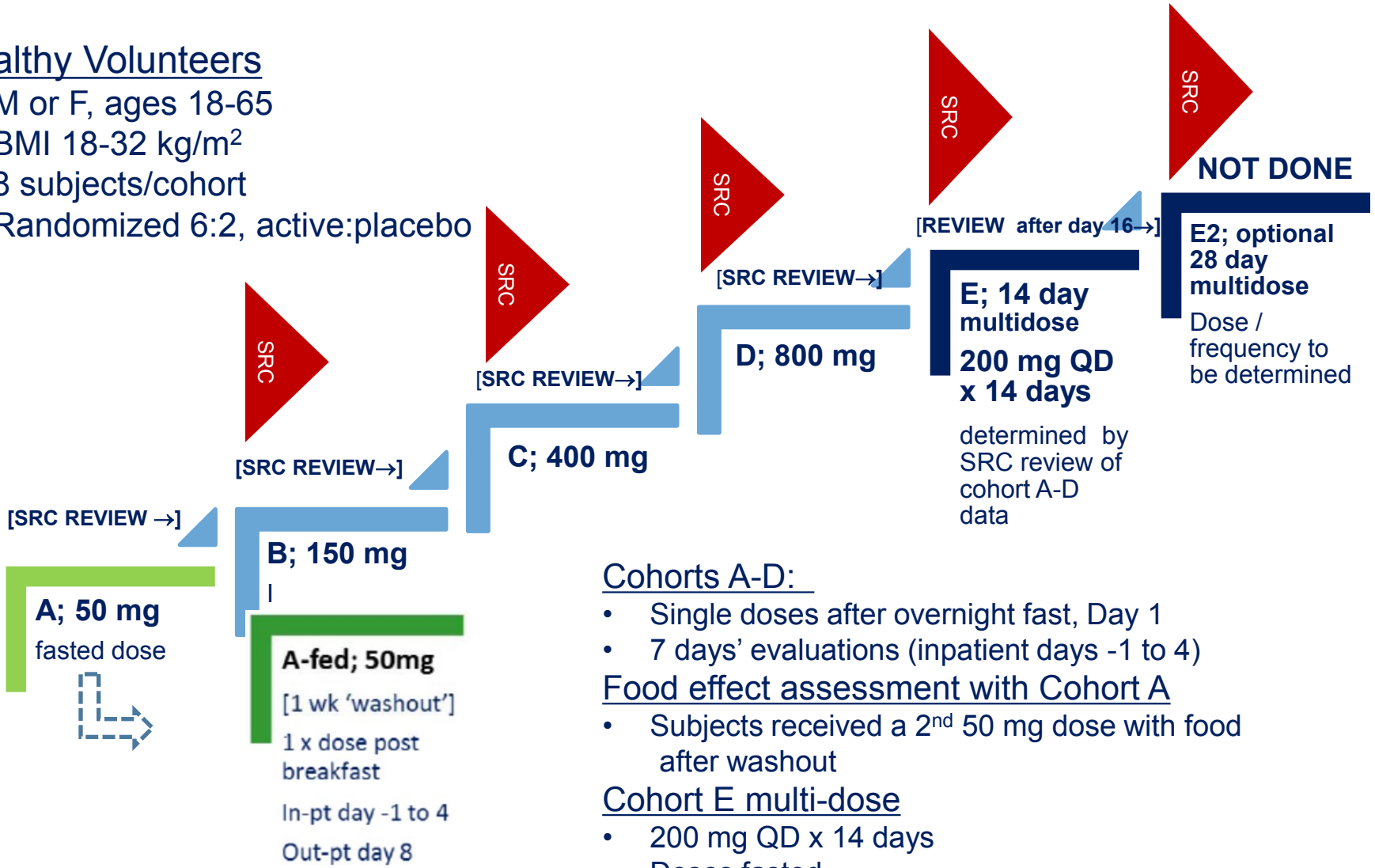
NVR 3-778: Preclinical Profile

- NVR 3-778 induces rapid mis-assembly of HBV core
- NVR 3-778 is a potent inhibitor of HBV replication in standard HBV-producing call line HepG2.2.15:
  - EC_{50} = 0.24 µM, EC_{90} = 0.62 µM, similar to NUCs
- in vitro activity against HBV genotypes A, B, C and D
- Preclinical toxicology supports clinical testing:
  - Negative genotoxicity assessments
  - No organ toxicity in animal studies
- Oral administration

NVR 3-778: Phase 1 MAD study in Healthy Subjects

Healthy Volunteers

- M or F, ages 18-65
- BMI 18-32 kg/m^2
- 8 subjects/cohort
- Randomized 6:2, active:placebo



Cohorts A-D:

- Single doses after overnight fast, Day 1
- 7 days' evaluations (inpatient days -1 to 4)

Food effect assessment with Cohort A

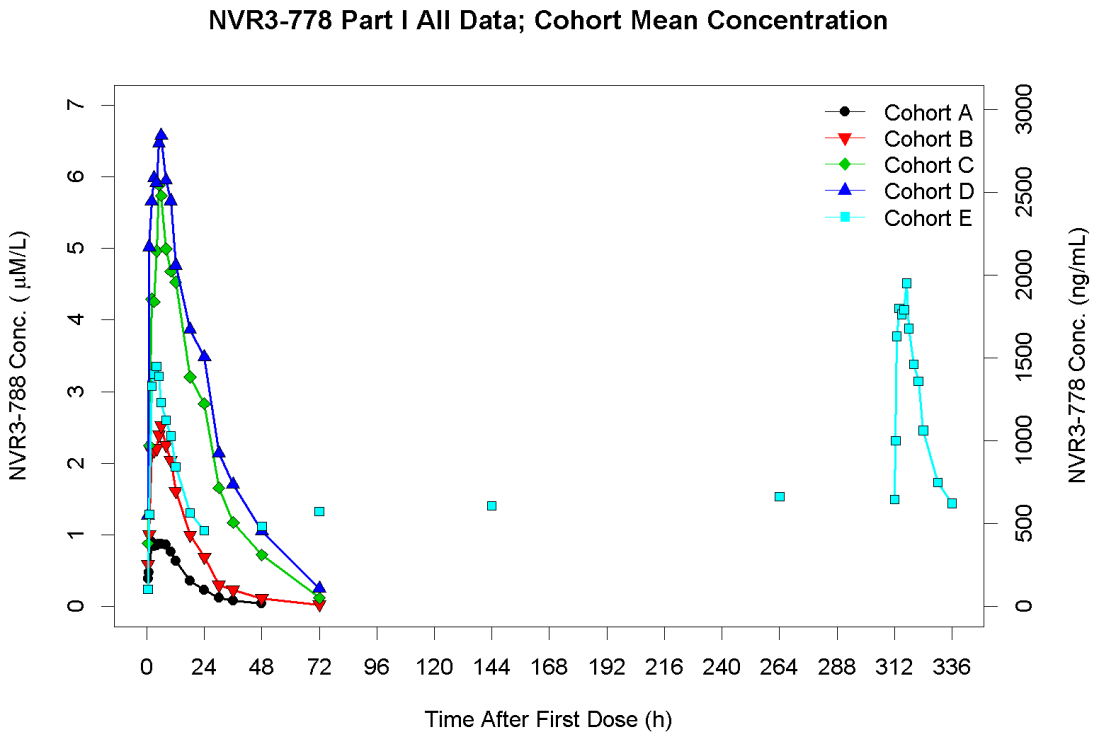
- Subjects received a 2nd 50 mg dose with food after washout

Cohort E multi-dose

- 200 mg QD x 14 days
- Doses fasted

NVR 3-778: Phase 1 MAD study in Healthy Subjects

- NO treatment-related AEs or Lab abnormalities



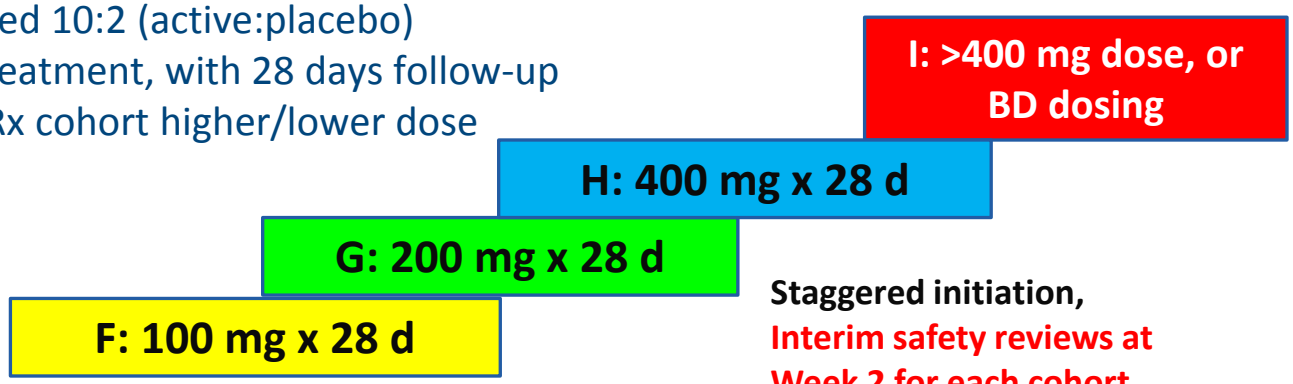
- Predictable dose-related exposure with little variability
- PK supports once daily oral dosing
- 200mg QD exceed inhibitory concentrations in HepG2
- Doses ≥ 200 mg may afford continuous HBV inhibition

NVR 3-778 Phase 1b Trial Design

(i) Phase 1b MonoRx Dose-Ranging in HBeAg+ Patients (nuc-naïve)

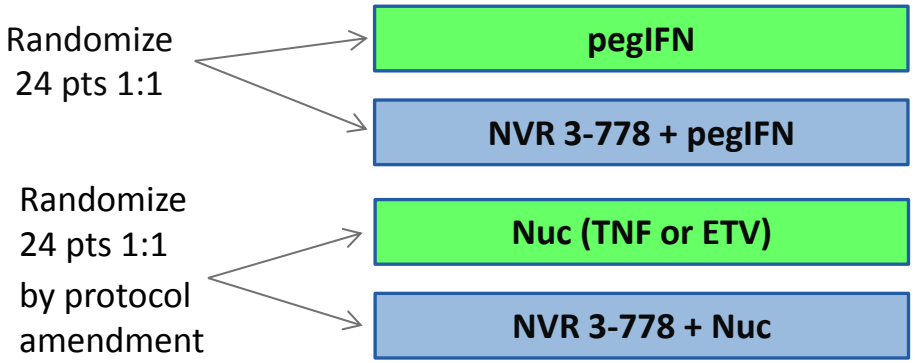
Safety, PK, Preliminary Efficacy

- Initial NVR 3-778 3 monoRx dose cohorts
- Randomized 10:2 (active:placebo)
- 28 days treatment, with 28 days follow-up
- 4th monoRx cohort higher/lower dose



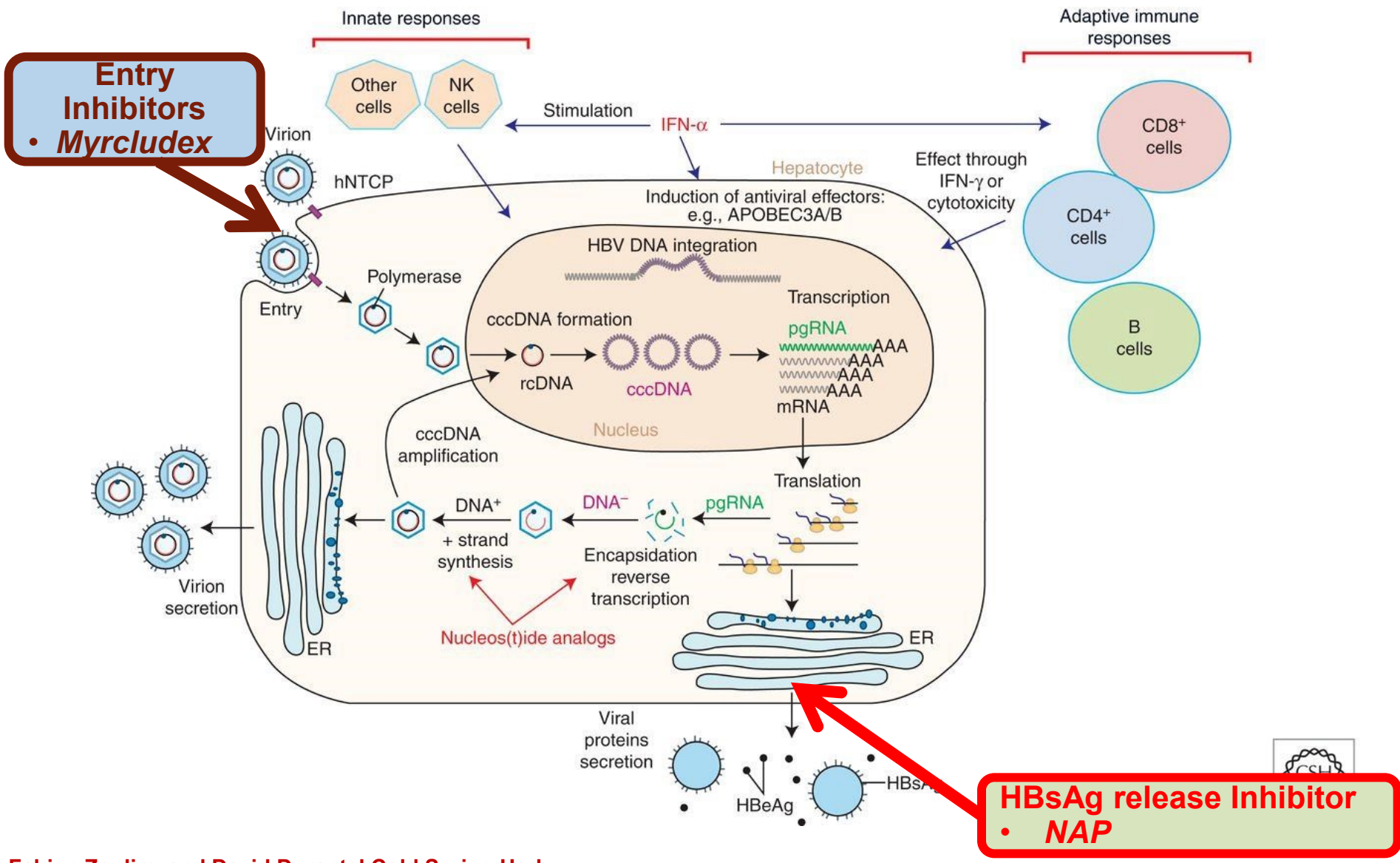
Staggered initiation,
Interim safety reviews at Week 2 for each cohort

(ii) 28-day Phase 1b Combination Assessment(s)



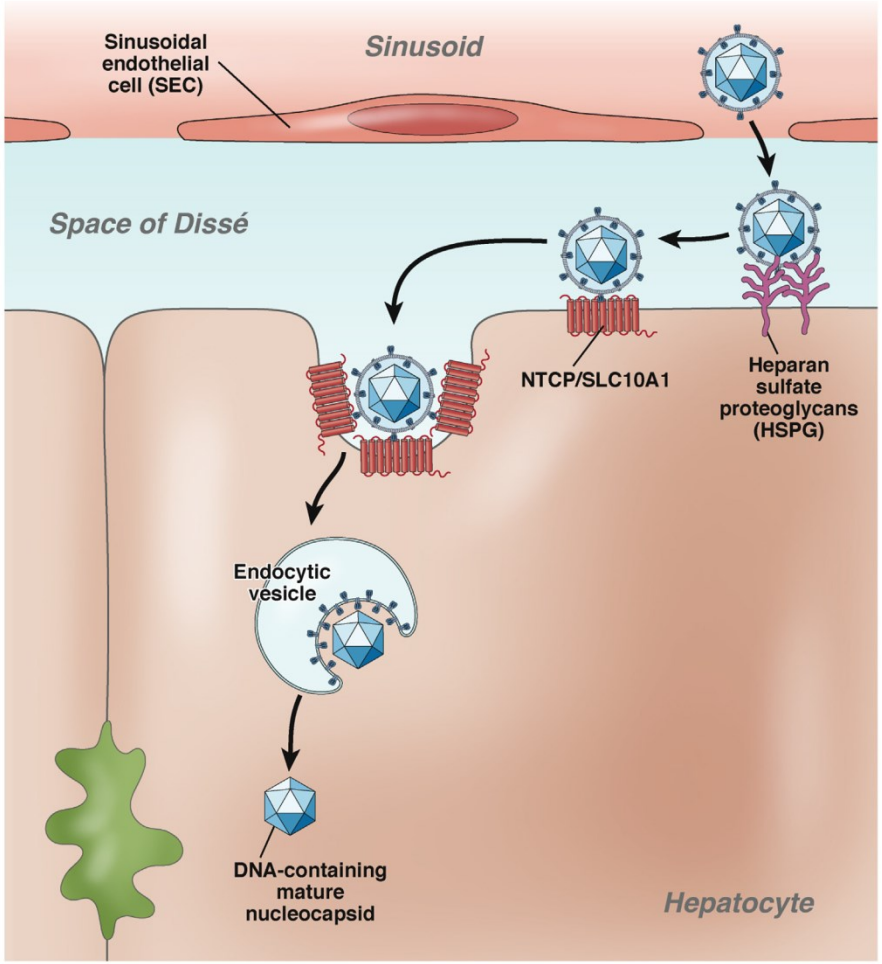
NVR 3-778 assessed at maximal effect dose, in combination regimens

New Targets for HBV "Cure"



Fabien Zoulim, and David Durantel Cold Spring Harb Perspect Med 2015;5:a021501

Entry Inhibitors in CHB



- Myrcludex B is synthetic N-acylated preS1 lipopeptide which blocks receptor functions of NTCP and virus entry
- Ongoing clinical studies in HBV and HDV infection

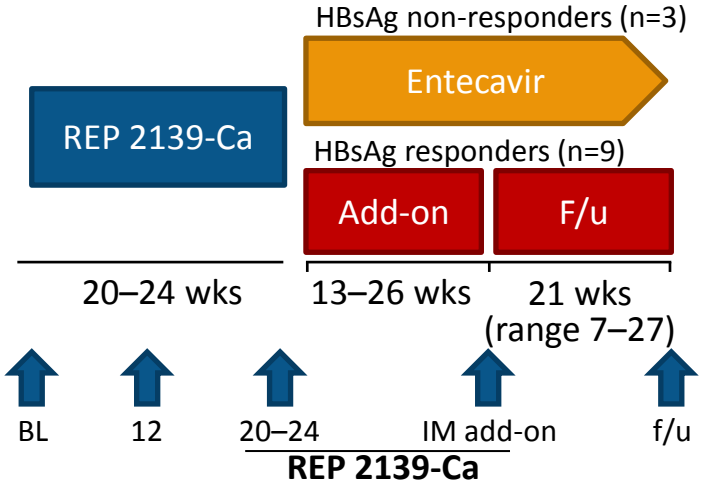
Urban et al. Gastroenterology 2014; 147: 48-64

Nucleic Acid Polymers (NAPs) in CHB

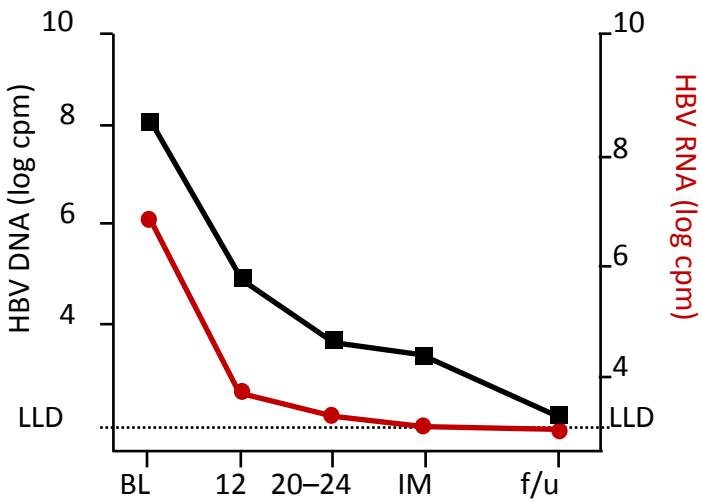
- NAPs are oligonucleotides that interact with multiple intracellular amphipathic targets
- **NAPs have multiple anti-HBV mechanisms**
  - Block HBV entry
  - Post-entry activity
    - Blocks subviral particle (SVP) formation
  - Restore host immune response
- **NAPs may also have anti-delta effects**
  - block HDV entry
  - Block HDV production from a <u>SVP-related assembly mechanism</u>
  - "liberated" anti-HBs directly target HDV

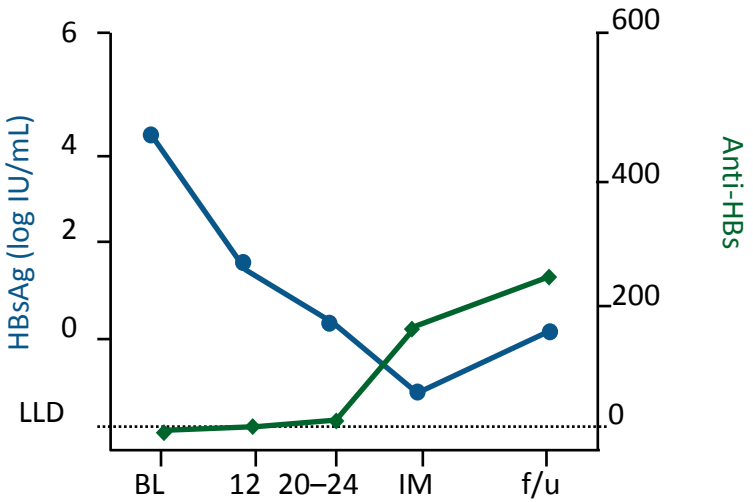
Nucleic Acid Polymers (NAPs)
(i) HBeAg+ CHB

- 12 HBeAg+ pts in Moldova
- Rep 2139-Ca IV 500mg weekly
- Continued for 20-38 weeks
- 9 responded (fall in HBV DNA)



Responders (n=9)



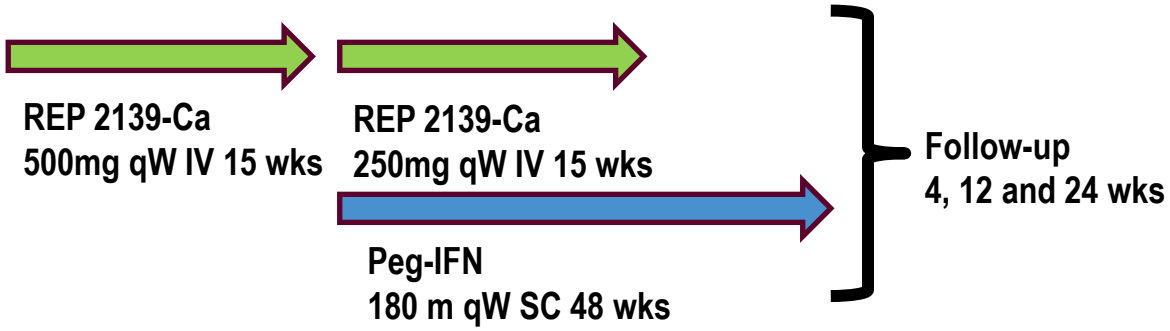


- At f/u, 4/9 patients had HBsAg <0.05 IU/mL and anti-HBs+
- Long-term safety?

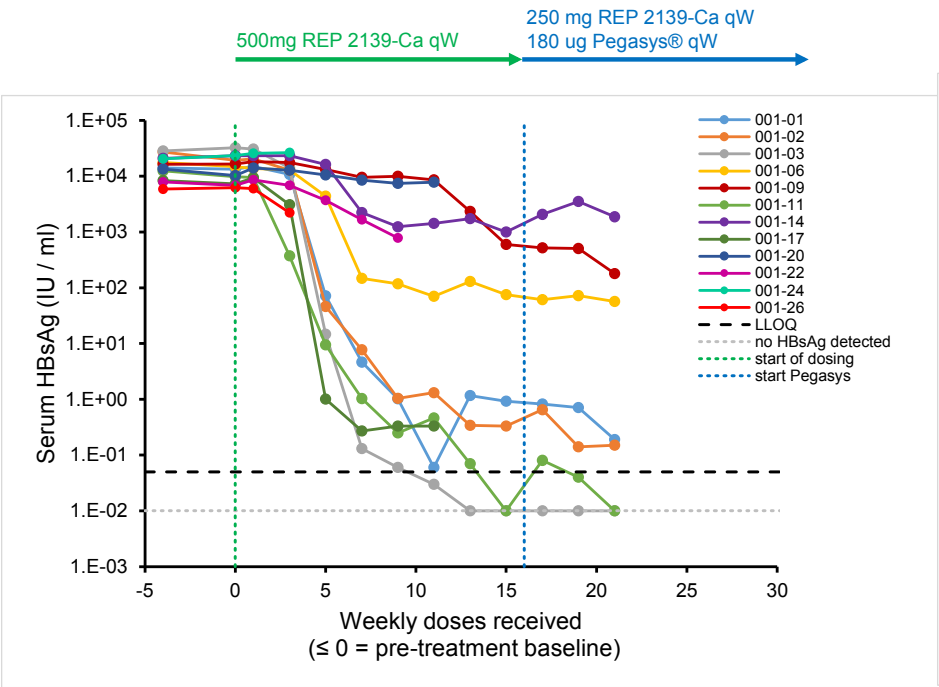
Jansen L, et al. EASL 2015, Vienna. #O114

Nucleic Acid Polymers (NAPs)
(ii) HBV/HDV coinfection

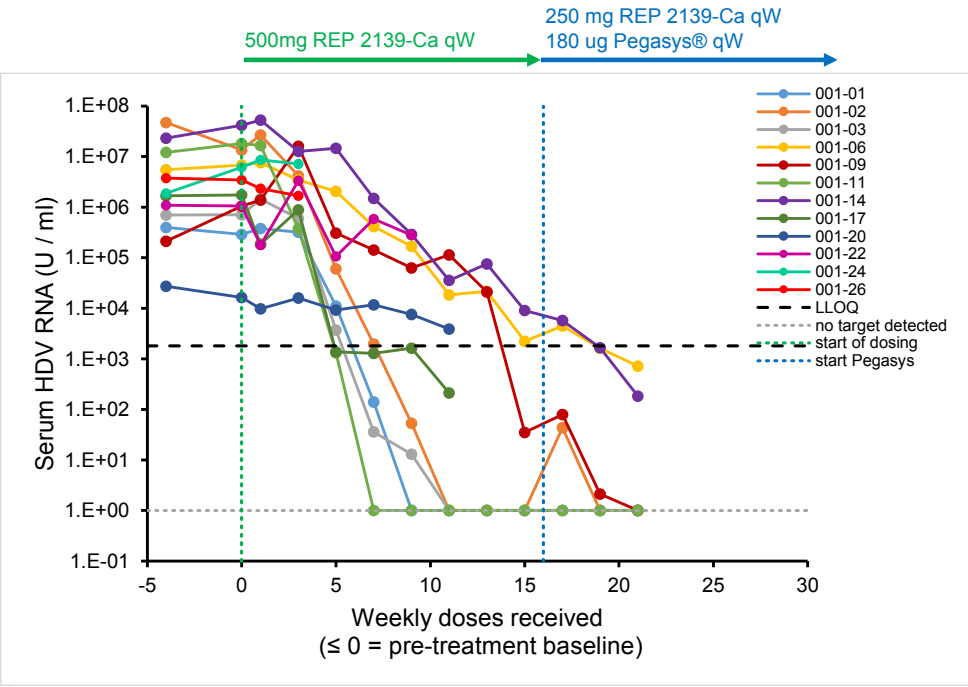
- 12 HDV pts in Moldova
- Anti-HDV/RNA +
- HBsAg >1000
- Non-cirrhotic



Results: (1) HBsAg

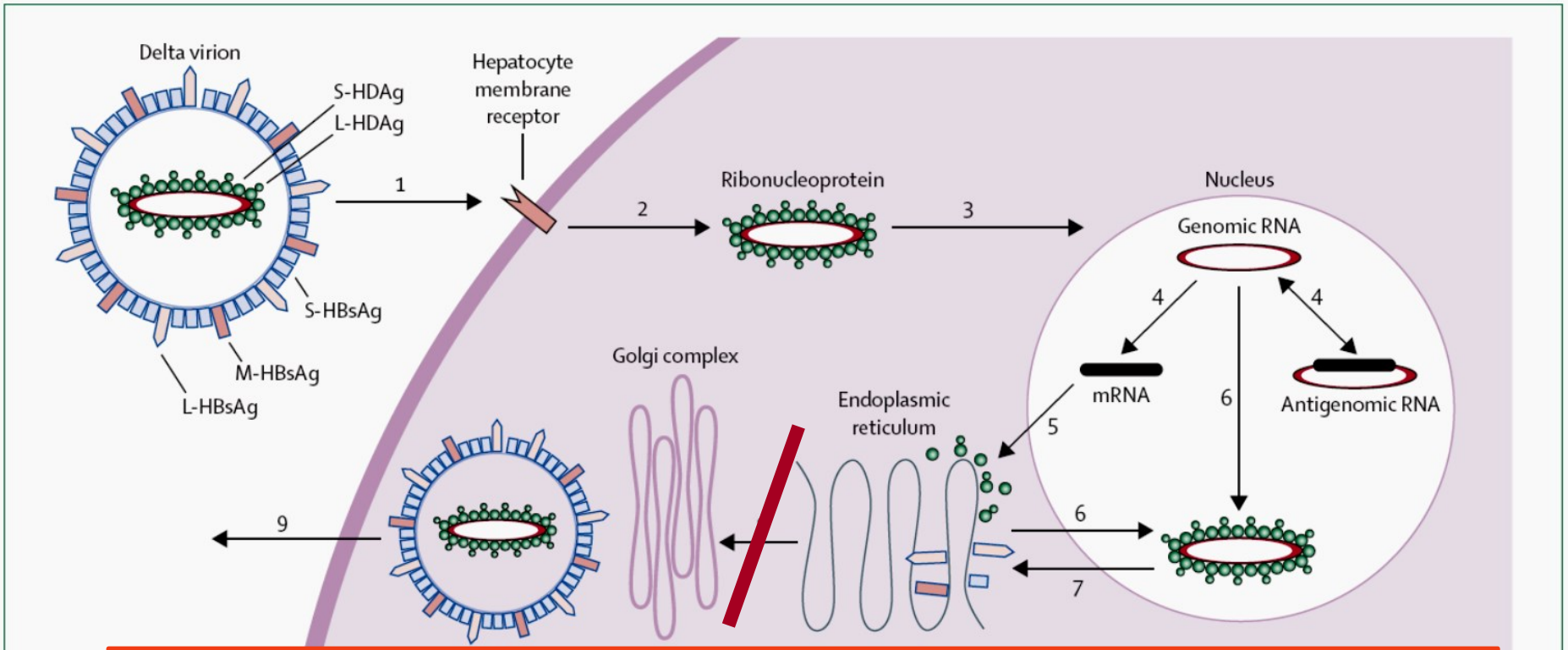


(2) HDV RNA



Vaillant A, et al. EASL 2015, Vienna. #LO2

Prenylation Inhibitors for HDV

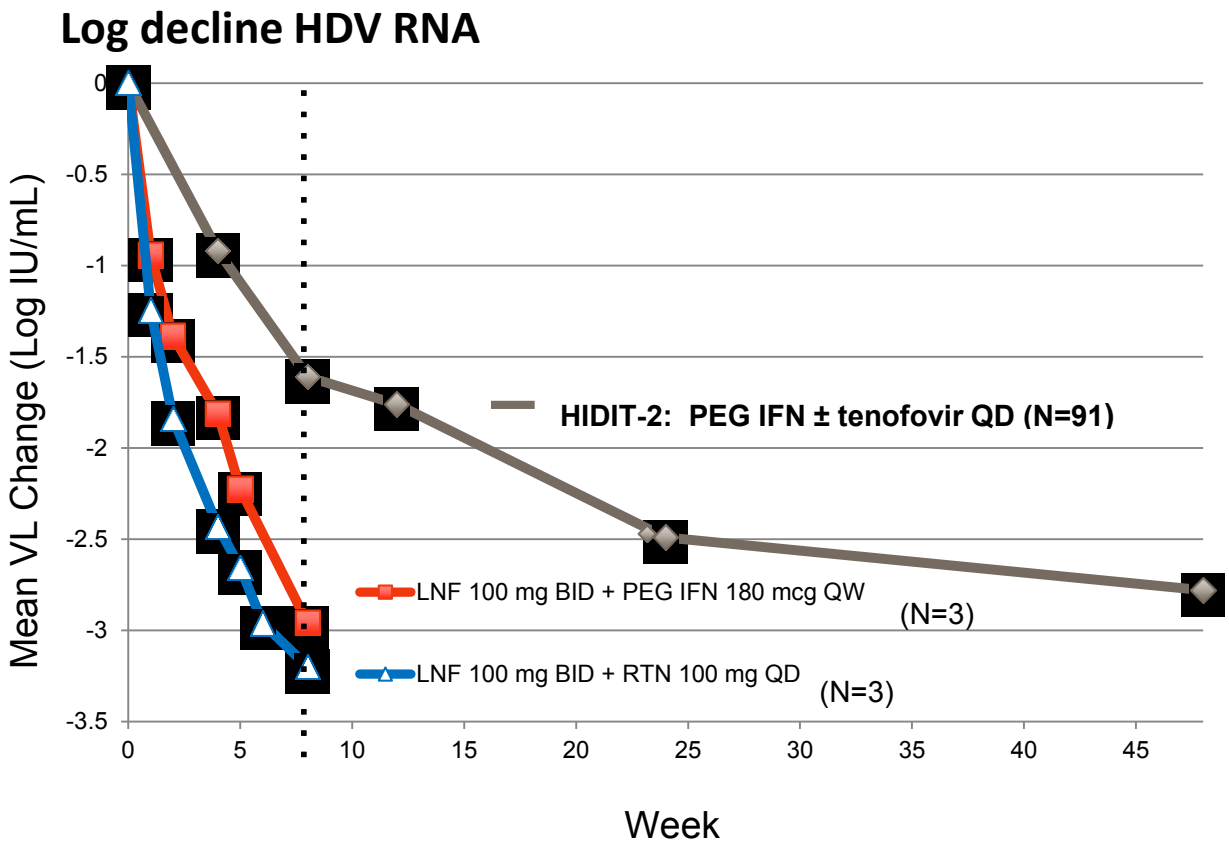


post-translational modification via inhibition of farnesyltransferase (**prenylation**, site-specific lipid modification of proteins)
→ Preventing prenylation abolishes virus particle formation.

*J. Glenn et al., J Virol. 1998 Nov;72(11):9303-6.
*J. Glenn et al., Science. 1992 May 29;256(5061):1331-3.

Prenylation Inhibitors in HDV coinfection Lonafarnib

- 15 HDV pts in Turkey treated with oral lonafarnib for 8 weeks
  - 200/300mg bid vs. 100mg bid +PEG vs. 100mg OD + ritonavir

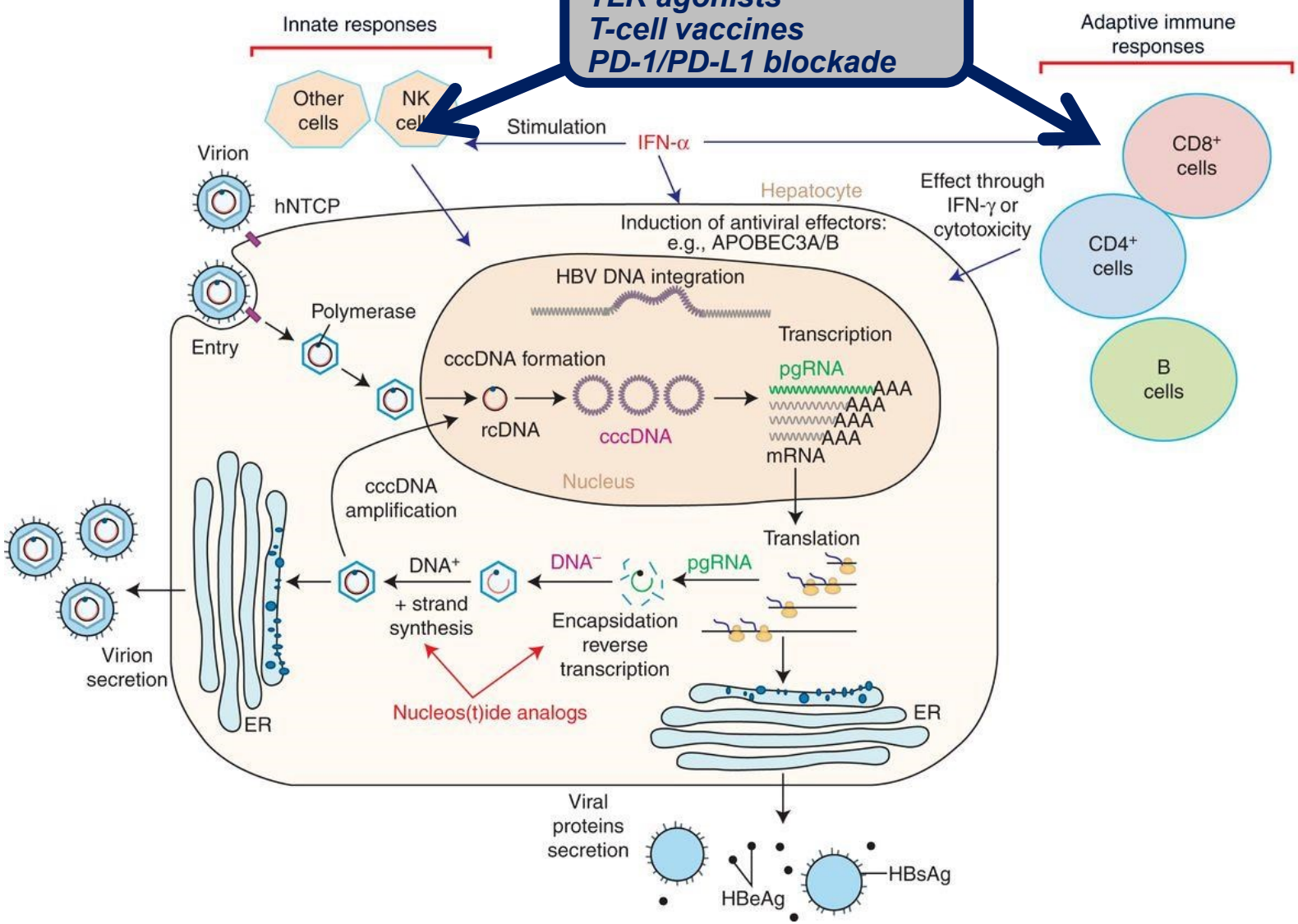


- Ritonavir boosting increased efficacy and reduced GI side-effects

Yurdaydin et al., O118 EASL 2015 Dahari et al., LP36 EASL 2015

New Targets for HBV "Cure"

Immunodulators
TLR agonists
T-cell vaccines
PD-1/PD-L1 blockade



Strategies of Immune Modulation for CHB

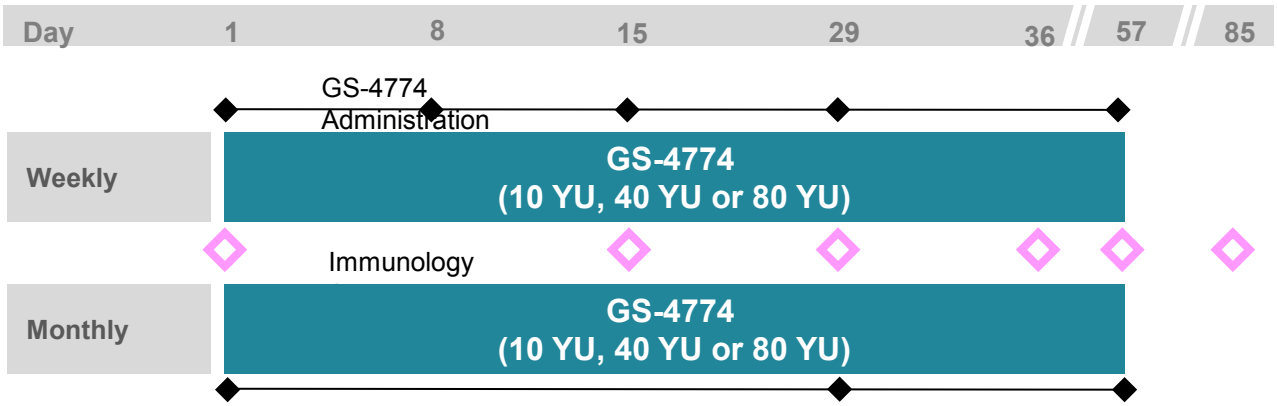
Adaptive Immunity[1-3]

HBV T-cell Vaccine

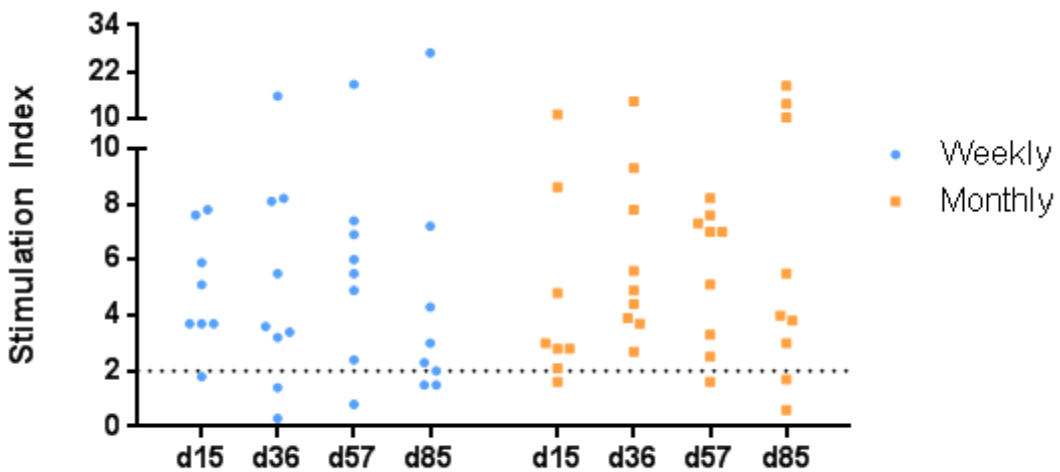
GS-4774

1. Fisicaro P, et al. Gastroenterology 2012;143:1576-85; 2. Liu J, et. al. PLOS Pathogens 2014; 10; 1; 3. Martinet J, et al. Gastroenterology 2012;143:1586-96; 4. Xu N, et al. Inflamm Res 2012;61:997-1004; 5. Vincent IE, et al. PLoS One 2011;6:e26315.

GS-4774: Phase 1 Study in Healthy Volunteers



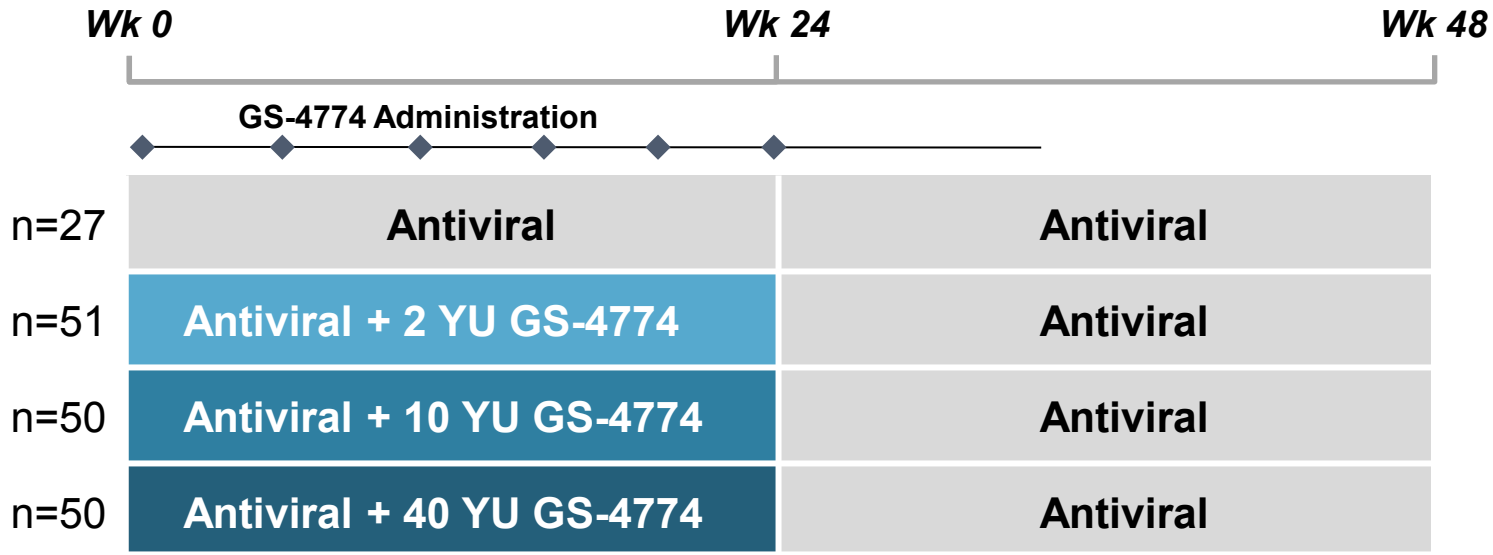
Lymphocyte Proliferation Assay (LPA)



- Immunogenicity to HBsAg, HBcAg and HBx
- Well tolerated with mild injection site reactions

Gaggar A, et al. Vaccine. 2014;32:4925-31

GS-4774: Phase 2 Study in CHB Patients



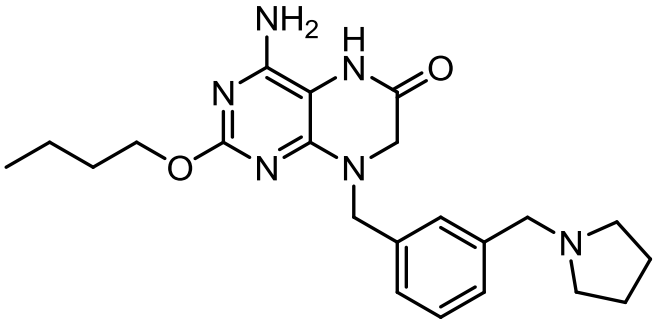
- Noncirrhotic CHB pts on oral antiviral treatment for >1yr
  - GS-4774 subcut every 4 weeks x 6 doses
- Primary efficacy endpoint: HBsAg decline at Week 24
  - Secondary endpoint: HBsAg loss at Week 48
- Exploratory assessments of HBV-specific host immune responses
  - Flow cytometry, Pentamer, IFN-γ Elispot
  - Serum cytokines, RNAs

Strategies of Immune Modulation for CHB

Innate Immunity[4,5]

TLR-7/8 Agonist)

GS-9620
(Oral TLR-7 Agonist)



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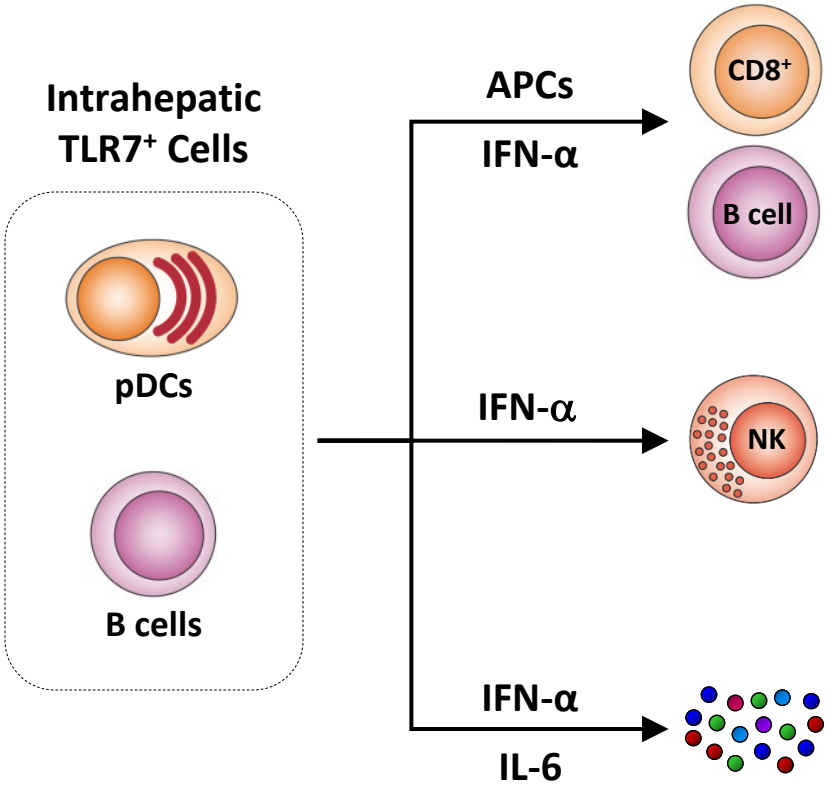
Toll-like Receptor 7 (TLR7) for HBV



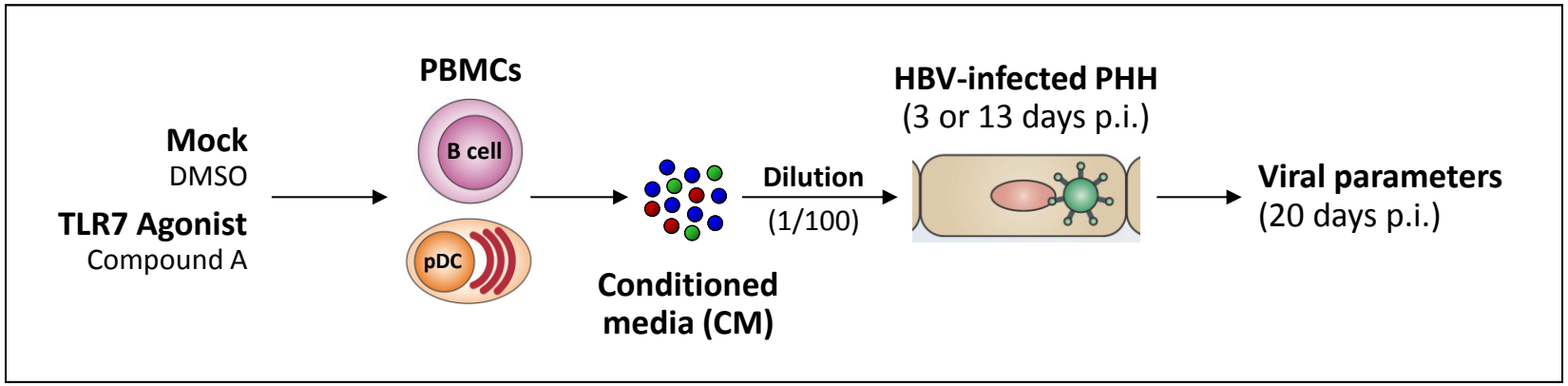
❶ Adaptive immunity
- Kill infected cells
- Antiviral cytokines (e.g. IFN-γ)
- Neutralizing antibodies

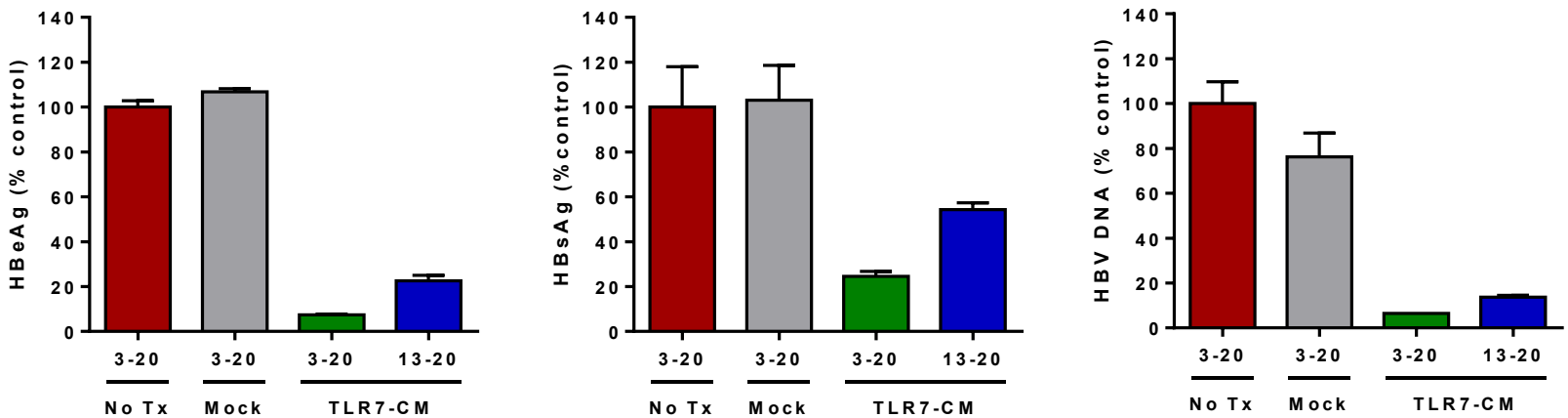
❷ Innate Immunity
- Kill infected cells
- Antiviral cytokines (e.g. IFN-γ)

❸ Antiviral cytokines

pDC, Plasmacytoid dendritic cell
APC, Antigen presenting cell.
IFN, interferon

TLR7-induced Cytokines Exert Anti-HBV Effects in Vitro and Animal Studies



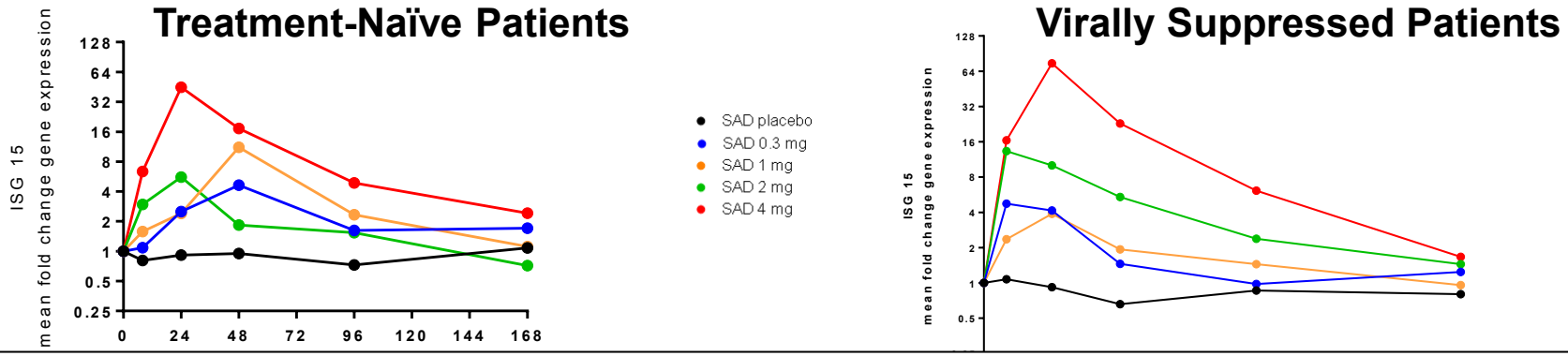


- In woodchucks and chimps, GS-9620 for 4-8 weeks lead to sustained HBV DNA suppression, HBsAg loss and ↓HCC

Niu C et al. AASLD 2014..

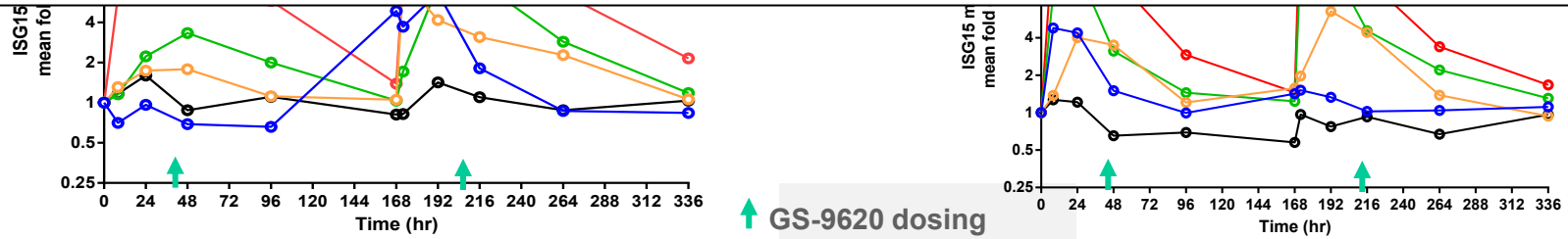
GS-9620 Phase 1 SAD/MAD study in CHB Patients
ISG15 (mRNA) Induction

(a) Single Dose



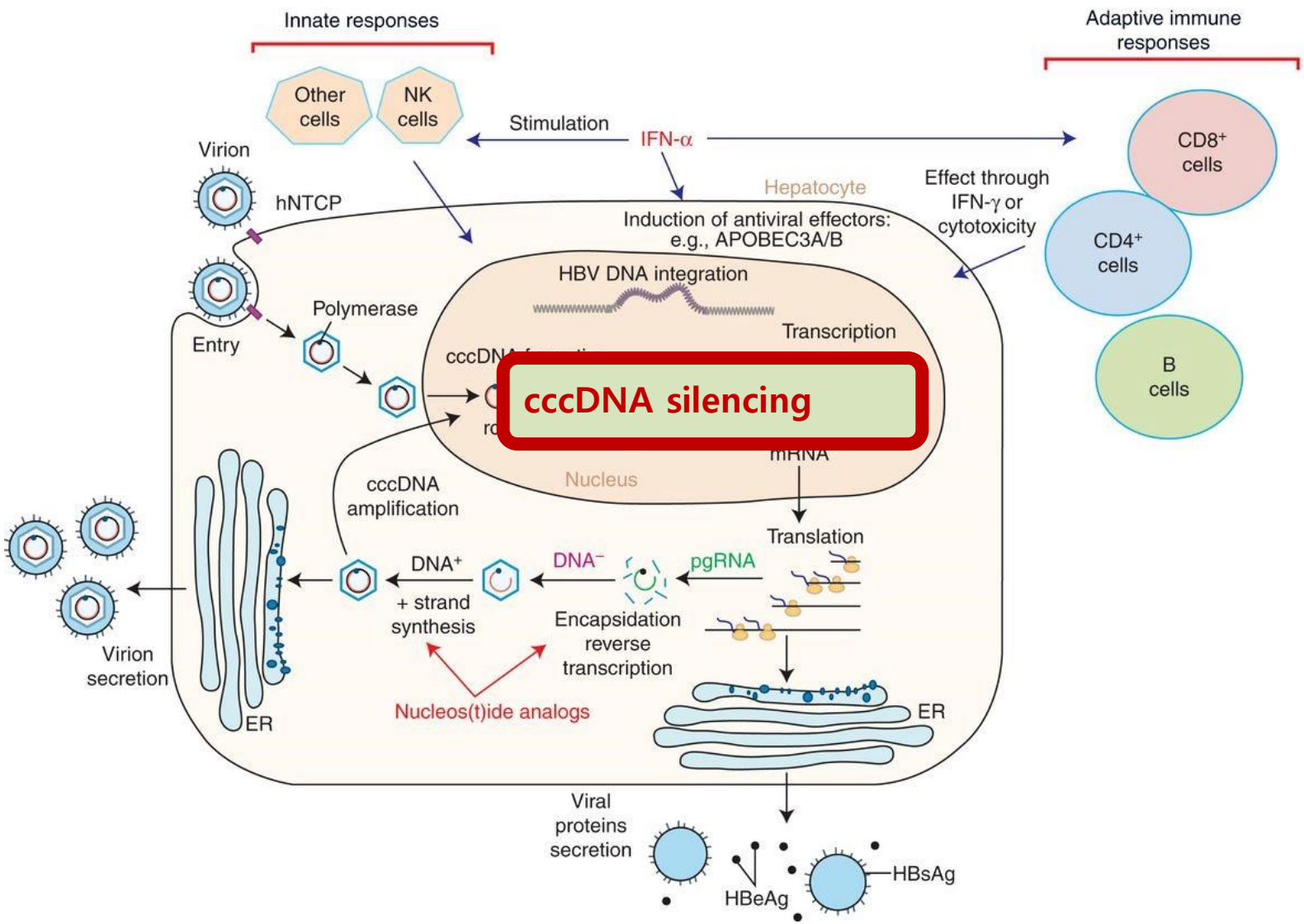
- **Safety**
  - Safe and well tolerated,
  - No systemic IFN, no flares, no cytopenias

➡ **Phase II study:** 150 pts with 4-12 weekly doses



Gane EJ, et al. J Hepatol 2015 (in press)

HBV "Cure" is the aim!



Can we eliminate cccDNA?

- cccDNA is the transcription template for all mRNAs, and is responsible for chronicity in an infected cell and rebound after OAV withdrawal.
- cccDNA is the reservoir which prevents cure
- cccDNA formation utilises the host cell's own nuclear enzyme/DNA repair machinery
- Strategies which could eliminate cccDNA include
  - cccDNA silencing by specific small molecules but against virus not host targets to avoid toxicity
  - cccDNA depletion through increased hepatocyte turnover (but potential risk of hepatocarcinogenesis)
  - cccDNA cleavage through by CRISPR-Cas9 nucleases

SCIENTIFIC REPORTS

OPEN

CRISPR/Cas9 cleavage of viral DNA efficiently suppresses hepatitis B virus

www.nature.com/scientificreports.DOI:1038/srep10833

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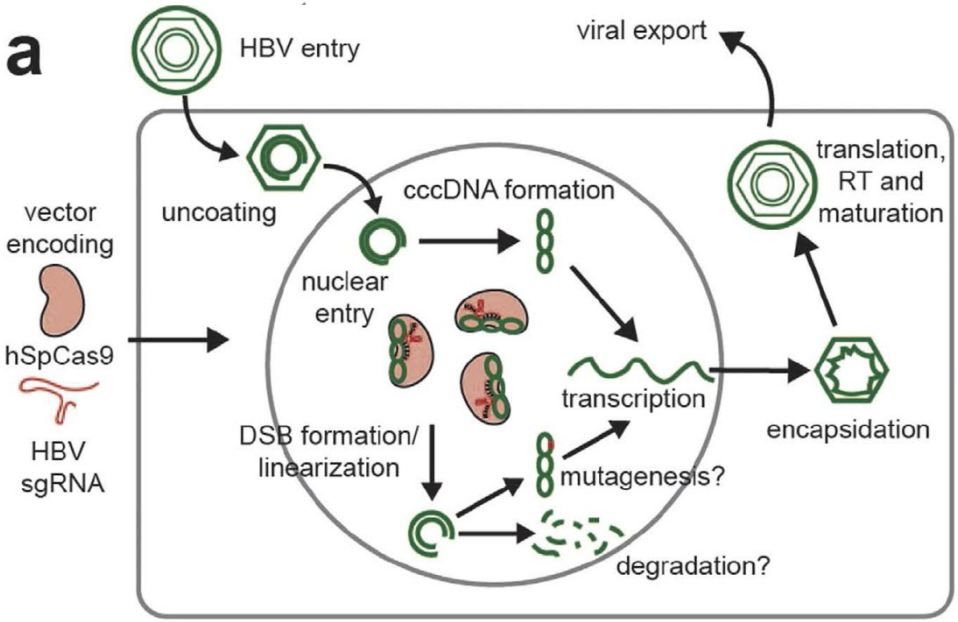
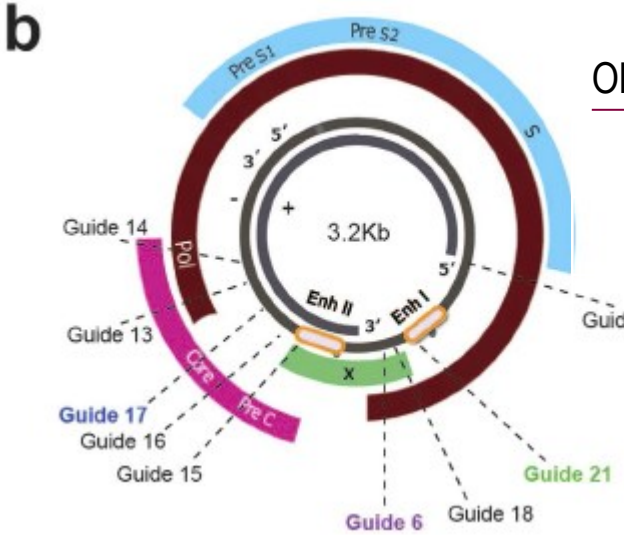
Vyas Ramanan[1,*], Amir Shlomai[2,*,#], David B.T. Cox[1,6,9,*], Robert E. Schwartz[1,3,4], Eleftherios Michailidis[2], Ankit Bhatta[2], David A. Scott[6,11], Feng Zhang[1,6,10,11], Charles M. Rice[2] & Sangeeta N. Bhatia[1,3,5,6,7,8]





ORF Targets	
S	35
C	27
X	28
P	126

- Guide RNA sequences deliver Cas9 nuclease to conserved regions within HBV cccDNA, induce ds DNA breaks
  ⇨ ↓ cccDNA, gene expression and DNA replication

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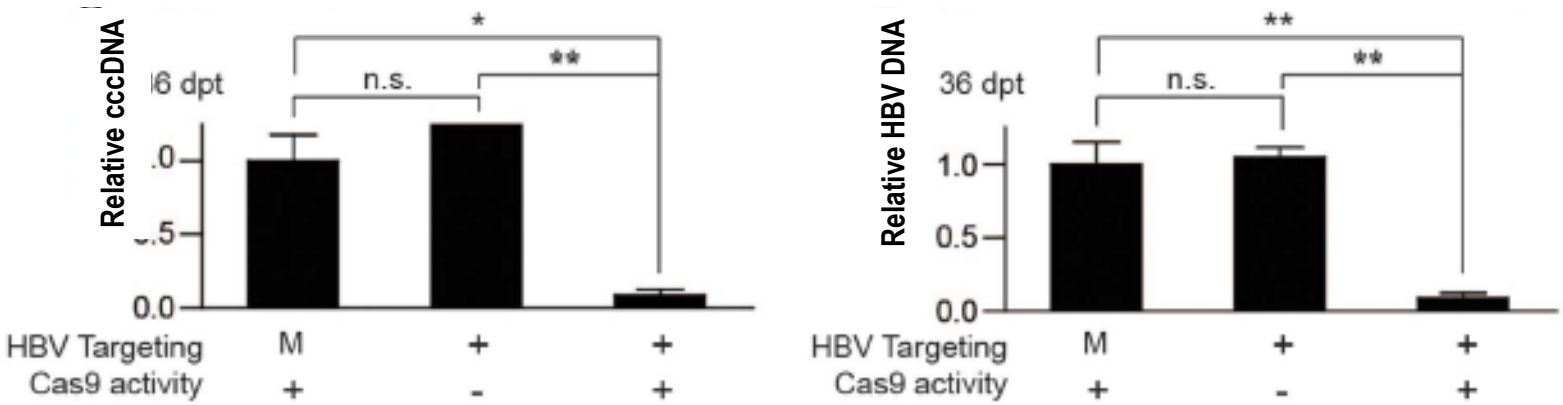


- Has potential to eliminate persistent HBV infection but will need to target EVERY infected hepatocyte
- Need safe and effective in vivo drug delivery system (AAV vector)
- Extensive genome-wide profiling to exclude off-target Cas-9 cutting (but little homology between HBV and human DNA)

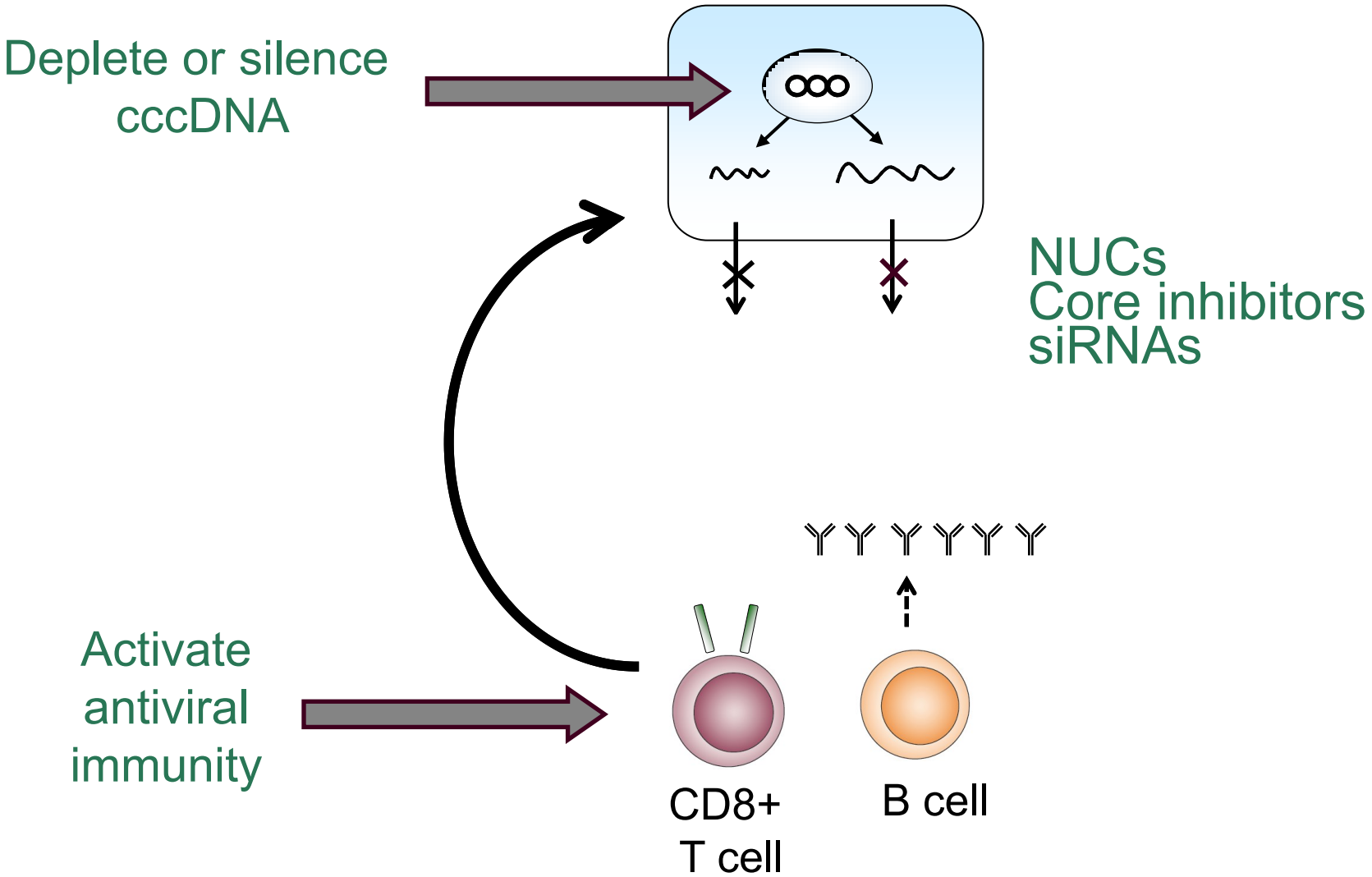
HBV CURE Conclusions

- Viral suppression with oral antiviral therapy can prevent disease progression and liver-related complications
- Current duration of OAV is lifelong with high cost and risk of breakthrough from non-adherence/resistance
- Future therapies will aim to induce HBsAg loss and enable discontinuation of long-term therapy
- Ultimate goal of CHB management will be to develop a new targeted therapy which can provide “HBV Cure” after a finite duration of treatment

HBV CURE: Conclusions

- HBV Cure programs stem from better understanding of HBV lifecycle and identification of new targets
- Several promising candidates already in preclinical and early clinical development
- Target patient population still undefined wrt phase of HBV infection, stage of disease, suppressed on OAV vs. treatment naïve vs. “immune tolerant”
- Safety will be the priority for these new therapies, in order to avoid severe hepatitis flares and other toxicity
- Convenient administration important (oral, subcut)
- HBV cure will ultimately require combinations which inactivate cccDNA and restore host immune responses

HBV CURE: A Multi-Step Approach



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