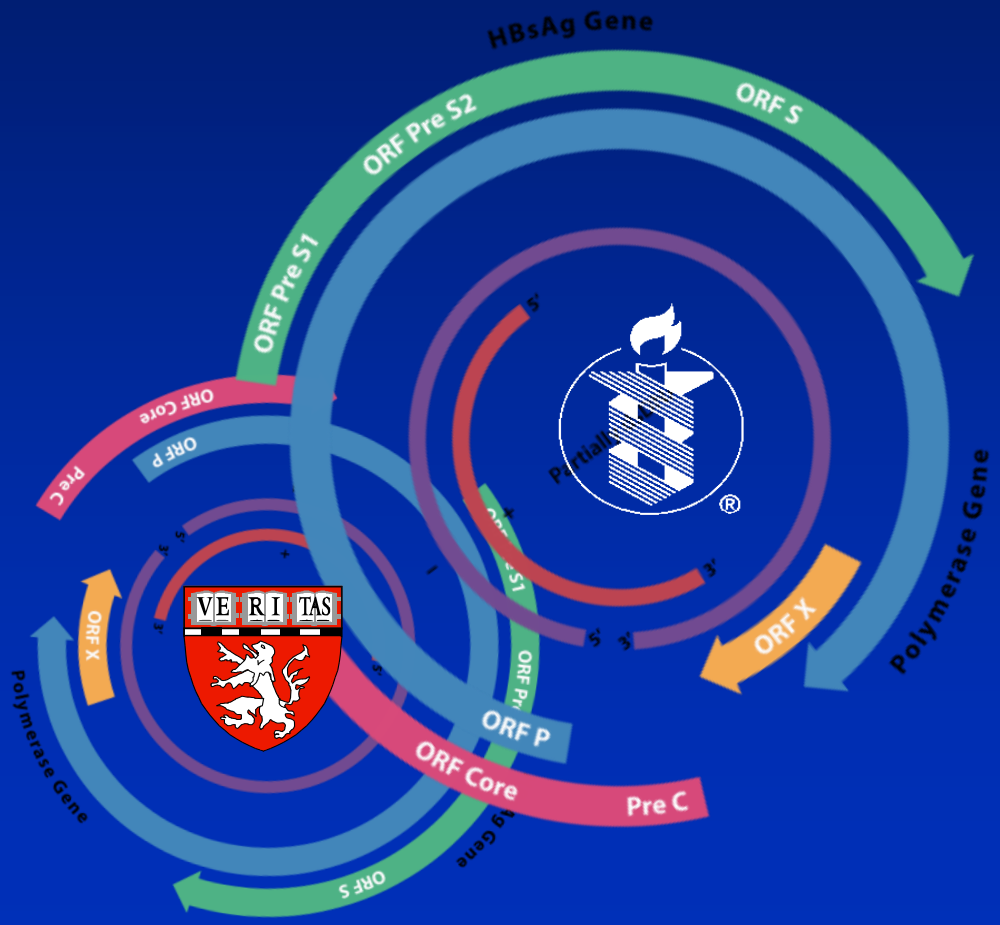
An Update HBV Treatment



Epidemiology

Natural history

Treatment

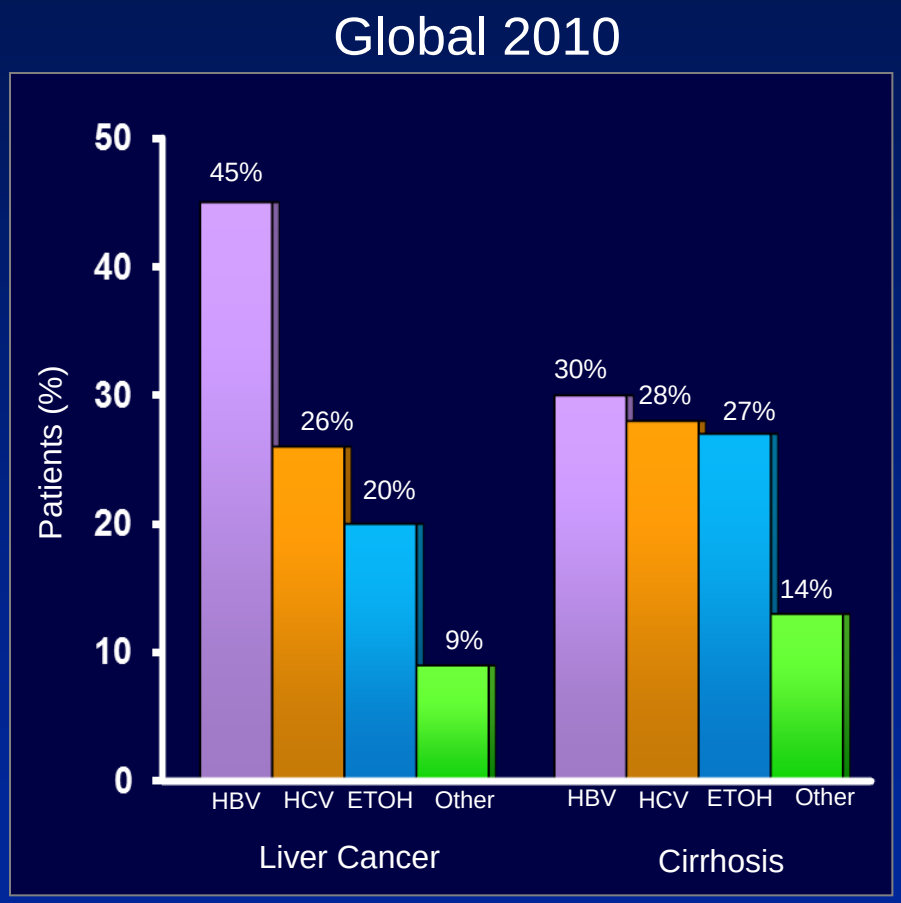
Daryl T.-Y. Lau, MD, MPH
Associate Professor of Medicine
Director of Translational Liver Research
Division of Gastroenterology
BIDMC, Harvard Medical School

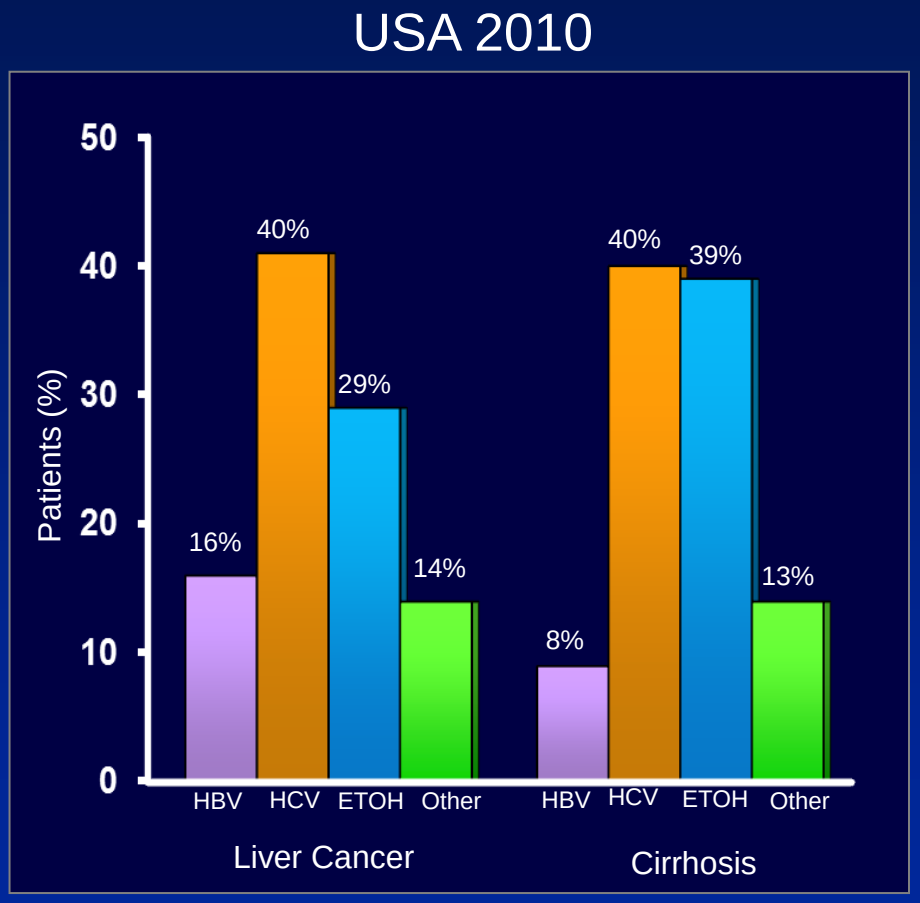
HBV Discovered in Korean Mummy Dated to the 16th Century AD

- Laparoscopic liver biopsies performed on mummified Korean child dated to 16th Century A.D.
- Complete sequence of the oldest HBV isolate and the most ancient full viral genome known so far
- Genome (3,215 base-pairs) analysis of the ancient HBV revealed a unique HBV genotype C2 (HBV/C2) sequence commonly spread in Southeast Asia
- Comparison of the ancient genome with contemporary HBV/C2 DNA sequences from various regions in East Asia showed significant differences
- Sequence likely dates back to 3,000-100,000 years ago

Bar-Gal G, et al. 63rd AASLD; Boston, MA; November 9-13, 2012; Abst. 927.

Global Burden of Disease Study 2010: Causes of Death From Chronic Liver Disease

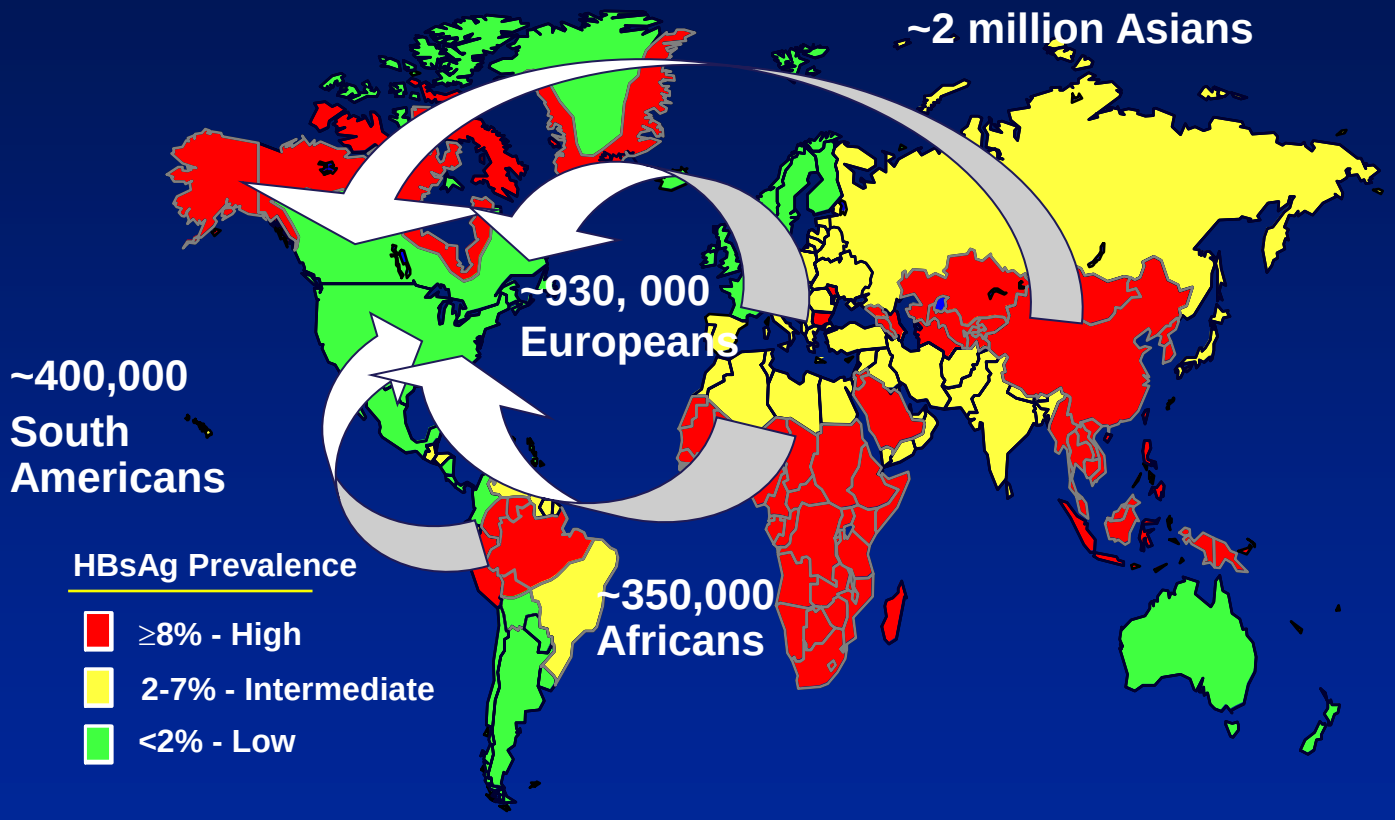




Increase in liver-cancer deaths (past 20 years):
Globally (from 1.25 to 1.75 million/year); USA (45,000 to 70,000/year).

Cowie BC, et al. *Hepatology.* 2013;58(suppl 1):218A-219A. Abstract 23.

Geographic Prevalence of Chronic Hepatitis B Impacted by Migration



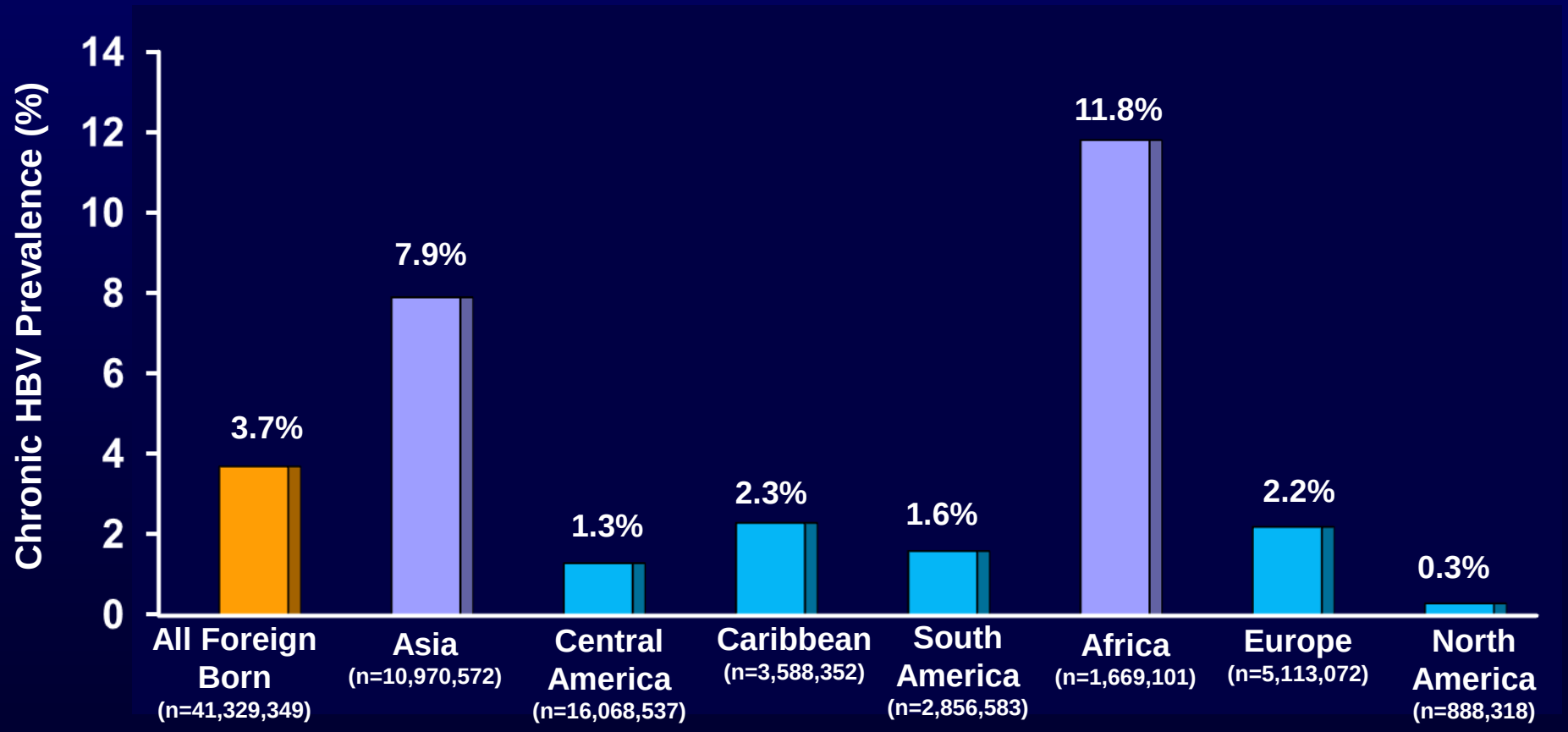
Immigration numbers summed by continent from 1996-2002

World Health Organization. Geographic Prevalence of HBsAg. Data from 1996 (unpublished). http://www.who.int/vaccines-surveillance/graphics/htmls/hepbprev.htm. Accessed: September 13, 2004.

Mahoney FJ. *Clin Microbiol Rev*. 1999;12:351-366.

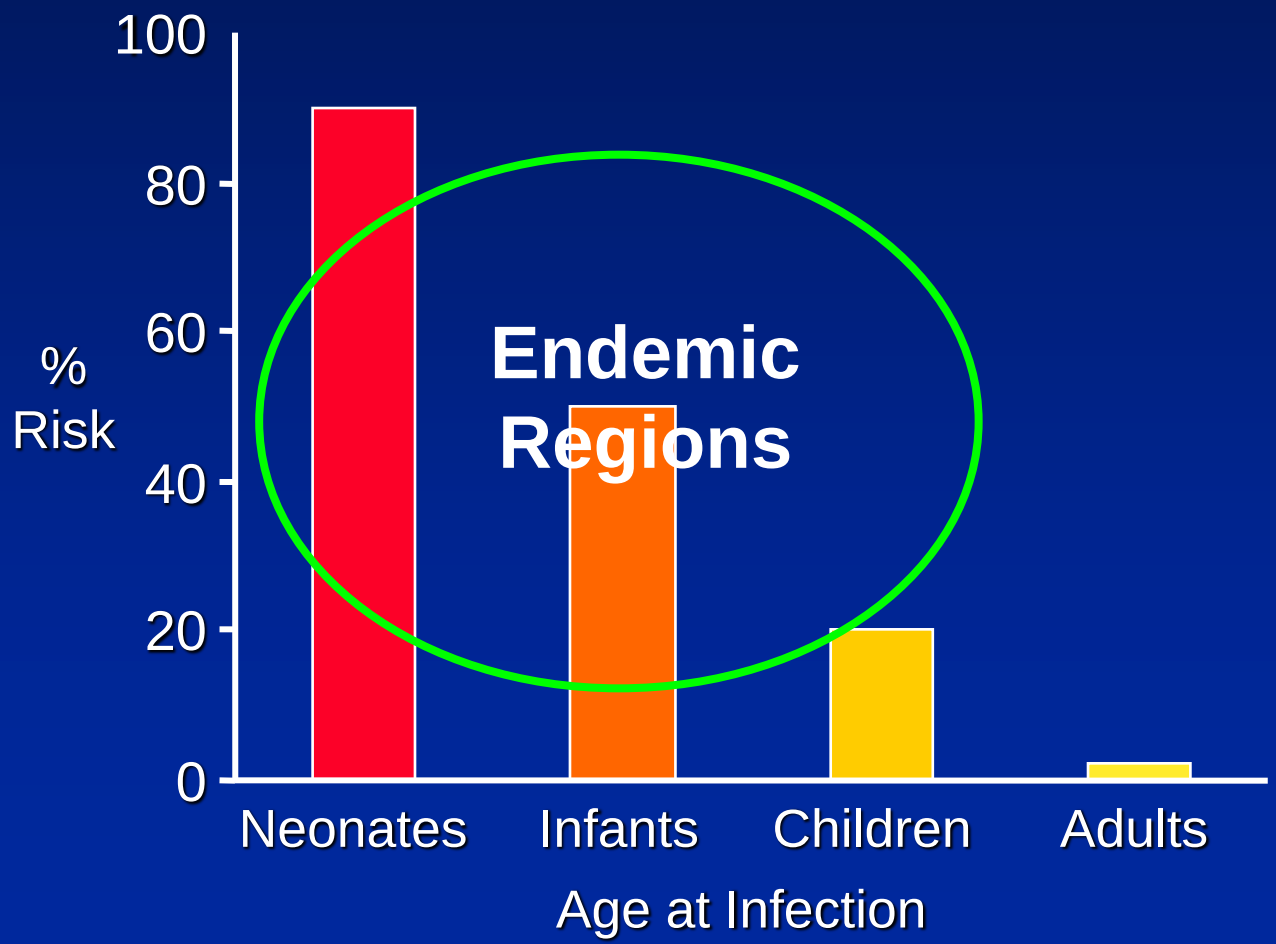
Estimated HBV Prevalence Among Foreign-Born Americans (2008)

Foreign-Born Americans: 13.6% of General Population

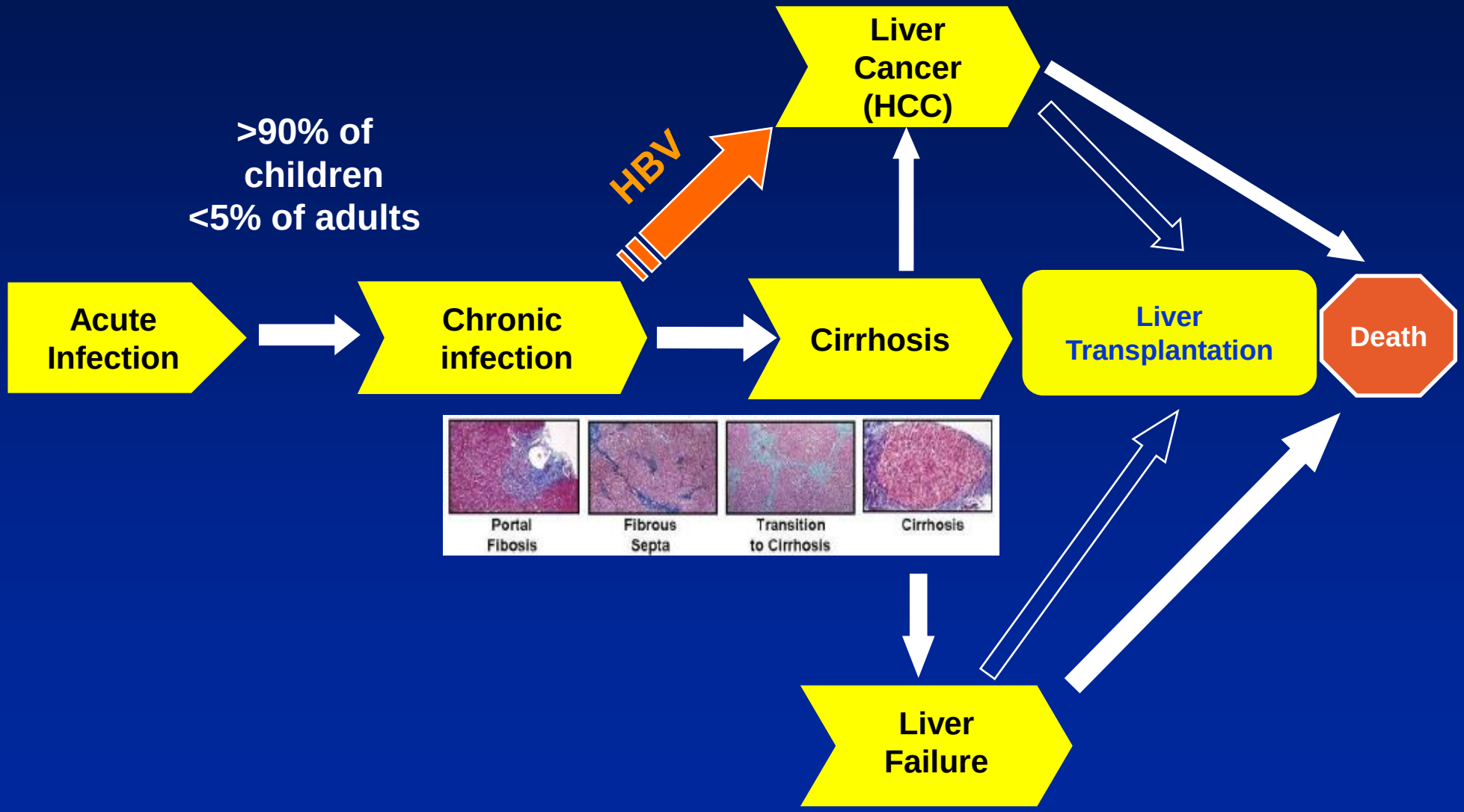


Welch S, et al. *Hepatology.* 2008;48(suppl):687A-688A. Abstract 853.

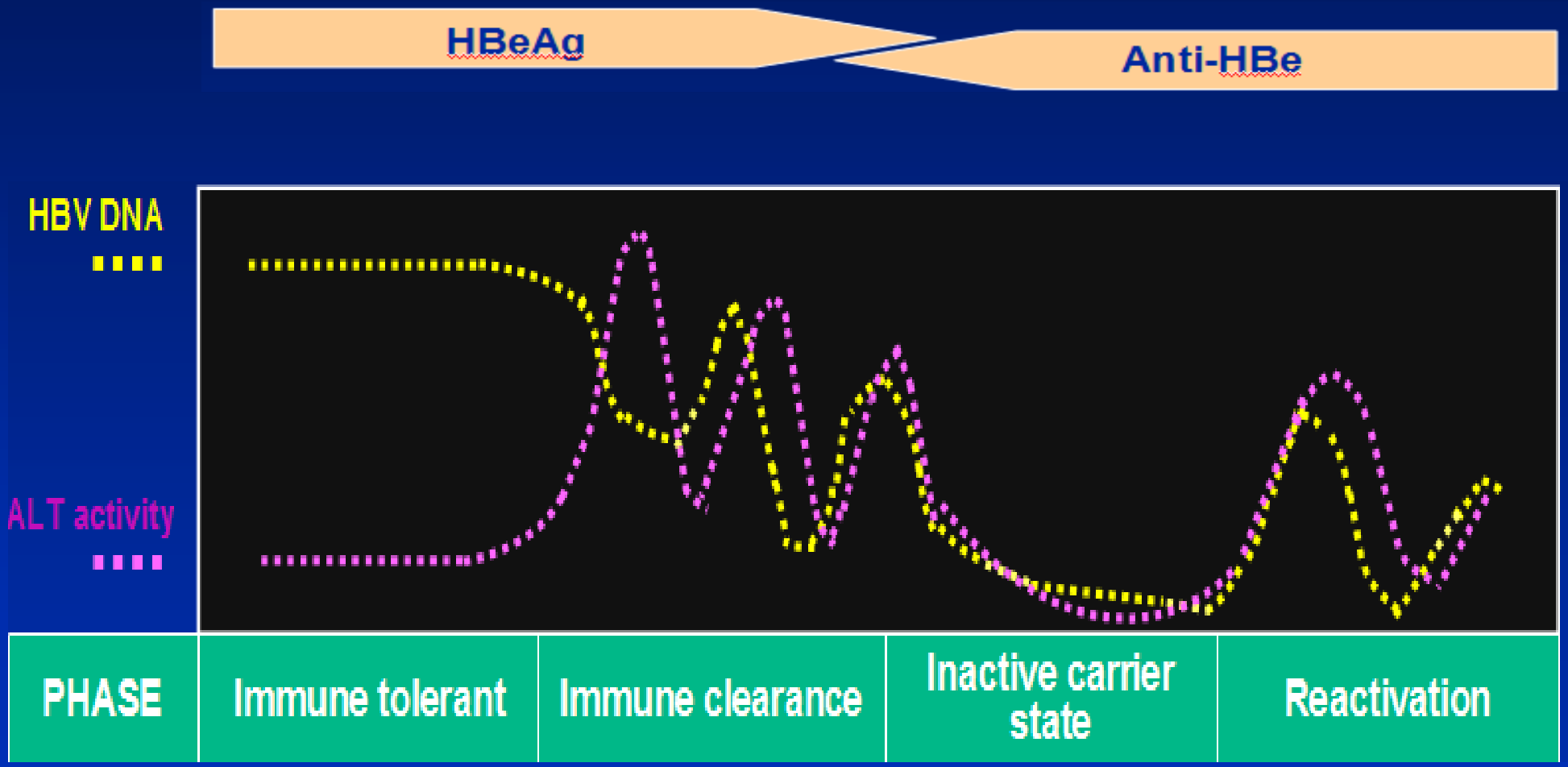
Risk of Chronic Infection is Inversely Related to Age at Infection



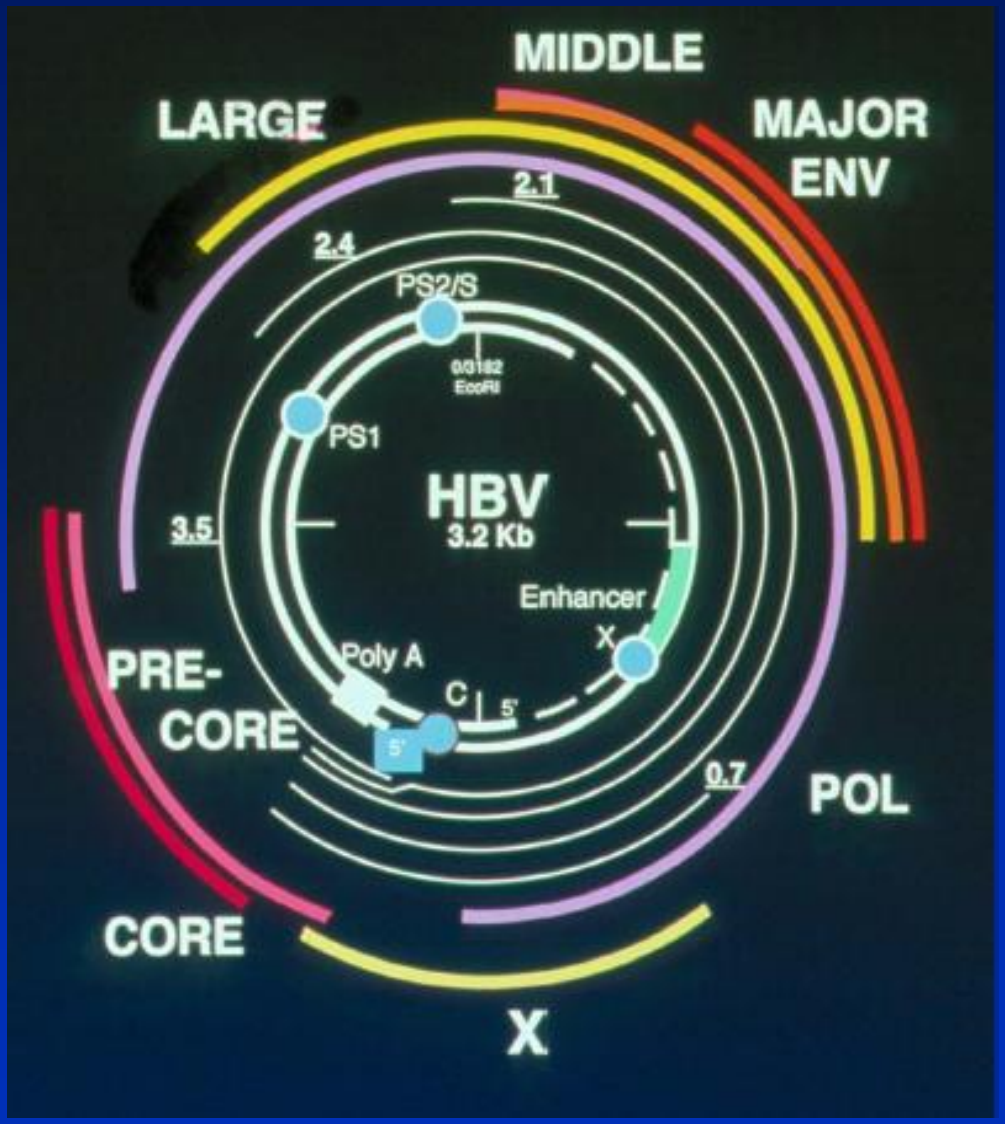
HBV : Liver Disease Progression



Phases of Chronic HBV Infection



HBV Genome Organization



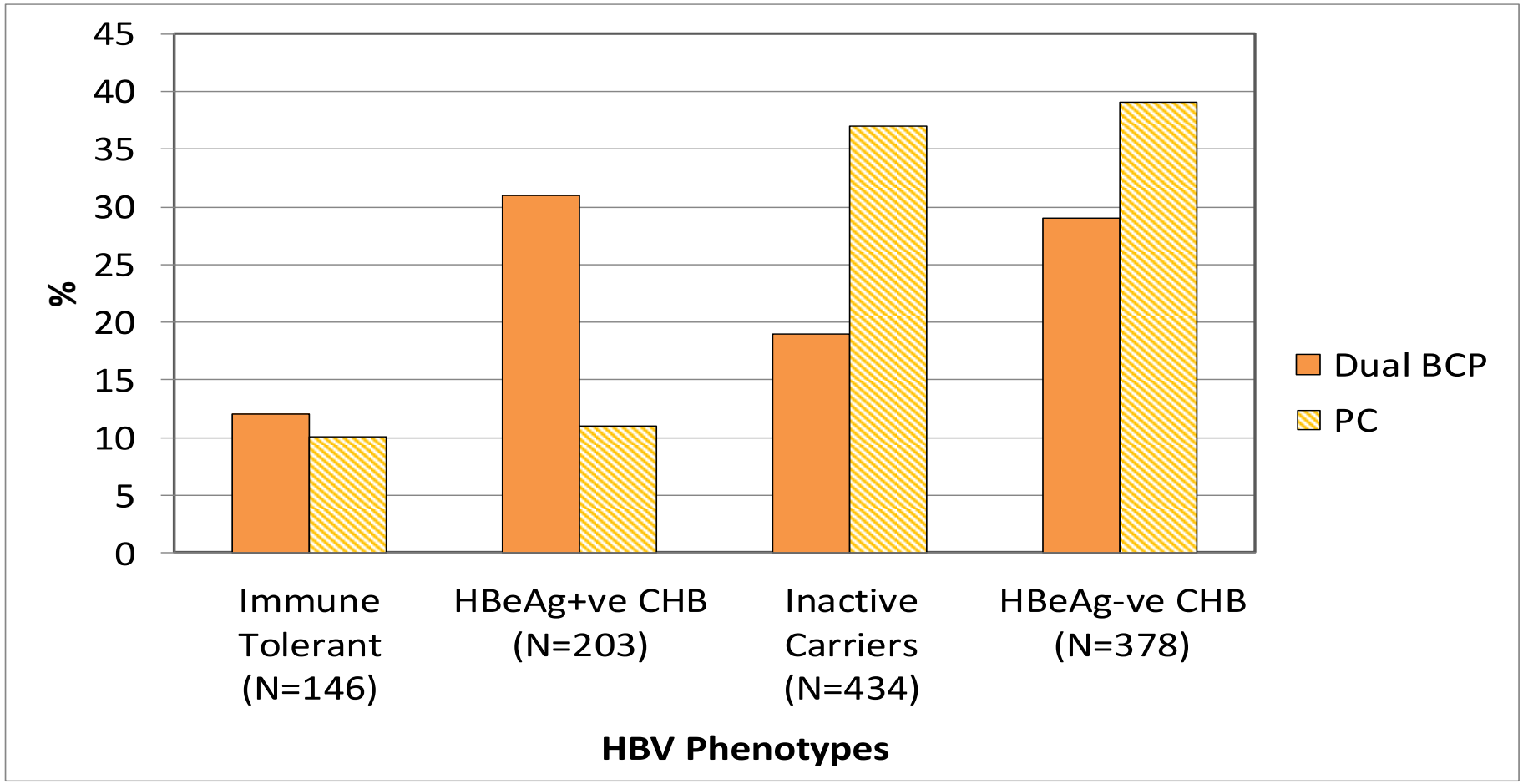
Hepatitis B Research Network (HBRN)

HBV Patient Populations in North America

- Evaluation of the prevalence of PC and BCP mutations
- 1349 baseline samples in the HBRN Cohort Study from 21 centers in US and Canada between 2011 and 2013 were included.
- Patients on antiviral therapy were excluded.

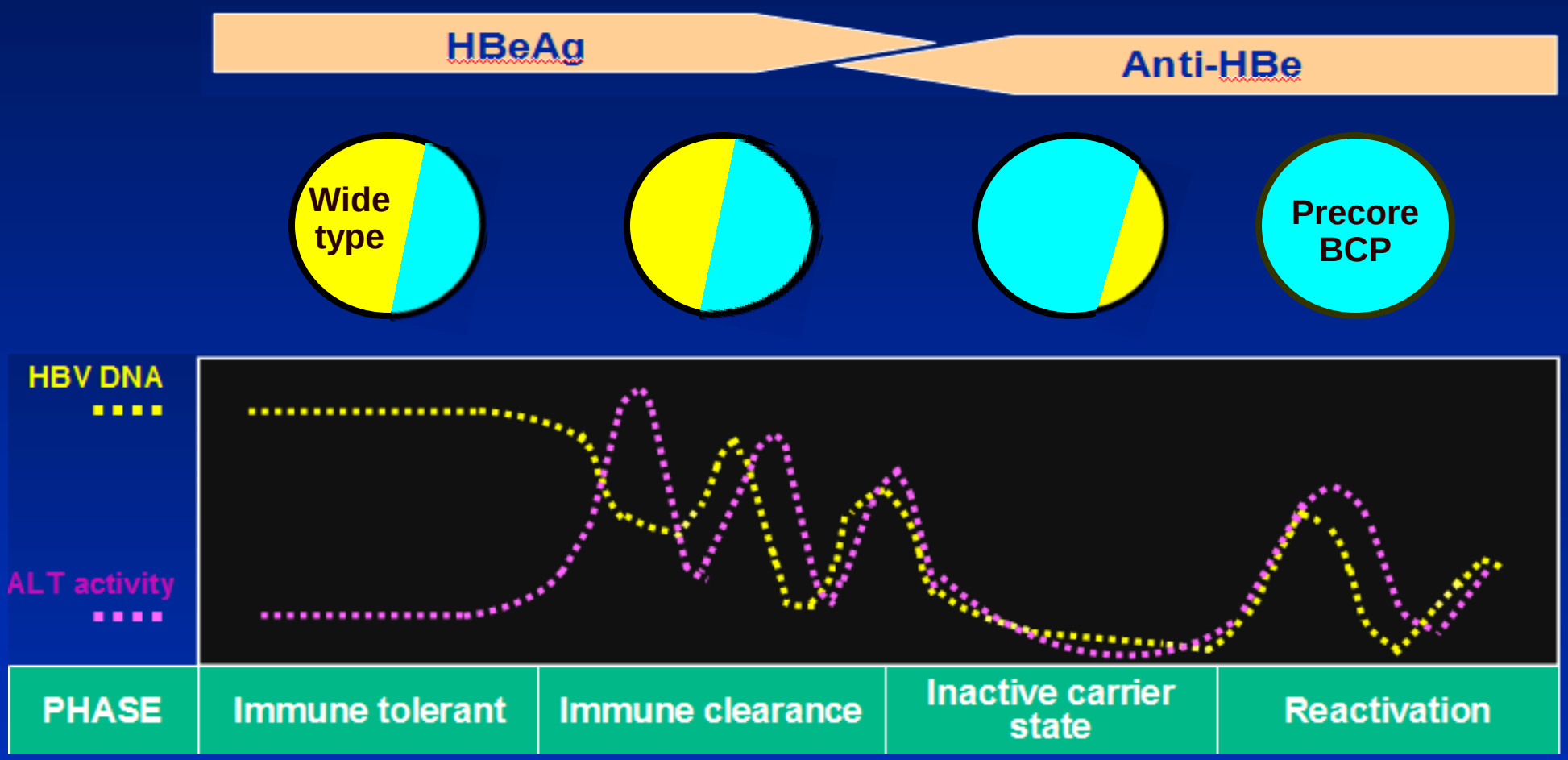
D. Lau and HBRN investigators, AASLD 2014, Boston, USA

BCP and PC Mutants Across HBV Phenotypes



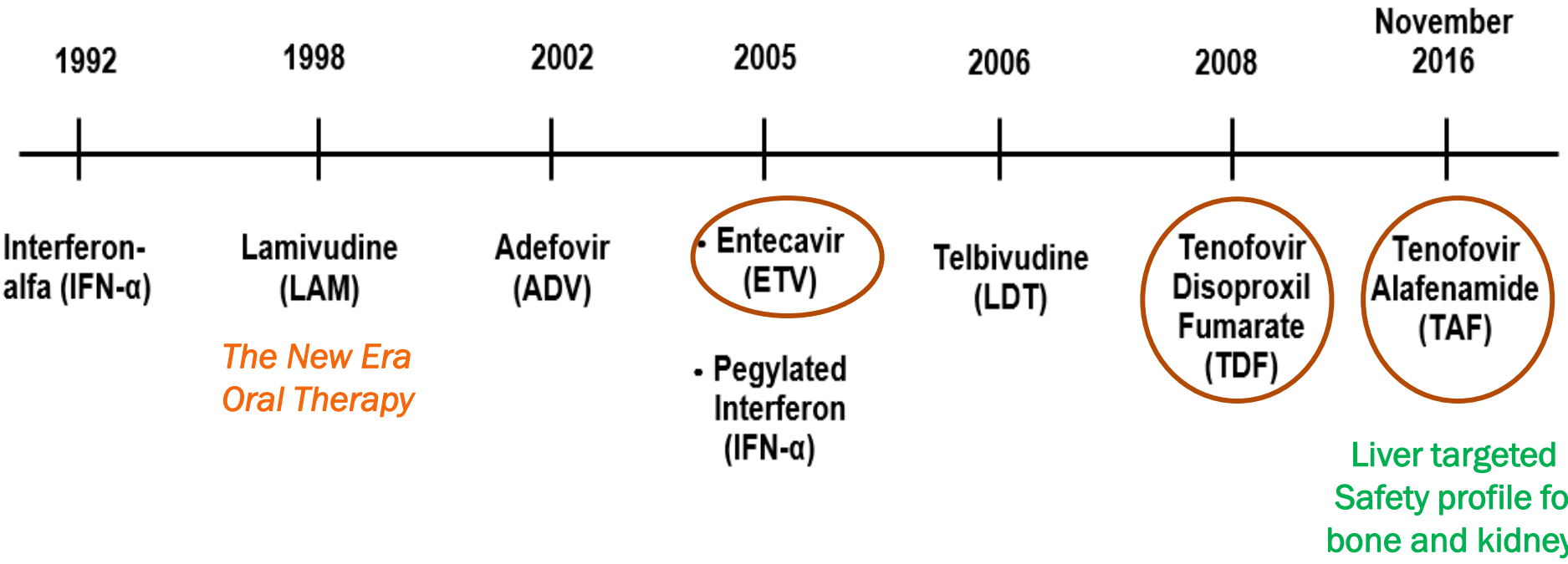
D. Lau and HBRN investigators,
AASLD 2014, Boston, USA

Phases of Chronic HBV Infection



Therapy of Chronic Hepatitis B

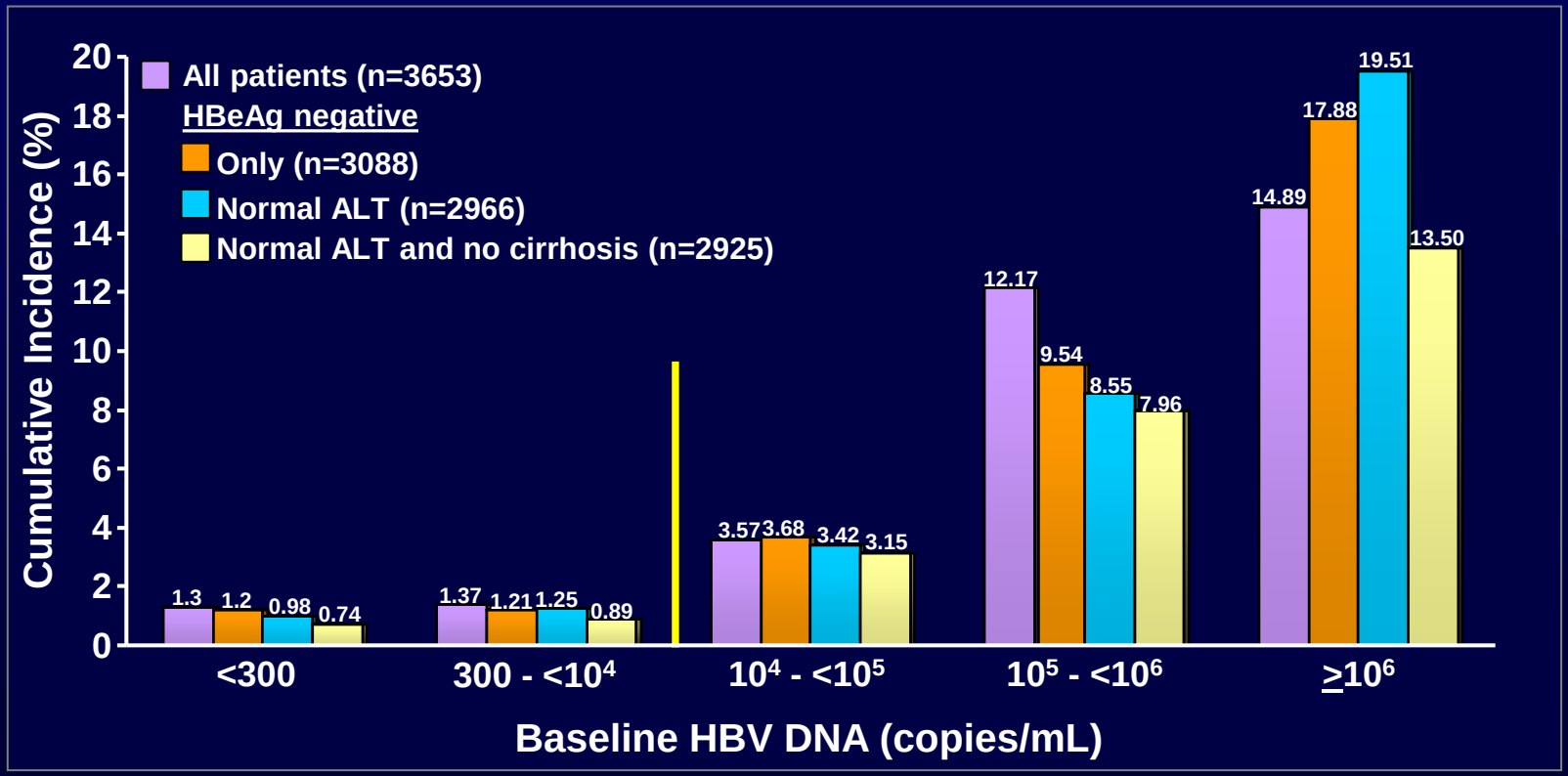
Timeline based on FDA approval in the United States



HBV: Current Treatment Guidelines

Guideline	HBeAg+		HBeAg-	
	HBV DNA IU/mL	ALT U/L	HBV DNA IU/mL	ALT U/L
EASL 2017	≥2,000	>ULN and/or at least moderate liver necro-inflammation or fibrosis	≥2,000	>ULN and/or at least moderate liver necro-inflammation or fibrosis
	≥20,000	>2 x ULN irrespective of fibrosis	≥20,000	ALT >2 x ULN irrespective of fibrosis
AASLD 2018	>20,000	>2x ULN or significant histological disease	>2,000	>2x ULN or significant histological disease
APASL 2015	≥20,000	>2x ULN or significant histological disease	≥2,000	>2x ULN or significant histological disease

REVEAL-HBV Study: 13-Year Cumulative Incidence of Hepatocellular Carcinoma



Chen CJ, et al. *JAMA.* 2006;295:65-73.

Definition of Cure

	Complete Cure
HBV DNA	Undetectable
HBsAg	Negative
Anti-HBs	Positive
HBeAg	Negative
Anti-HBe	Positive
cccDNA Eliminated	Yes
cccDNA transciptionally silent	Yes
Integrated HBV DNA eliminated	Yes

Definition of Cure

	Complete Cure	Functional Cure
HBV DNA	Undetectable	Undetectable
HBsAg	Negative	Negative
Anti-HBs	Positive	Positive/Negative
HBeAg	Negative	Negative
Anti-HBe	Positive	Positive
cccDNA Eliminated	Yes	No
cccDNA transciptionally silent	Yes	Yes
Integrated HBV DNA eliminated	Yes	No

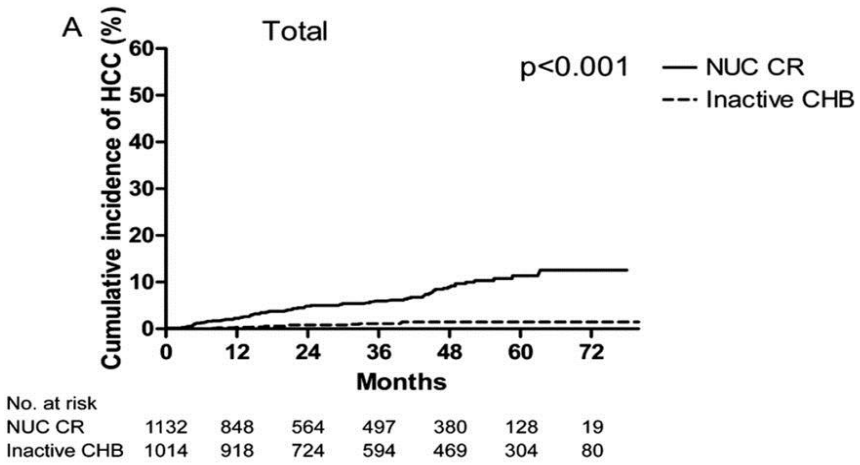
Definition of Cure

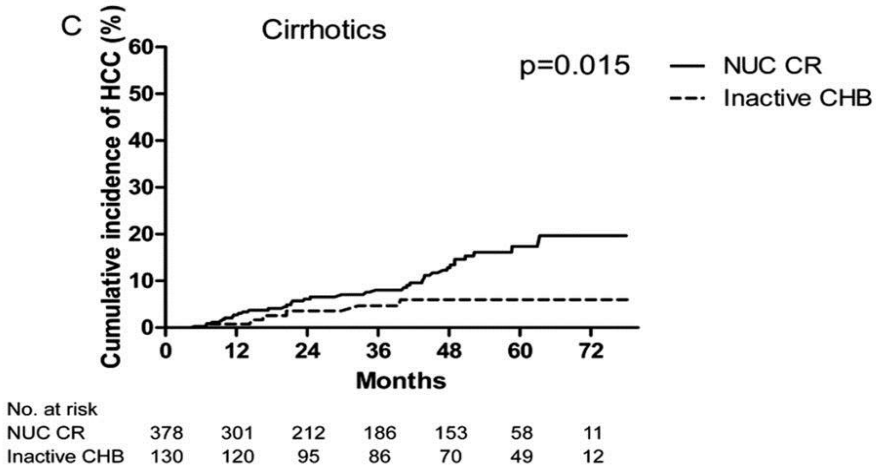
	Complete Cure	Functional Cure	Partial Cure
HBV DNA	Undetectable	Undetectable	Undetectable
HBsAg	Negative	Negative	Positive
Anti-HBs	Positive	Positive/Negative	Negative
HBeAg	Negative	Negative	Negative
Anti-HBe	Positive	Positive	Positive
cccDNA Eliminated	Yes	No	No
cccDNA transciptionally silent	Yes	Yes	No
Integrated HBV DNA eliminated	Yes	No	No

Partial Cure: Long-Term Suppression with NA

- ✓ALT normalization
- ✓Fibrosis regression
- ✓HCC reduction but **NOT elimination**

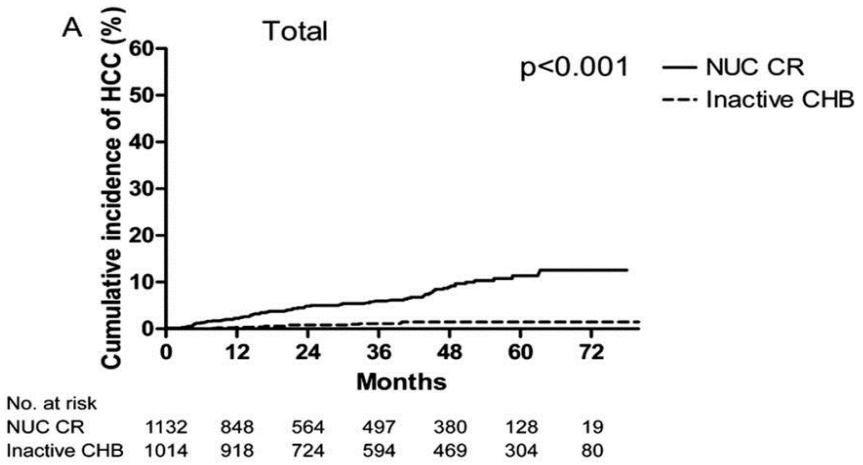
Higher HCC Risk with Complete Responders Compared to Inactive Carriers

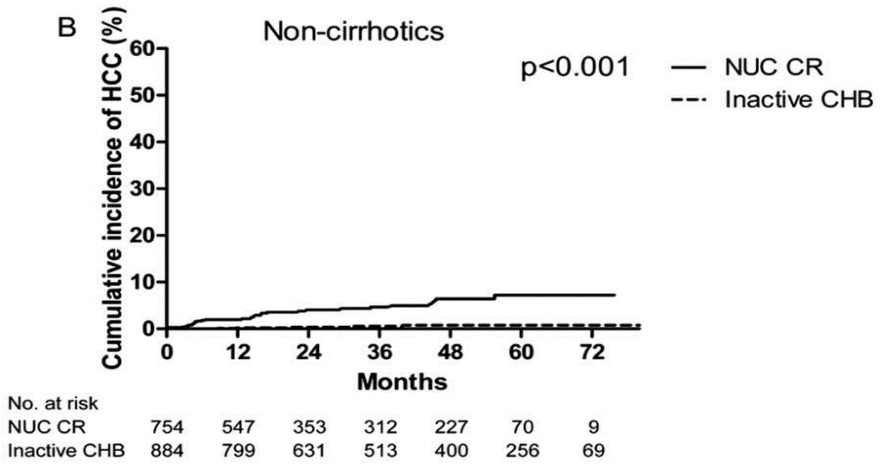


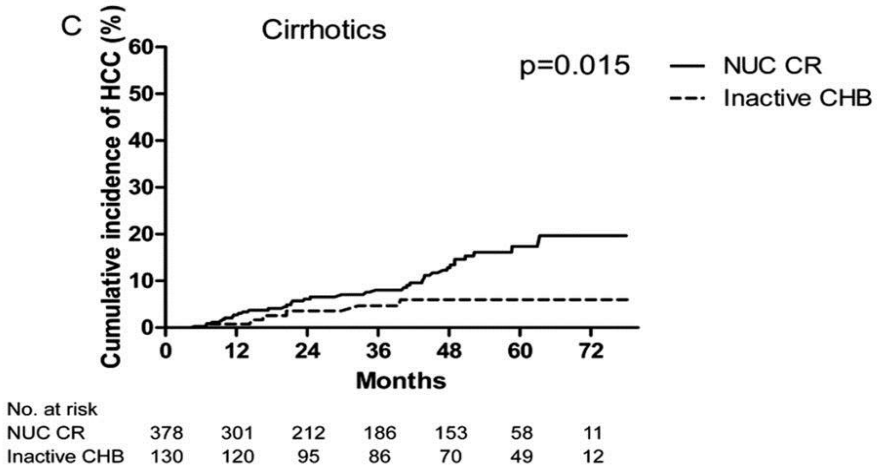


Ju-Yeon Cho et al. Gut 2014;63:1943-1950

Higher HCC Risk with Complete Responders Compared to Inactive Carriers



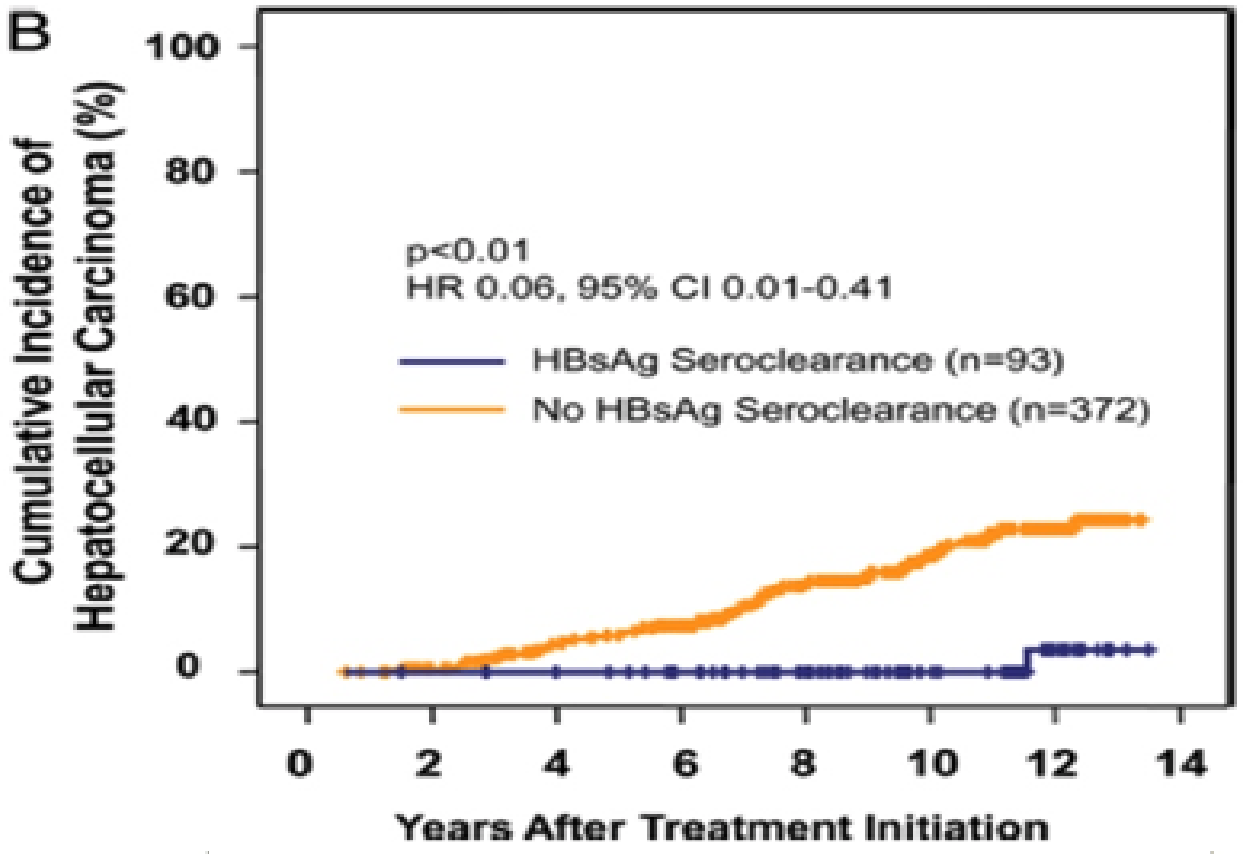




Ju-Yeon Cho et al. Gut 2014;63:1943-1950

Functional Cure: Loss of HBsAg

5409 Korean patients treated with LAM/ETV, 110 lost HBsAg



Kim et al. Gut 2014

Complete Cure

	Complete Cure
HBV DNA	Undetectable
HBsAg	Negative
Anti-HBs	Positive
HBeAg	Negative
Anti-HBe	Positive
cccDNA Eliminated	Yes
cccDNA transciptionally silent	Yes
Integrated HBV DNA eliminated	Yes

- Further eliminate HCC risk
- No risk of HBV reactivation

<u>However:</u>

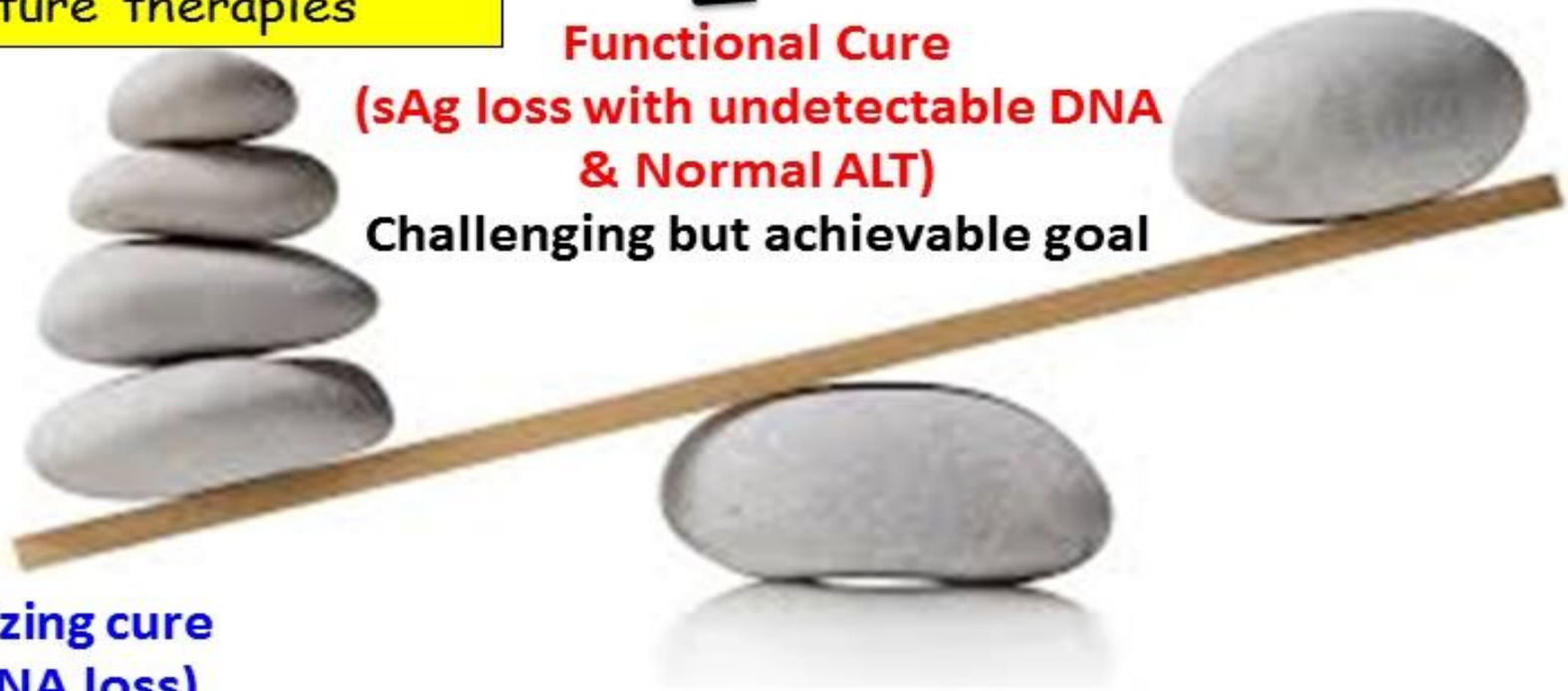
- cccDNA: Stable and persists even after recovery from acute infection
- Very difficult to eliminate integrated HBV DNA in host genome

Is there consensus?

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

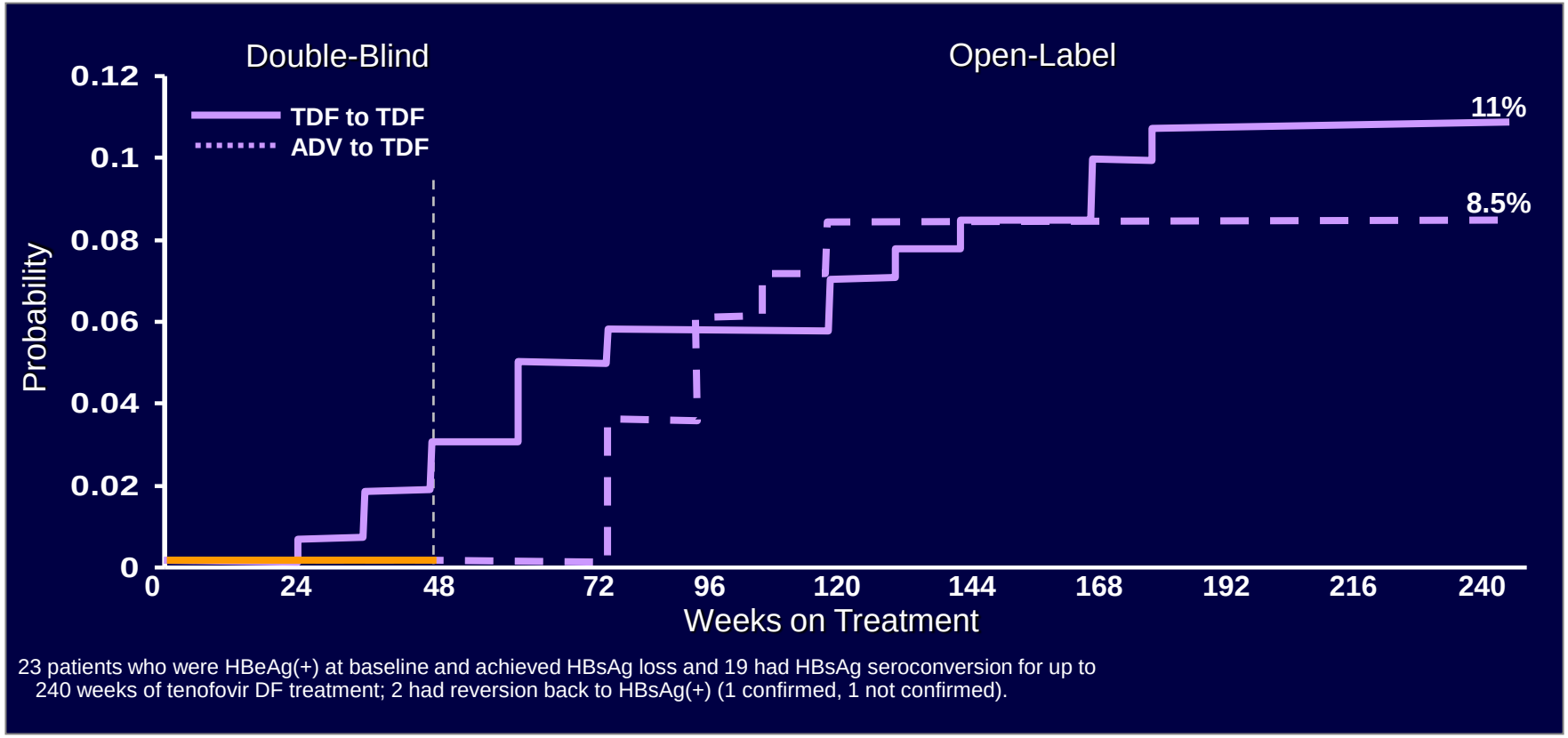
Sustained Virological Response
(sAg +ve, DNA negative, off therapy)
An advance but not enough of one

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



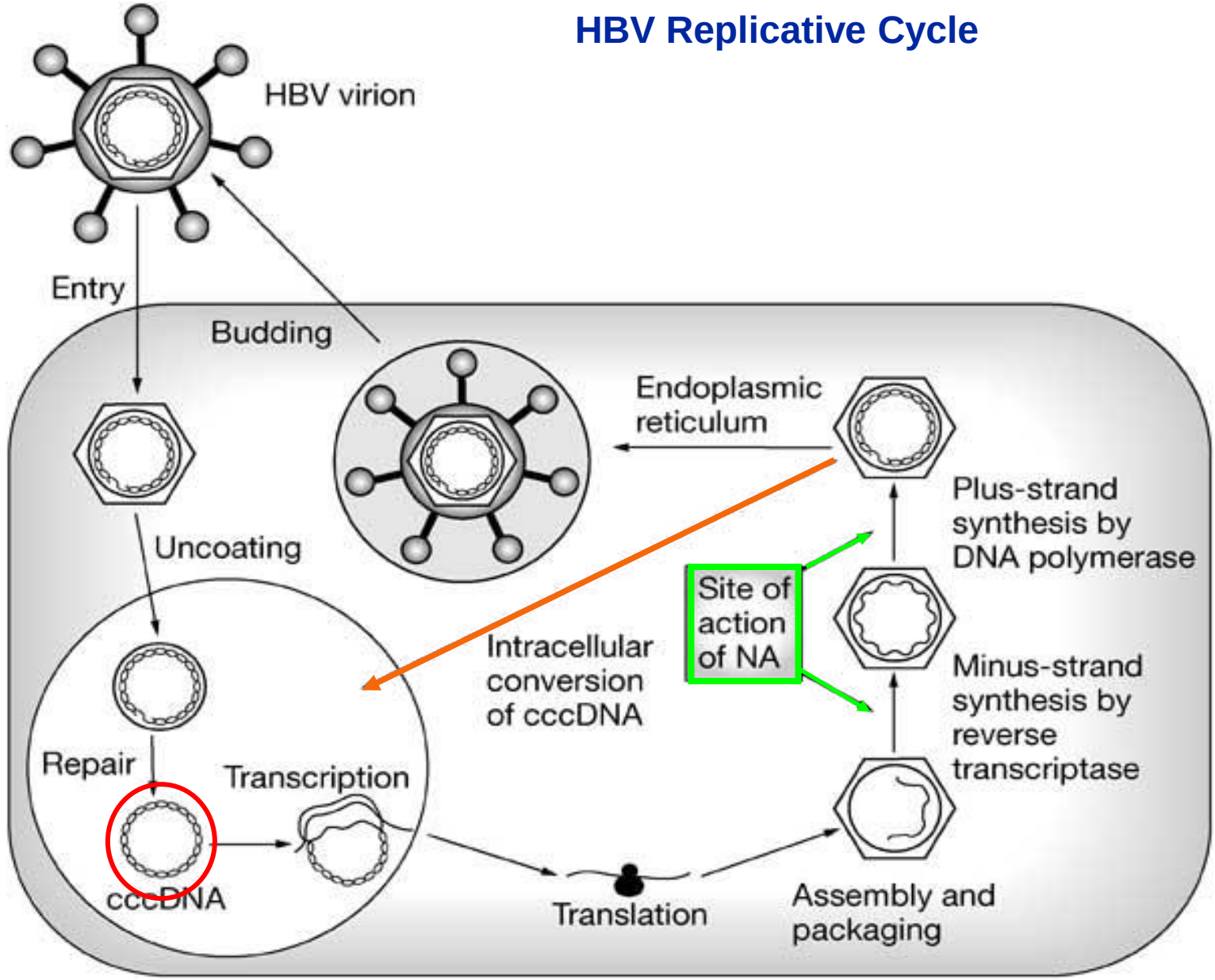
Sterilizing cure
(cccDNA loss)
Too hard to achieve

Prolonged Course of Tenofovir on HBeAg (+) Pts: Cumulative Probability of HBsAg Loss

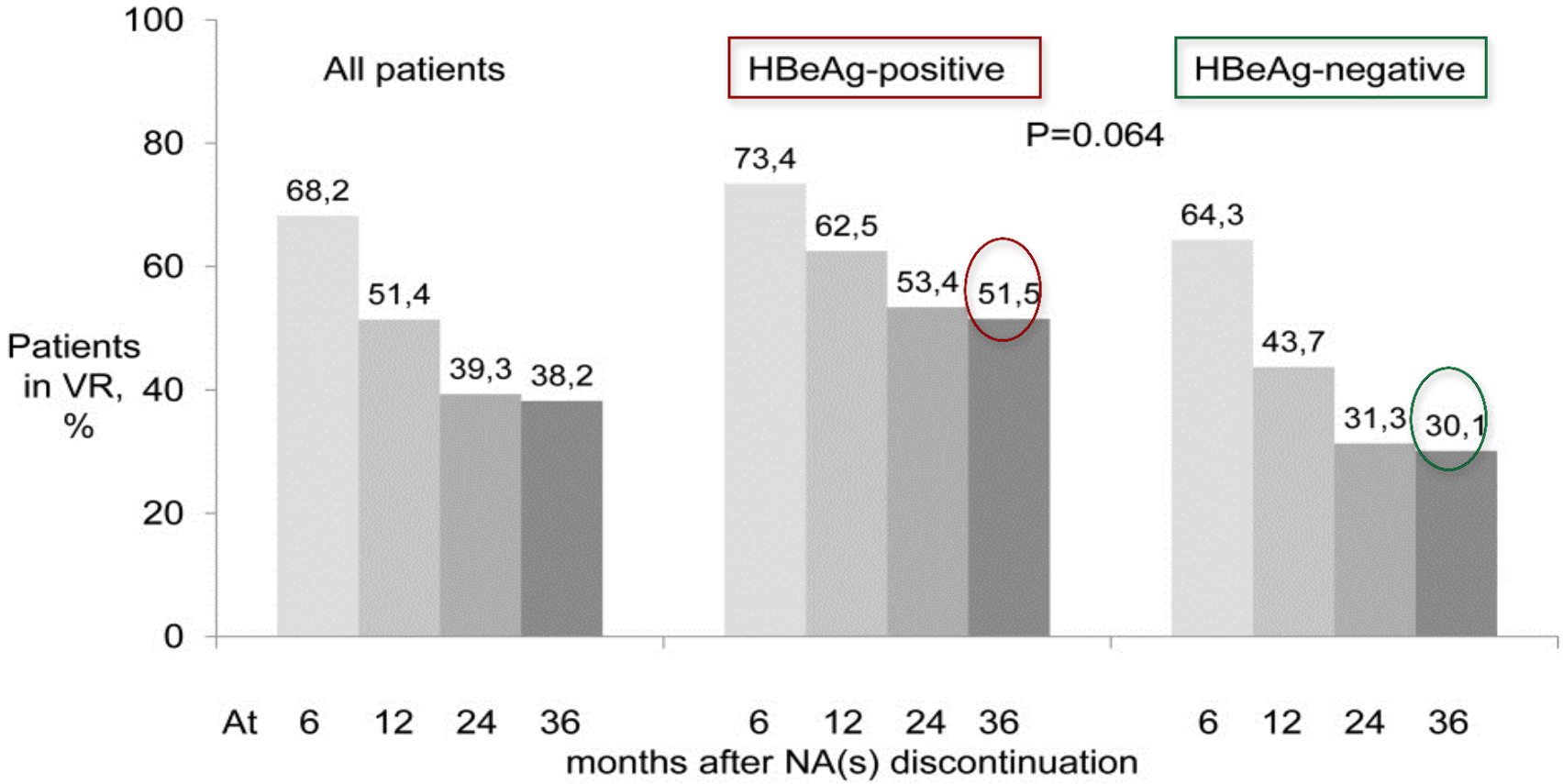


23 patients who were HBeAg (+) at baseline and achieved HBsAg loss
19 had HBsAg seroconversion for up to 240 weeks of tenofovir DF treatment;
2 had reversion back to HBsAg(+) (1 confirmed, 1 not confirmed).

HBV Replicative Cycle

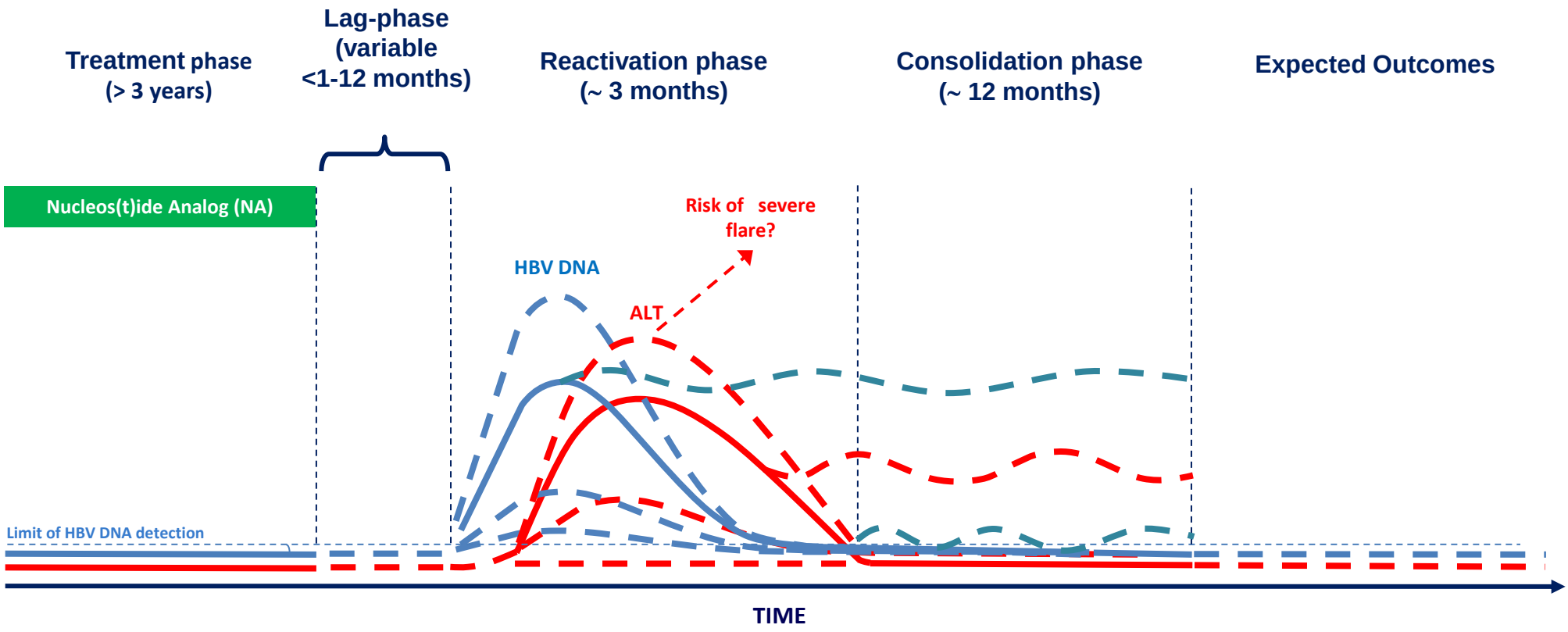


Off-therapy Virological Response



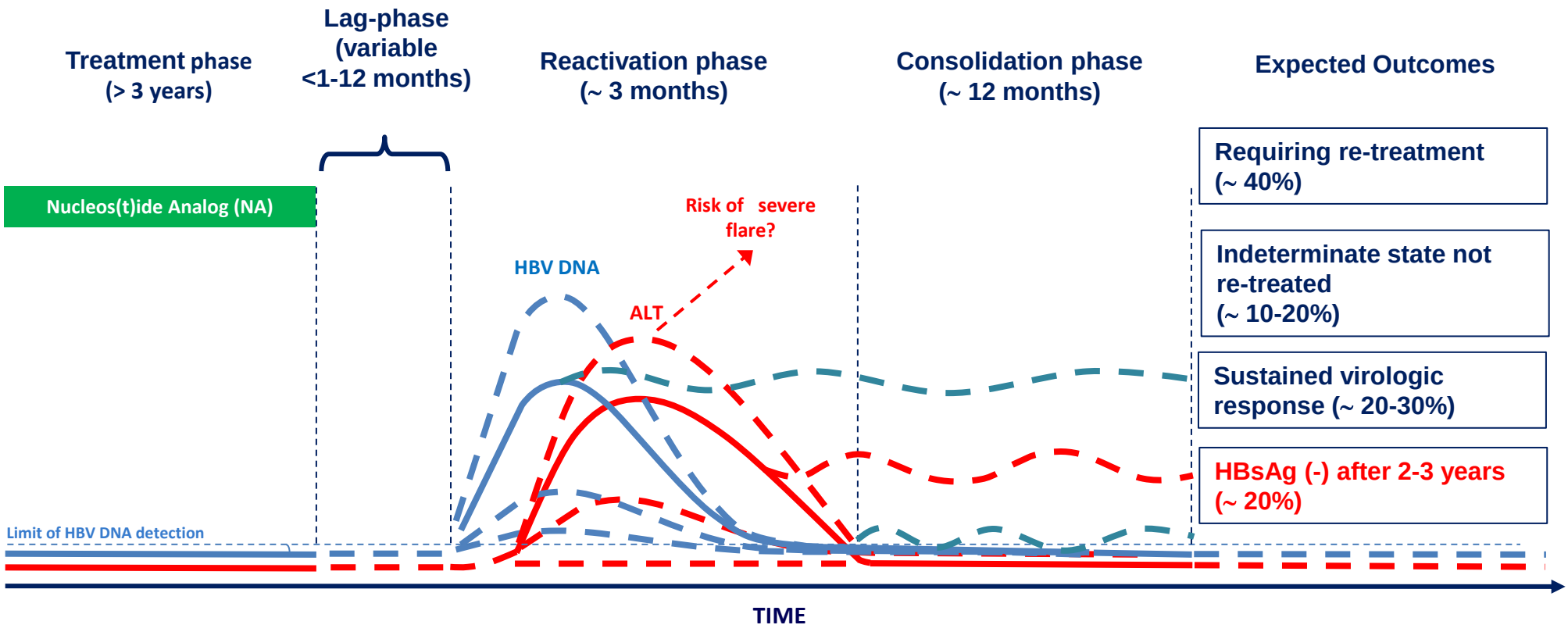
Papatheodoridis G et al, Hepatology 2016

HBeAg(-): Expected Outcomes Post-Therapy



Modified from Lampertico P & Berg T, Hepatology 2018

HBeAg(-): Expected Outcomes Post-Therapy



Modified from Lampertico P & Berg T, Hepatology 2018

HBeAg (-): STOP Therapy

Why stop:

- Functional cure with HBsAg loss
- Response can be sustained or increased off therapy
- *Cost of therapy*
- *Patients do not desire indefinite therapy*

When to stop:

- After a period of therapy consolidation???

HBeAg(-): HBsAg loss after NA Cessation

- 1,075 Taiwanese patients treated with ETV or TDF for 156 (61-430) weeks
- HBsAg loss during therapy: 6 patients (annual incidence of 0.15%)
- 691 patients stopped NA therapy, 308 (45%) had cirrhosis
- 3-year cumulative virologic relapse (79%) and clinical relapse (61%)
- 42 patients achieved HBsAg loss
- 6-year cumulative incidence of HBsAg clearance: 13%, estimated annual incidence 1.78%

Jeng WJ et al, Hepatology 2018

HBeAg(-): HBsAg loss after NA Cessation

Serious adverse events during follow-up after stopping therapy

- 7 of 308 (2.2%) patients with cirrhosis developed hepatic decompensation
- 3 (~1%) died despite retreatment

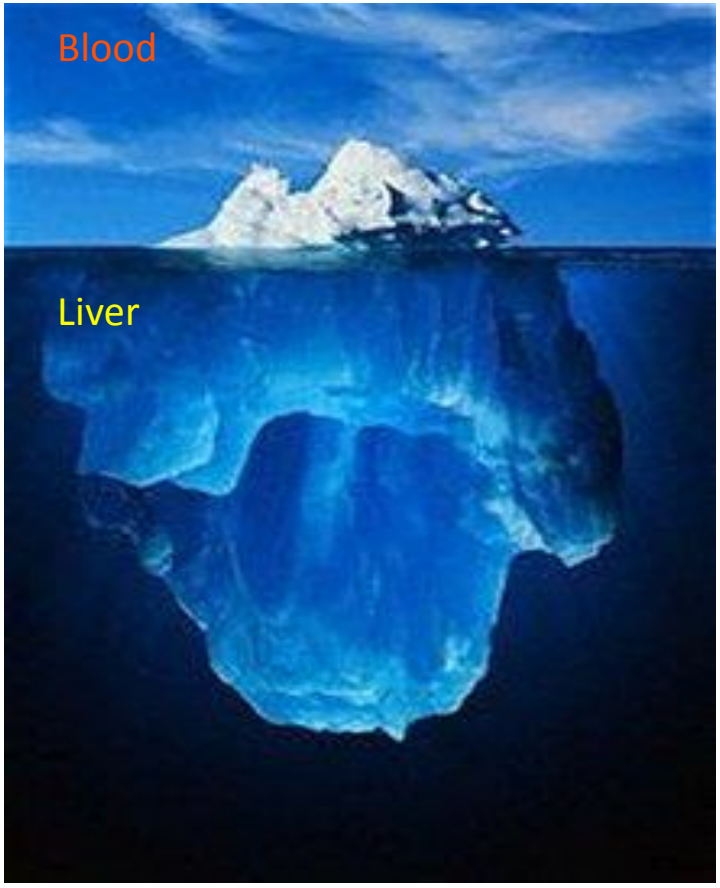
Jeng WJ et al, Hepatology 2018

HBeAg (-) Chronic Hepatitis B

- Only very selective patients should be considered for discontinuing therapy, ideally in clinical trial setting
- At least monthly monitoring is critically important off therapy
- Patients with advanced stage 3-4 hepatic fibrosis should NOT discontinue antiviral therapy.

HBeAg (-) Chronic Hepatitis B

Many unanswered questions

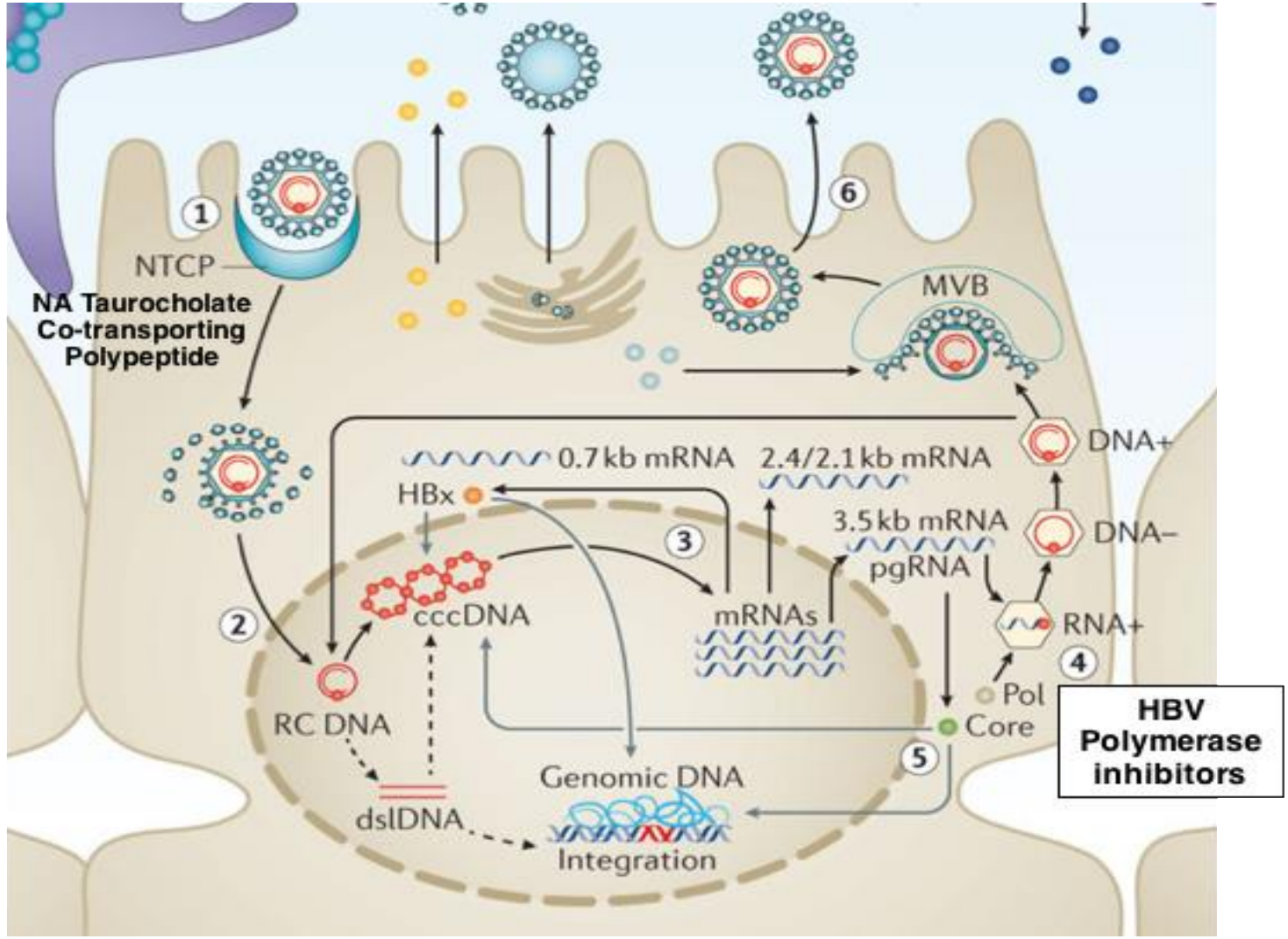


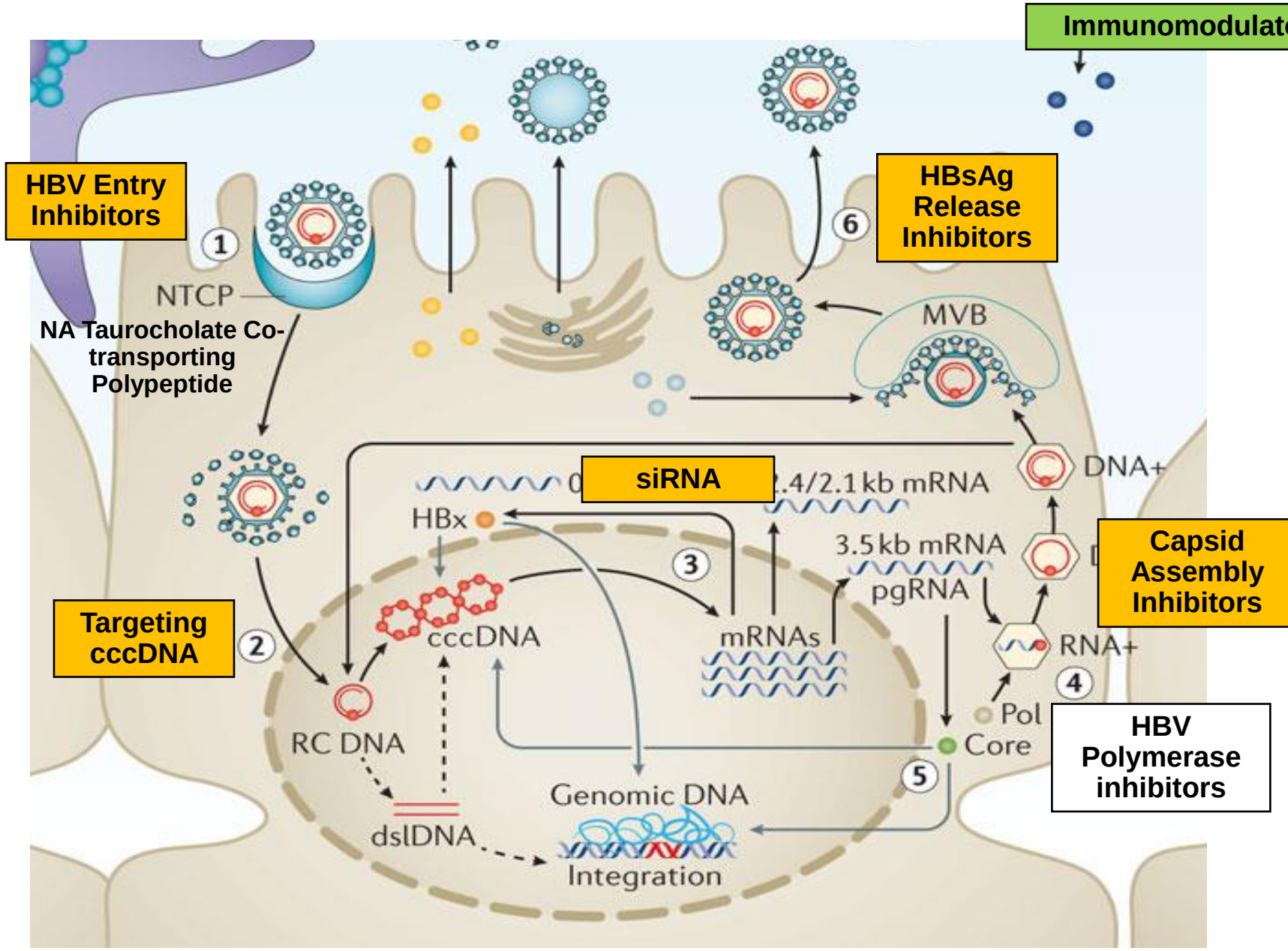
Predictors of HBsAg loss need to be confirmed

When to restart therapy during relapse

low level HBV DNA replication:
? HCC risk
? Increase cccDNA
? DNA integration

Novel HBV Therapy




Immunomodulators
HBV Entry Inhibitors
HBsAg Release Inhibitors
NTCP
NA Taurocholate Co-transporting Polypeptide
MVB
siRNA
HBx
3.5 kb mRNA
pgRNA
DNA+
RNA+
Capsid Assembly Inhibitors
Targeting cccDNA
cccDNA
mRNAs
RC DNA
Pol
Core
HBV Polymerase inhibitors
Genomic DNA
dslDNA
Integration
1
2
3
4
5
6

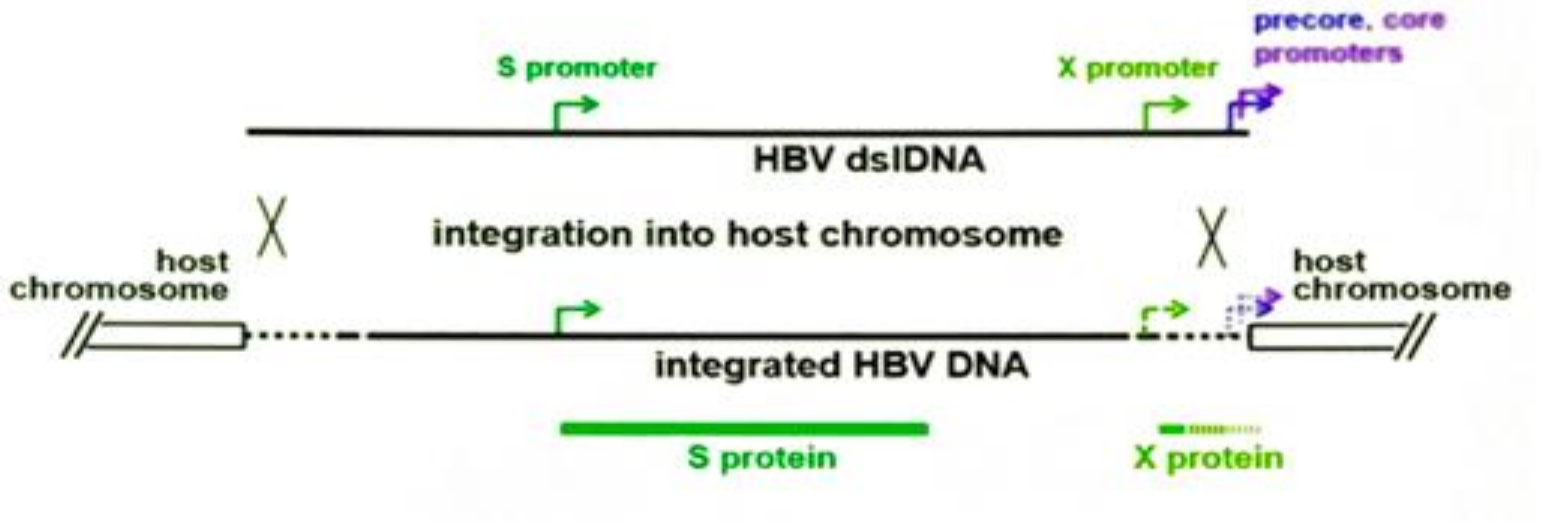
HBsAg Quantitative Assays

HBsAg levels depend on:

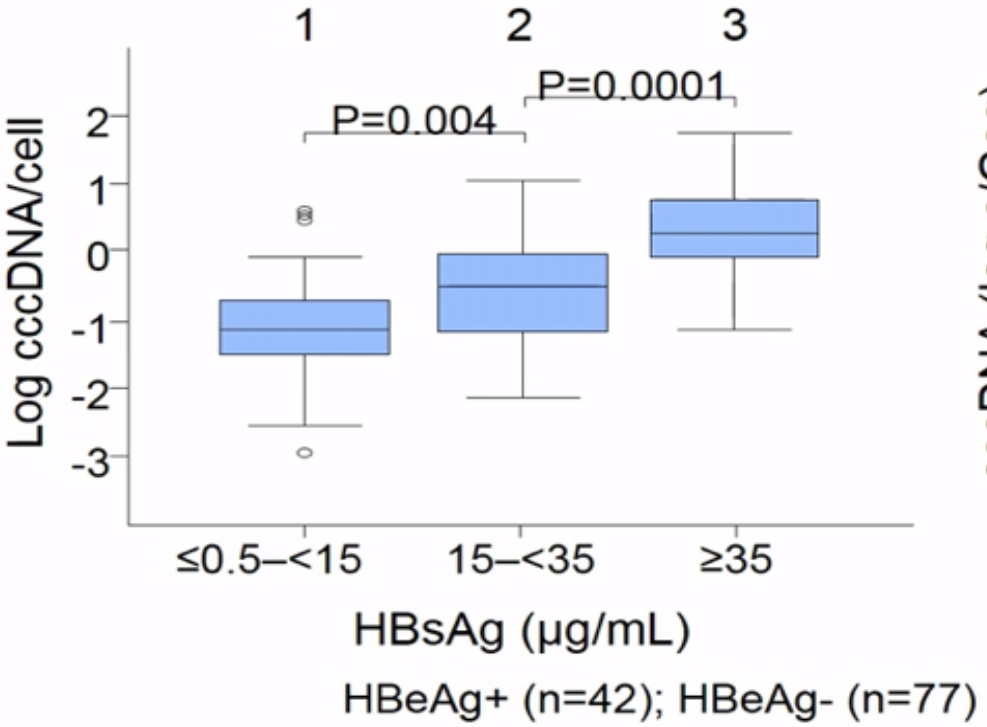
- ✓ Number of infected hepatocytes
- ✓ Amount of transcriptionally active cccDNA

Major challenge:

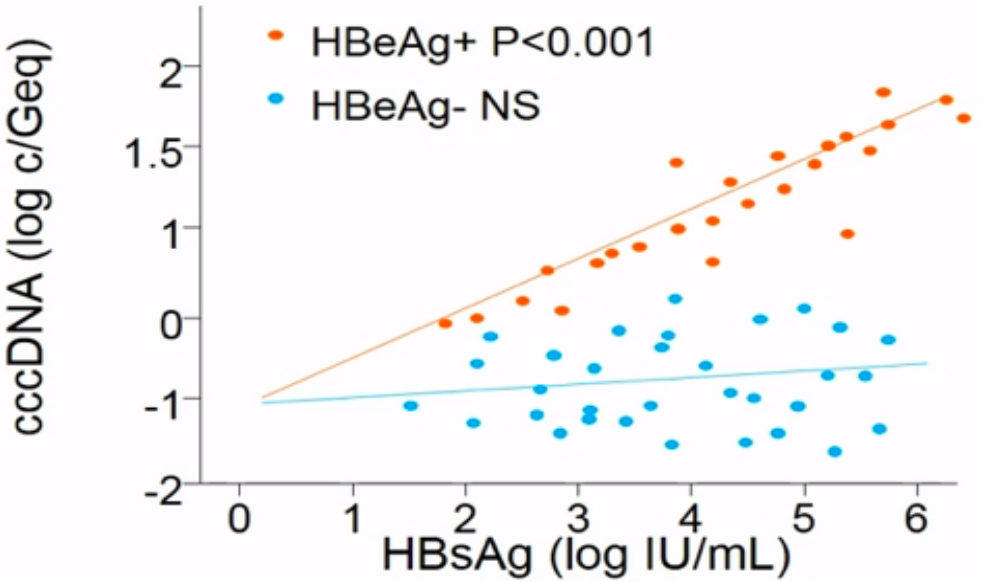
- ✓ Cannot distinguish transcriptionally active viral integrated sequences



qHBsAg : Correlation with cccDNA



HBeAg+ (n=42); HBeAg- (n=77)



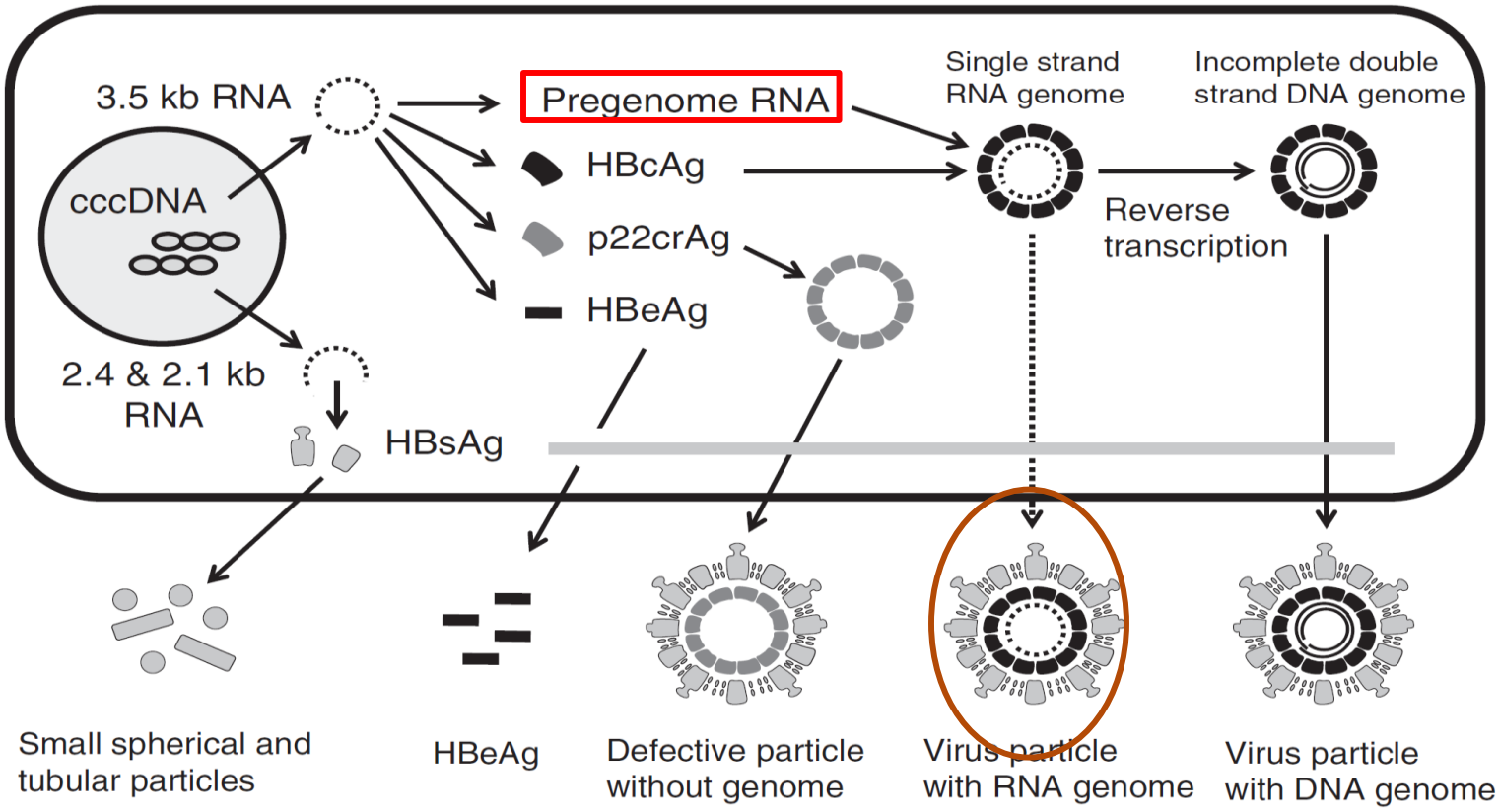
HBeAg+ (n=71); HBeAg- (n=78)

Volz T, et al. Gastroenterology 2007;133:843–52;
Adapted from Thompson AJ, et al. Hepatology 2010;51:1933–44.

c/Geq: copies per genome equivalent;
HBeAg: hepatitis B e antigen; NS: not significant

HBV RNA: Secreted HBV Antigens

Released in serum as enveloped 3.5 kb pregenomic RNA containing virions

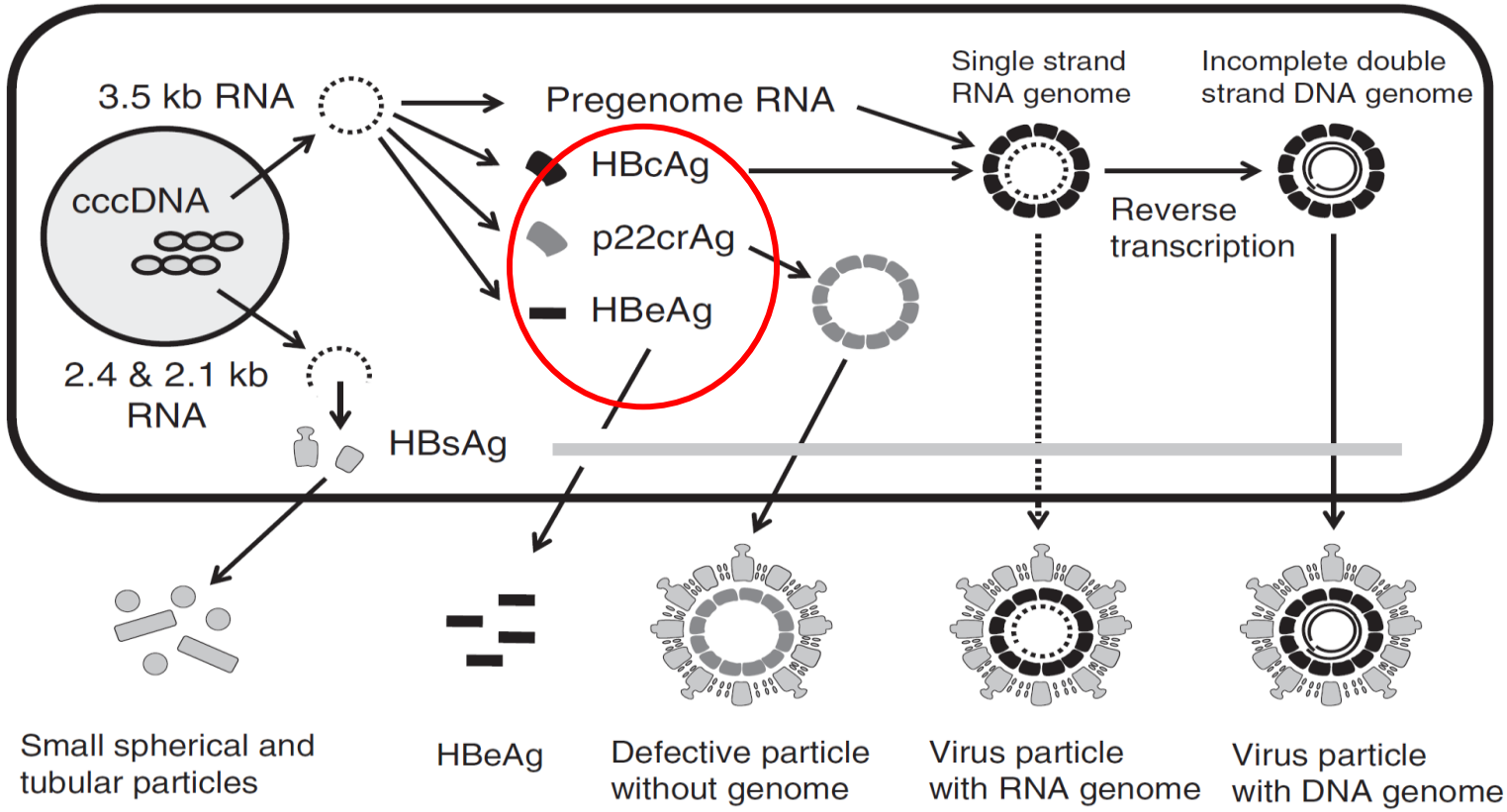


Wang et al. J Hepatol 2016

HBcrAg: Secreted HBV Antigens

Electrochemilumisesecent assay: Lumipulse G (Fujirebio)

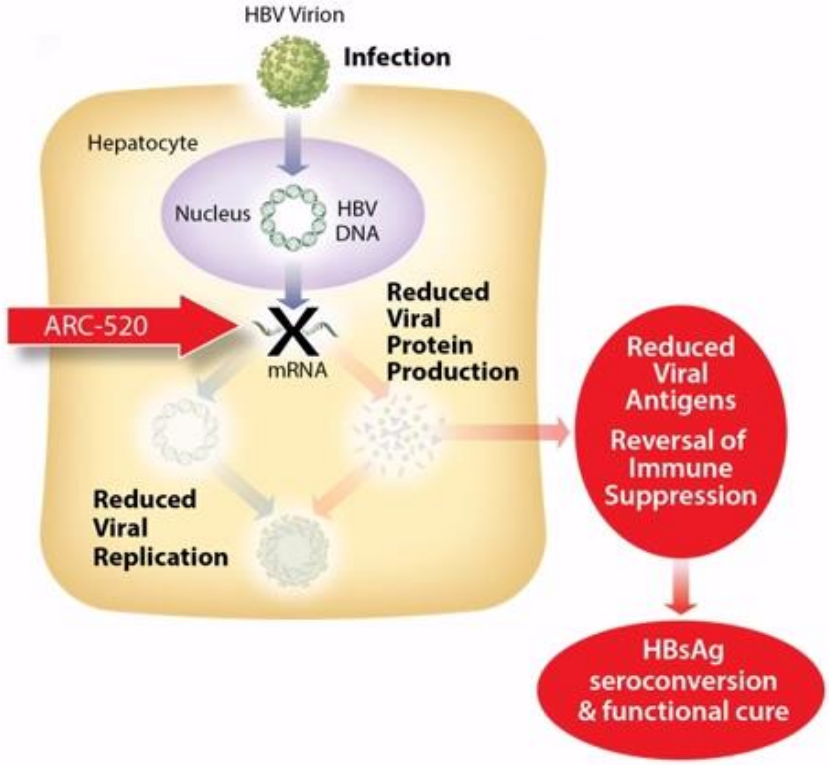
Simultenous determination of denatured HBeAg, HBcAg, p22crAg (same 149 amino acids)



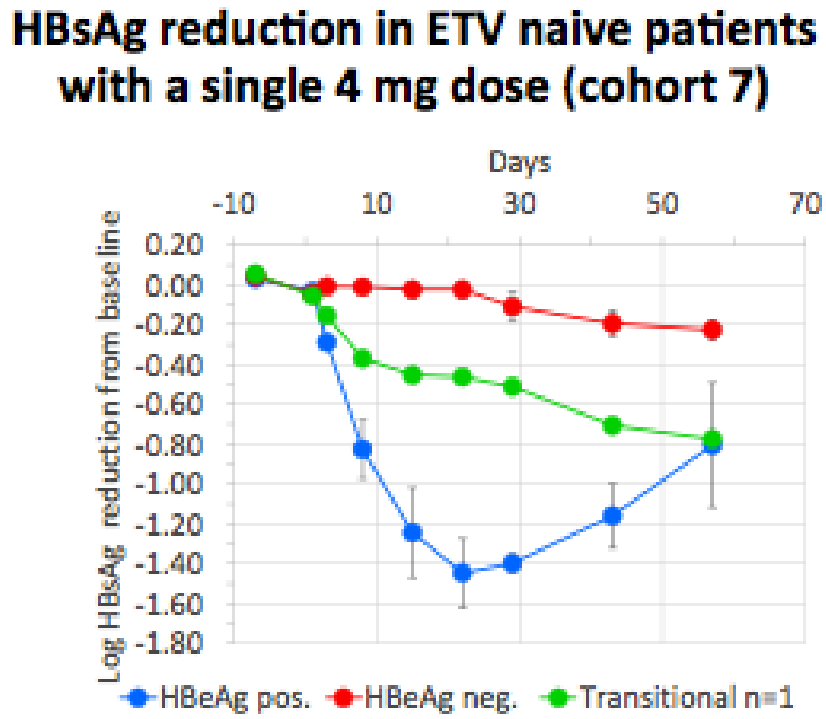
Luckenbaugh L et al. J Viral Hepat 2015; 22: 561

Interfering RNA

Theory Behind

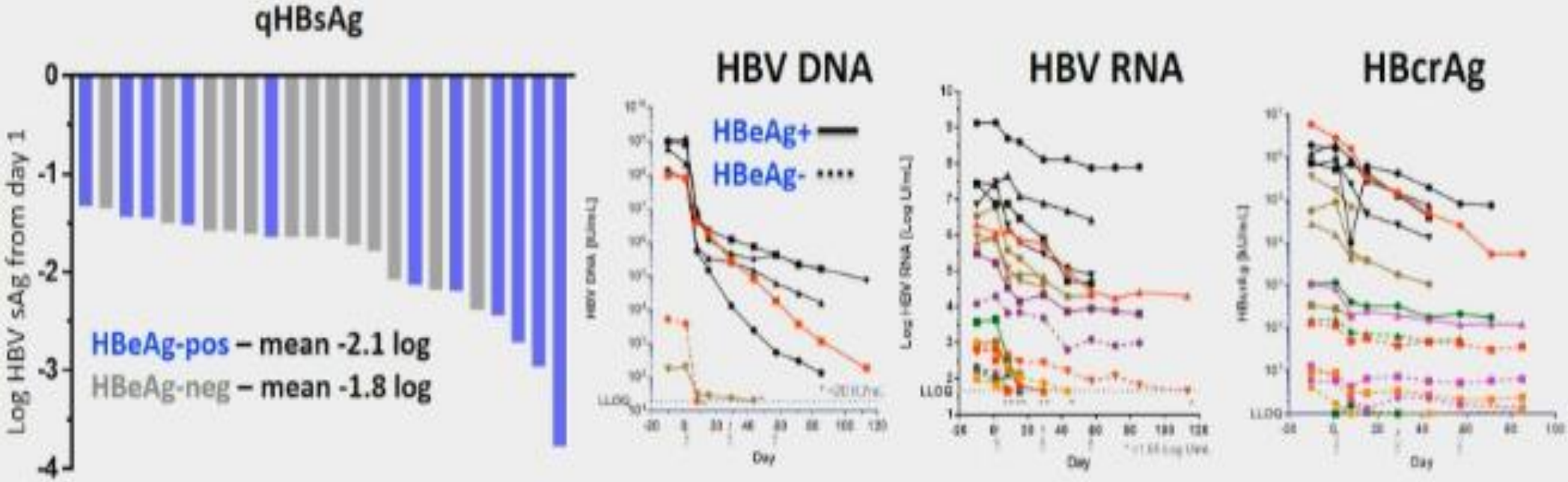


ARC-520



Improved RNAi – ARO-HBV

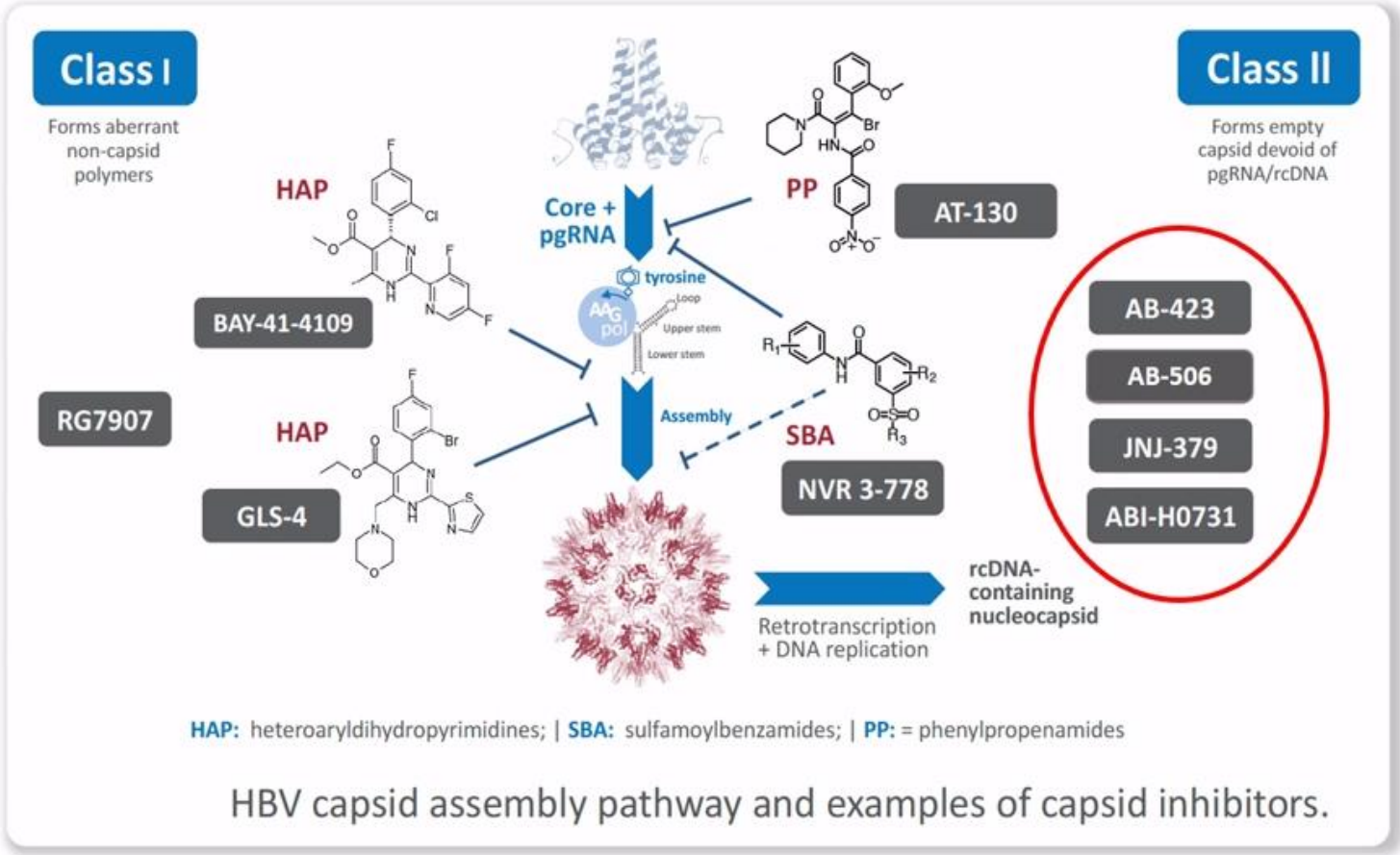
CHB mix of HBeAg-pos (n=11) and HBeAg-neg (n=13) **monthly ARO-ABV RNAi SC x 3 doses**



- Similar effect in HBeAg-pos and HBeAg-neg without a clear dose-response → ***suggests targets both cccDNA & integrated HBV DNA***
- Mild injection site reactions but otherwise well tolerated with no safety signals

Gane et al, AASLD 2018

Capsid protein allosteric modulator (CpAM)



HBV capsid assembly pathway and examples of capsid inhibitors.

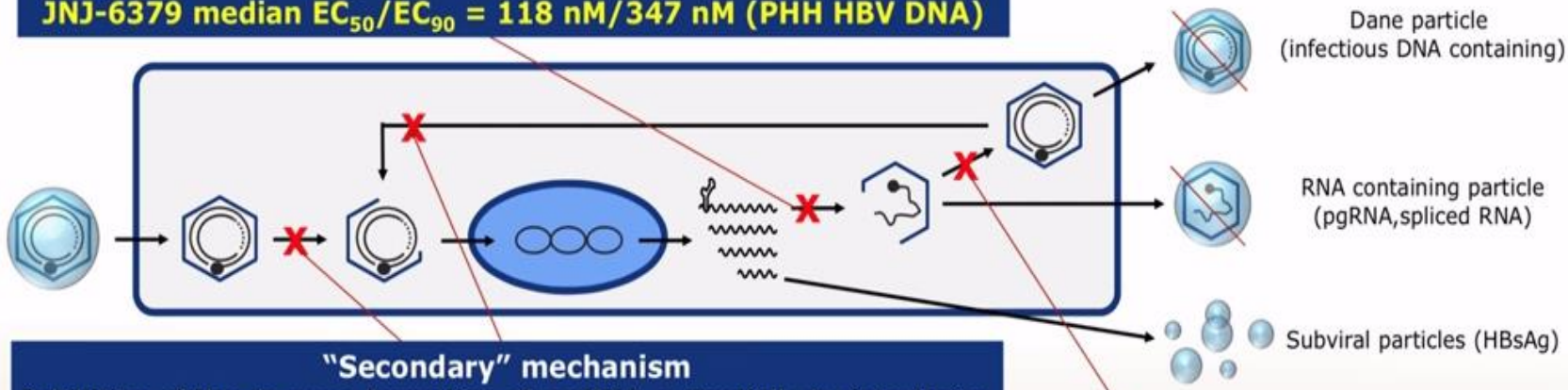
Mani M et al., AASLD 2017 abstract 953

CpAM: JNJ-6379

JNJ-56136379 (JNJ-6379) has a dual mechanism of action

JNJ-6379 is a Capsid Assembly Modulator (CAM) that binds to HBV core protein and disrupts early and late-stage processes in the HBV life cycle.

"Primary" mechanism
Interference with capsid assembly kinetics, preventing encapsidation of (pg)RNA and blocking HBV replication (late step in viral life cycle)
JNJ-6379 median EC_{50}/EC_{90} = 118 nM/347 nM (PHH HBV DNA)



"Secondary" mechanism
Inhibition of the de-novo formation of cccDNA, potentially by interfering with the capsid disassembly process (early step in viral life cycle)
JNJ-6379 median EC_{50}/EC_{90} = 604 nM/2698 nM (PHH HBV RNA)

Nucleos(t)ides analogs do not inhibit the production of RNA-containing particles

PHH Primary Human Hepatocytes

Berke JM et al., AASLD 2016 Abstract 234

CpAM: JNJ -56136379

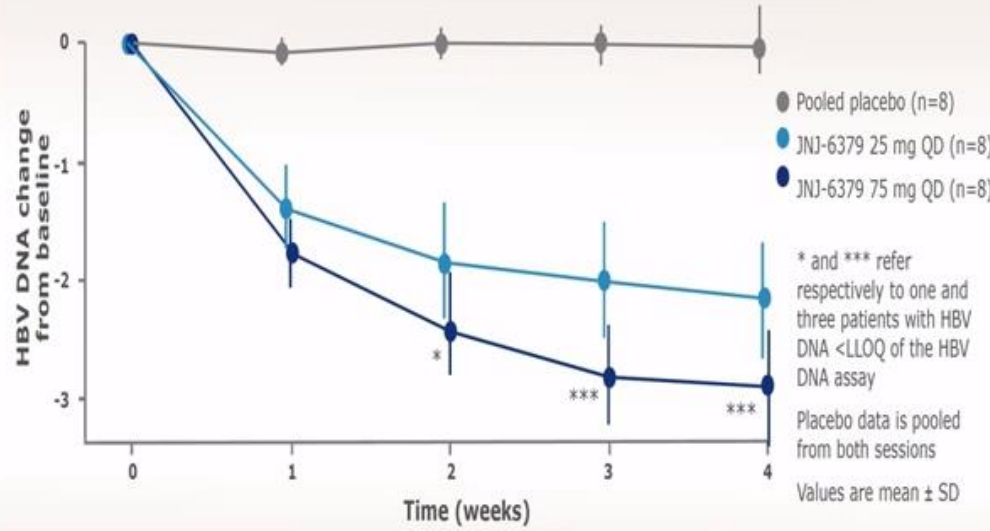
HPB1001 First-In-Human Study of JNJ-6379
Part 2 study design and objectives

The objective of **Part 2** is to evaluate safety, PK and antiviral activity for 28-day oral treatment of JNJ-6379 in treatment-naïve, chronic hepatitis B patients meeting the following criteria:

- Aged 18 to 65 years
- HBeAg-positive or -negative
- Plasma HBV DNA >2,000 IU/mL
- No signs of advanced liver disease (e.g. Metavir stage <F3)

Here we present the results from completed Dosing Sessions 8 and 9

HBV DNA change from baseline

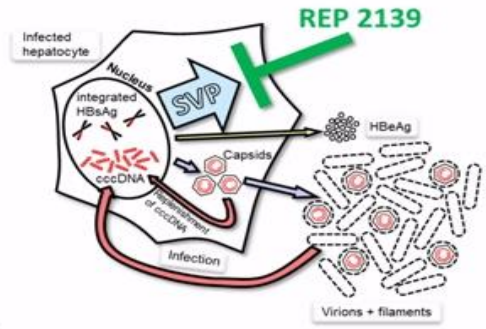


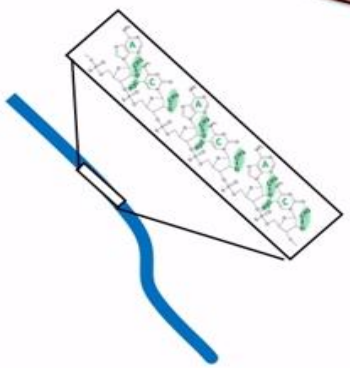
No notable changes in HBsAg or HBeAg

Buti M et al., APASL 2018 abstract HBV-01

HBsAg release inhibitor
Nucleic Acid Polymer (NAP) : REP 2139/2165

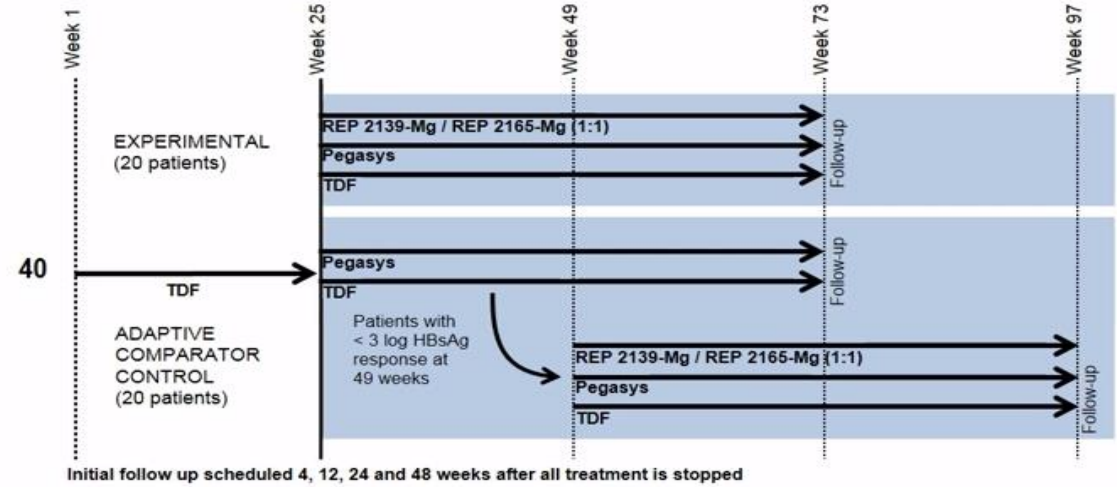
NAPs block subviral particle release (cccDNA and integration derived) → **Efficient HBsAg clearance from blood**





- 40 nucleotide phosphorothioate oligoribonucleotide (RNA)
- Hydrophobic interactions drive delivery to the liver and provide pharmacologic effect

REP 2139/2165 + Tenofovir + Peg-IFN

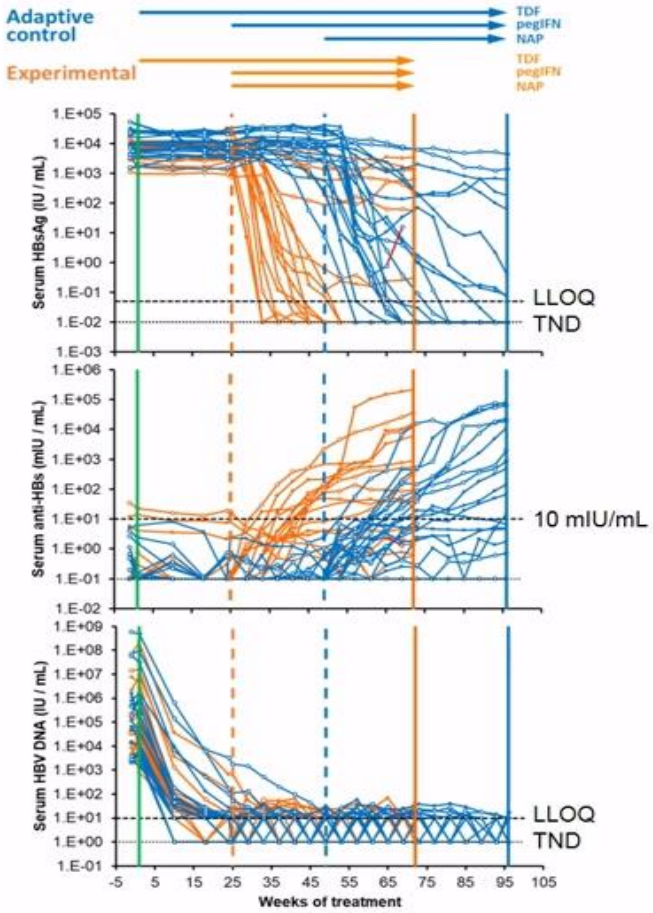


Initial follow up scheduled 4, 12, 24 and 48 weeks after all treatment is stopped

Dosing:
- TDF 300mg PO qD
- Pegasys 180ug SC qW
- NAPs: REP 2139-Mg or REP 2165-Mg 250mg IV qW
- REP 2165 = REP 2139 variant with improved tissue clearance

Valliant A et al., EASL 2018 abstract 343

REP 2139/2165 + Tenofovir + Peg-IFN



REP 401

REP 2139-Mg/REP 2165-Mg + TDF + pegIFN
(48 weeks combination)
HBeAg negative treatment naïve
chronic HBV infection

Patients entered into trial		**40** (20 with NAPs following 24 weeks of pegIFN)
End of treatment HBsAg response	> 1 log from baseline	36
	< 1 IU/mL	27
	< 0.05 IU/mL	23
Patients currently completed treatment and ≥ 12 weeks of follow-up		**33**
HBV DNA < 1000 IU/mL (repression)		25 (75%) (6 @ FW48)
HBV DNA < LLOQ (remission)		22 (65%) (5 @ FW48)
HBsAg < LLOQ		16 (2 @ FW48)

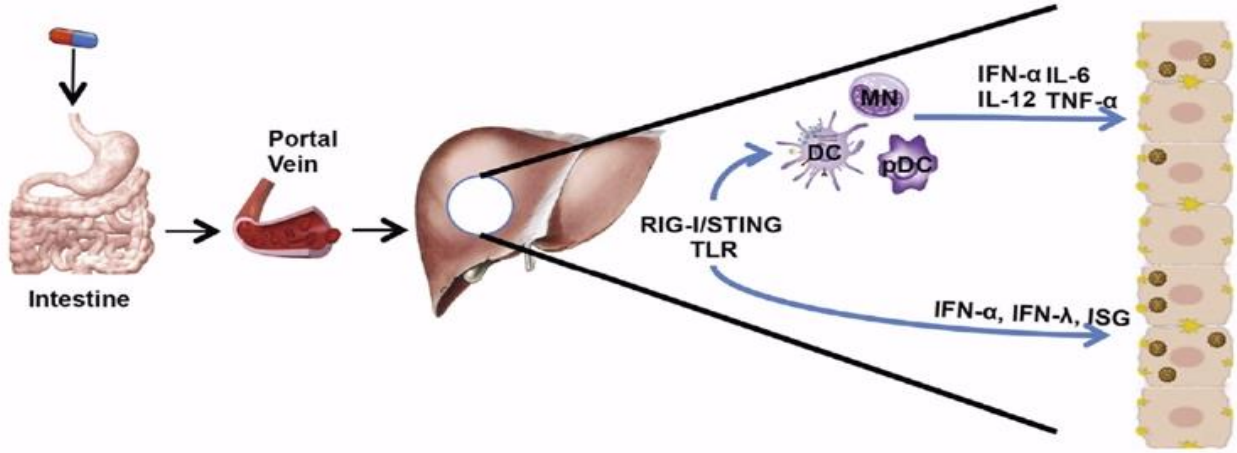
Valliant A et al., EASL 2018 abstract 343

Current Targets for Immunomodulatory Drug Development

Pattern Recognition receptors

Phase I/II Clinical Trials

- TLR-7
- TLR-8
- Rig-I



Indiscriminate

Induce innate/antiviral cytokine production

- Cytokines: IL-1α, IL-1β, IL-10, IL-6, IL-12, IL-18, TNF-α, IFN-α, IFN-λ — Antiviral
- Chemokines: CXCL-8, -9, -10, Mip1a, Mip1B, MCP-1 — Flares/Inflammation

Gehring, Best Pract Res Clin Gastroenterol. 2017 Jun;31(3):337-345

Is a Functional Cure Close?

- The future looks bright but with many new challenges
- The current nucleos(t)ide analogue therapy is safe and effective but low rate of functional cure
- The novel therapy likely need to be used in combination. Their efficacy and safety yet to be determined
- New treatment endpoints and biomarkers need to be evaluated
- Therapeutic options for different HBV populations need to be determined and standardized

Question?