Is Hepatitis B Curable?

Marion G. Peters, MD
Professor of Medicine
Chief of Hepatology Research
University of California San Francisco
San Francisco, California

IAS–USA

Learning Objectives

After attending this presentation, learners will be able to:

- List the limitations of current therapies for HBV
- Describe types of HBV cure
- Describe HBV latency
- List mechanisms of action of putative new therapies for HBV

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ARS 1: HBV status in 2019: which is true?

1. Acute HBV in adults leads to loss of HBsAg usually
2. HBV infection can be cured
3. Currently available drugs lead to loss of HBsAg usually
4. HBV is not a latent virus

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ARS 2: New drugs in Phase I/II: which is false?

1. Target Hepatitis B core protein
2. Target HBV entry into hepatocyte
3. Target cccDNA in nucleus
4. Target HBV mRNA
5. Target HBV secretion

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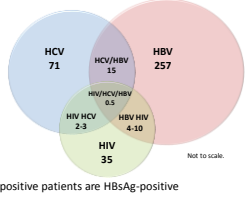
Prevalence of HBV/HCV Coinfection in People with HIV

Estimated Number of Persons Infected Worldwide, in Millions



Not to scale.

- About 5% to 10% of anti-HCV-antibody–positive patients are HBsAg-positive
- Hepatitis C superinfection of chronic HBsAg carriers is common in HBV endemic regions, such as Southeast Asia

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Fernandez-Montero JV, Soriano V. *Best Pract Res Clin Gastroenterol*. 2012;26:517-530; WHO 2019

HBV is a life long, dynamic disease

- Changes over time
- Risk of end stage liver disease and cancer increases with ongoing inflammation and viremia in adults
- Fibrosis can be reversible
- Drugs can decrease fibrosis progression
- HBV can be controlled but not cured
- Reactivation can occur even in those who have lost HBsAg
- HBV infection in neonates and young children leads to chronicity >90-95%
- HBV infection in adults (HIV) leads to chronicity <5% (~20%)

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HBV Control

- Inflammatory: normalize serum ALT, biopsy
- Virologic: decrease HBV DNA
- Immune: seroconversion
  - HBeAg to anti-HBe
  - HBsAg to anti-HBs
- HBV as of 2019 not "cured" but controlled

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Approved HBV treatments 2019

- Interferon alfa-2b – 1991
- Lamivudine – 1998
- Adefovir – 2002
- Entecavir – 2005
- Peginterferon alfa-2a – 2005
- Telbivudine – 2006
- Tenofovir Disoproxil– 2008
- Tenofovir alafenamide- 2017

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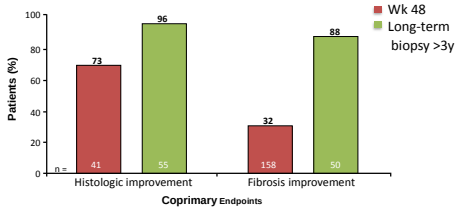
Long-term Entecavir Treatment Improves Liver Histology and Fibrosis



Chang TT, et al. Hepatology. 2010;52:886-893 CCO Hepatitis.

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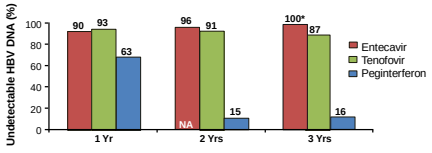
Undetectable HBV DNA Over Time in HBeAg Negative Patients

Not head-to-head trials; different patient populations and trial designs

Extended Treatment With Nucleos(t)ide Analogues vs 1 Yr Peginterferon Treatment



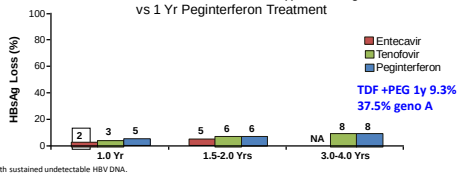
*Single center study.

Lok AS, et al. Hepatology. 2009;50:661-662. Marcellin P, et al. AASLD 2008. Abstract 146. Marcellin P, et al. AASLD 2009. Abstract 481. Marcellin P, et al. Gastroenterology. 2009;136:2169-2179. BaqaiS, et al. AASLD 2009. Abstract 476. Lai CL, et al. Hong Kong International Liver Congress 2006.

HBsAg Loss Over Time in *HBeAg Positive* Patients

Not head-to-head trials; different patient populations and trial designs

Extended Treatment With Nucleos(t)ide Analogues*
vs 1 Yr Peginterferon Treatment



*With sustained undetectable HBV DNA.

Chang TT, et al. N Engl J Med. 2006;354:1001-1010. Marcellin P, et al. N Engl J Med. 2008;359:2442-2455. Buster EH, et al. Gastroenterology 2008;135;459-467. Gish R, et al. Gastroenterology. 2007;133:1437-1444. Heathcote J. AASLD 2008. Abstract 158. Heathcote J, et al. AASLD 2009. Abstract 483. Janssen HL, et al. Lancet. 2005;365:123-129; Marcellin Gastro 2016

HBsAg Loss Over Time in *HBeAg Negative* Patients

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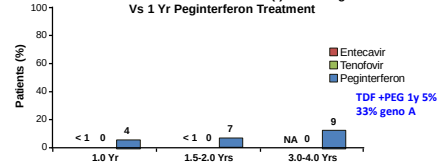

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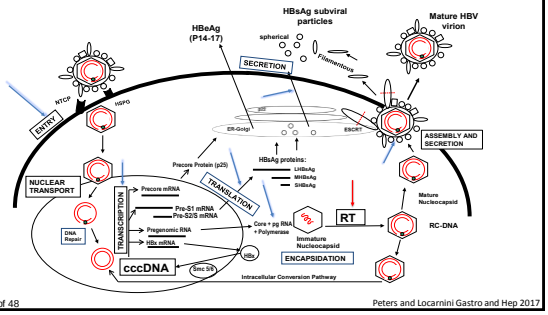

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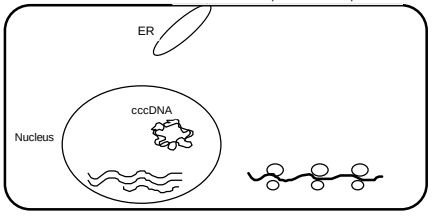
Viral Life Cycle- latent or "recovered" HBV

Immune system considers this "recovered"
BUT cccDNA is template for viral replication



HBsAg neg
Anti-HBs
Anti-HBc

Types of HBV cure

Functional Cure- clinical resolution
Sustained, off drug:

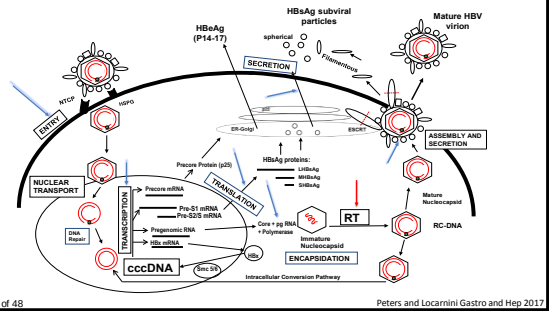
- No inflammation: ALT and liver biopsy
- HBsAg loss
- +/- anti-HBs gain

Complete cure- virological cure

- All of above plus
- Loss of cccDNA in liver

Inactive state -an interim goal

- No inflammation: ALT and liver biopsy
- HBV DNA low or u/d
- HBsAg positive



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Strategies to Eradicate HBV

Virologic approaches

- Entry inhibitors
- Block cccDNA
- Transcription inhibitors
- RNA interference
- HBV capsid inhibitor
- Polymerase inhibitors
- Secretion inhibitors

Host immune approaches

- Interferons
- RIG-I agonists
- TLR-7
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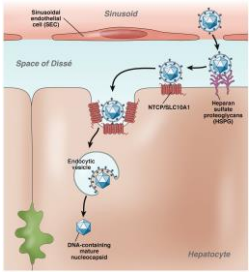
HBV entry through NTCP receptor



HBV Targeting cell entry

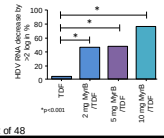
Small molecule compounds binding to Sodium taurocholate cotransporting polypeptide (NTCP)

- HBV pre-S1-derived lipopeptide Myrcludex-B competes with HBV/HDV for binding to NTCP
  - Prevents HBV/HDV entry
  - Blocks entry at pM concentrations increased serum bile acids
  - Stops new infection of hepatocytes

Multicentre, open-label Phase 2b clinical trial to assess safety and efficacy of Myrcludex B + TDF in chronic HBV/HDV coinfection

- 120 HBeAg negative HDV patients in 4 arms were treated in the MYR 202 study for 24 weeks
- Excellent safety in 239 subjects dosed so far (2, 5, 10 mg sq +TDF 24 w)
- No persistent, drug-related AEs/SAEs
- **Primary endpoint was met**: HDV RNA >2 log decline or undetectable
- Strong on-treatment decrease in ALT, liver stiffness, intrahepatic HDV RNA
- Relapse in most patients in the follow-up: ?? longer treatment needed

Primary endpoint: <2 log HDV RNA decline or undetectable Week 24

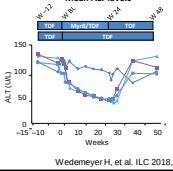


Median RNA log_{10} change to BL		
	Week 24	Week 48
2 mg MyrB/TDF	–1.75	–0.35
5 mg MyrB/TDF	–1.60	–0.12
10 mg MyrB/TDF	–2.70	–0.39
TDF	–0.18	+0.07

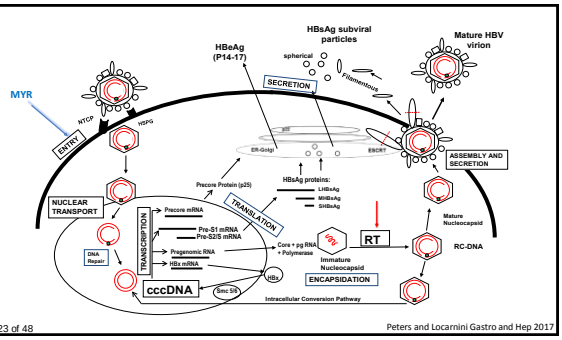
TDF
2 mg MyrB /TDF
5 mg MyrB /TDF
10 mg MyrB /TDF

Negligible effects on qHBsAg

Mean ALT levels



Wedemeyer H, et al. ILC 2018, #GS-005



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cccDNA inhibitors

Drug Class	Antiviral agent	Trials	Manufacturer
cccDNA Blocking	Disubstituted sulphonamides	Preclinical	
cccDNA Degradation	RNA guided nucleases CRISPR/CAS9) EBT106 Anti-HBV sgRNA	Preclinical	Excision Biotherapeutics
Silencing	histone acetyltransferase (HAT) inhibitors HBx targeting drugs		

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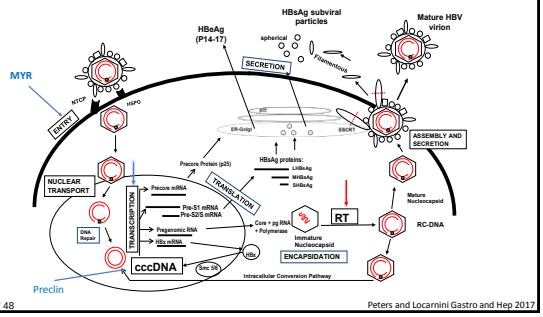

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RNA interference

Antiviral agent	Trials	Manufacturer
ALN-HBV (siRNA)	Phase I-II	Alnylam
ARC-520 (siRNA)	Terminated	Arrowhead pharmaceuticals
ARB-1467 (siRNA)	Phase II	Arbutus Biopharma
ARB-1740 (siRNA)	Preclinial	Arbutus Biopharma
RO7020322 (RG7834) (small molecule mRNA inhibitors)	Phase I	Roche
IONIS-HBVRx (GSK3228836) (antisense molecule)	Phase I	Ionis Pharma/GSK
IONIS-HBVLRx (GSK33389404) (antisense molecule)	Phase I	Ionis Pharma/GSK
AB-452 (RNA destabilizer)	Preclinical	Arbutus Biopharma

Silencing HBV gene expression using RNAi-based therapy

- ARC-520 is a combination of siRNAs directed against conserved HBV RNA sequences and efficiently knocks down HBV RNA, proteins and DNA levels.
- 2 siRNAs (cover 99.6% of known HBV sequences) conjugated to cholesterol and hepatocyte-targeted ligands
- Taken up by endosomes in hepatocyte then released into cytoplasm after lysis of endosomal membrane
  - Given (Arrowhead Hepdart 2015)
  - Arbutus ARB-1740 decreases HBsAg, HBeAg, HDV RNA (AASLD 2016)
  - ARO-HBV EASL 2018
  - *1 month human data*

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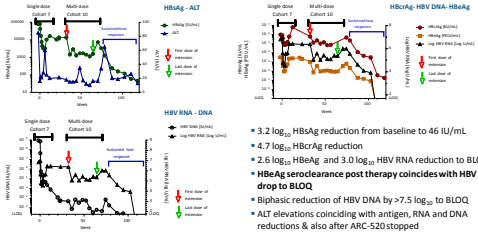
RNA interference therapy with ARC-520 injection – Case 1: HBeAg positive patient flared when ARC-520 stopped



- 3.2 log_{10} HBsAg reduction from baseline to 46 IU/mL
- 4.7 log_{10} HBcrAg reduction
- 2.6 log_{10} HBeAg and 3.0 log_{10} HBV RNA reduction to BLOQ
- **HBeAg seroclearance post therapy coincides with HBV RNA drop to BLOQ**
- Biphasic reduction of HBV DNA by >7.5 log_{10} to BLOQ
- ALT elevations coinciding with antigen, RNA and DNA reductions & also after ARC-520 stopped

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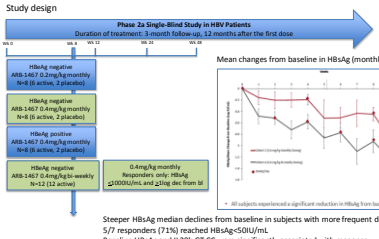
Yuen M-F, et al. EASL 2018, Paris. #FRI-362

Bi-weekly Dosing of ARB-1467 LNP siRNA in HBeAg Negative, Virally Suppressed Patients with Chronic HBV Infection Leads to Deeper Declines in HBsAg and Potential Association with IL28b

Study design



Mean changes from baseline in HBsAg (monthly vs. biweekly)

- All subjects experienced a significant reduction in HBsAg from baseline

Steeper HBsAg median declines from baseline in subjects with more frequent dosing (biweekly vs. monthly)
5/7 responders (71%) reached HBsAg<50IU/mL
Baseline HBsAg and IL28b GT CC were significantly associated with response
Most AEs mild and transient

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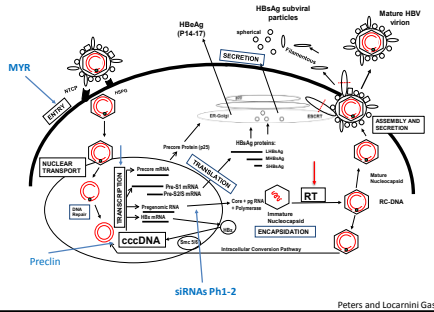
KoshAgarwal et al. AASLD 2017



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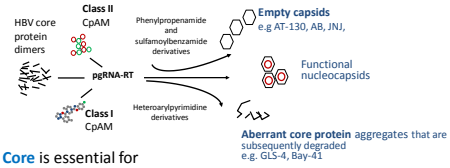
CpAM: core protein allosteric modulator- Roche, ABI
CAM: capsid assembly modulator - J&J, Roche



Core is essential for

- HBV genome packaging
- Reverse transcription
- Intracellular trafficking
- Maintenance of chronic infection as encapsidated HBV genomes are imported into the nucleus.

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Nucleocapsid assembly inhibitors/ modulators

Antiviral agent	Trials	Manufacturer
GLS-4	Phase II	HEC Pharm, Sunshine
NVR 3-778	Phase Ia	Novira Pharmaceuticals/Janssen
BAY41-4109	Phase I	
JNJ56136379	Phase II	JnJ Janssen
Core protein allosteric modulators (CpAMs)	Phase I (ABI-H0731) IND enabling (ABI-H2158) Clinical candidate (ABI-Nx)	Assembly Biosciences
AB-423	Phase I	Arbutus Biopharma
AB-506	IND enabling	Arbutus Biopharma

Antiviral Activity of JNJ-56136379, a novel HBV Nucleocapsid Inhibitor

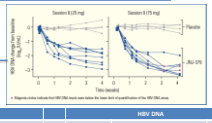
Session 8
JNJ-379 100mg or placebo (Day 1)
25mg (D2-28) or placebo (D2-28), QD

Session 9
JNJ-379 75mg or placebo, QD

Session 10
JNJ-379 150mg or placebo, QD

Session 11
JNJ-379 75mg or placebo

Sessions 8 and 9
n=12 per session
(8 active/4 placebo)
28 days of treatment followed by 8 weeks of follow-up

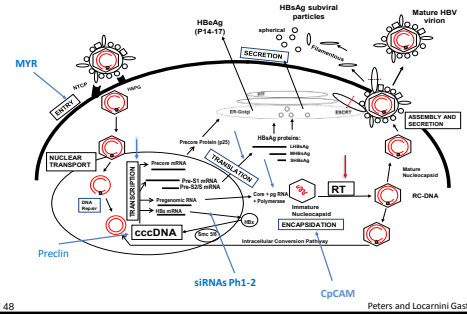


		HBV DNA	
		Baseline	Day 29	
Treatment Arm	N	Mean (SD), log10IU/mL	Mean (SD) change from baseline log10IU/mL	<LLOQ
25mg QD	8	6.90 (1.91)	-2.16 (0.49)	0
75mg QD	8	5.26 (1.50)	-2.89 (0.48)	3
Pooled placebo	8	5.49 (1.77)	-0.01 (0.31)	0

An oral dose regimen of 250 mg daily for 28 days is being evaluated
Phase 2a study is ongoing in treatment-naïve and virologically suppressed CHB patients (NCT03361956)

56% with one AE, no SAEs, treatment d/c or deaths
One patients with Grade III elevations in ALT and AST- TDF started

Zoulim F et al. AASLD #LBO-004, 2017



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HBsAg inhibitors

Antiviral agent	Trials	Manufacturer
REP2139 & REP2165	Phase II	Replicor
BM601 (benzimidazole derivative)	Preclinical	

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REP 2139-Mg and REP 2165-Mg Combination Therapy in CHB (REP 401 - NCT02565719)

Global summary of follow-up responses after removal of all therapy (2018)

Participants entered into trial	N=40 (20 with NAPs following 24 weeks of pegIFN*)
Participants currently completed treatment and ≥ 24 weeks of follow-up	**34**
Functional cure (HBsAg negative, HBV DNA TND)	**14/34** (41%)
Inactive chronic HBV state (HBV DNA < 2000 IU/mL, normal ALT)	**15/34 (44%)**

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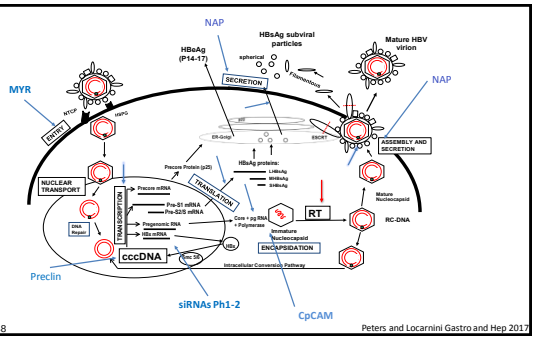
Personal communication, Vaillant A et al. 2018



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- TLR-7- no effect on HBsAg but increased IFN-γ and IL-2
- PD-1/ PDL-1
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- Birinapant selectively induces TNF mediated apoptosis (Pelligrini WEHI)
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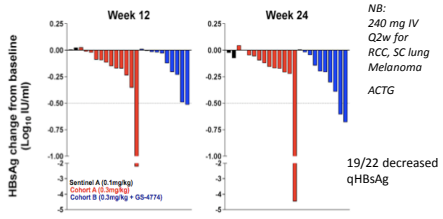
qHBsAg change on anti-PD1 0.3mg/kg (Nivolumab)



NB:
240 mg IV Q2w for RCC, SC lung Melanoma

ACTG

19/22 decreased qHBsAg

PD-1 receptor occupancy up to 84 d post anti PD-1: yeast vaccine
Verdon et al AASLD 2017

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Emerging DAAs against HBV

Many currently in the pipe-line

- Novel polymerase inhibitors
- Capsid inhibitors
- cccDNA inhibition or eradication
- Core protein packaging inhibitors
- Small interfering RNA (siRNA)-based strategies
- Secretion inhibitors
- Immune activators

Combination therapy will likely be required for cure

- Inhibitors of polymerase, entry, core, cccDNA etc
- IFN, immune stimulant, TLR 7
- Checkpoint inhibitors PD-1/L1

BUT

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- cccDNA inhibition or eradication
- Core protein packaging inhibitors
- Small interfering RNA (siRNA)-based strategies
- Immune activators

Combination therapy will likely be required for cure

- Inhibitors of polymerase, entry, core, cccDNA etc
- IFN, immune stimulant, TLR 7
- Checkpoint inhibitors PD-1/L1

BUT Selection of HBV patient will be critical
Optimization of HBV endpoints needed

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ARS 2: HBV status in 2019: which is true?

1. Acute HBV in adults leads to loss of HBsAg usually
2. HBV infection can be cured
3. Currently available drugs lead to loss of HBsAg usually
4. HBV is not a latent virus

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ARS 2: New drugs in Phase I/II: which is false?

1. Target Hepatitis B core protein
2. Target HBV entry into hepatocyte
3. Target cccDNA in nucleus
4. Target HBV mRNA
5. Target HBV secretion

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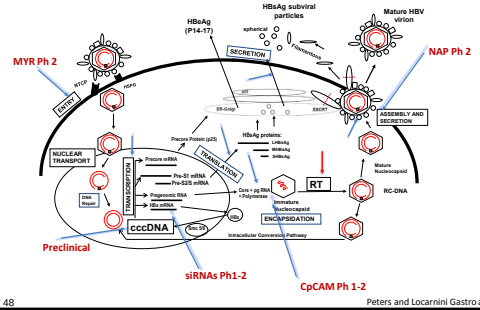

Peters and Locarnini Gastro and Hep 2017

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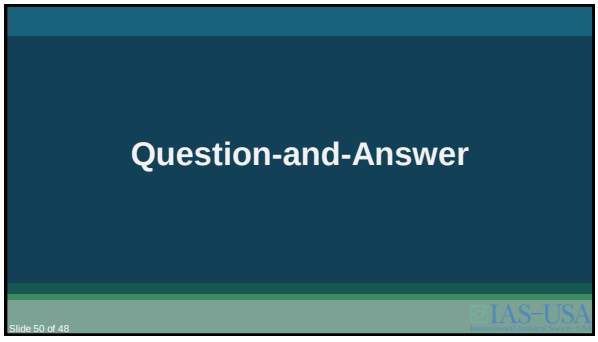
Question-and-Answer
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