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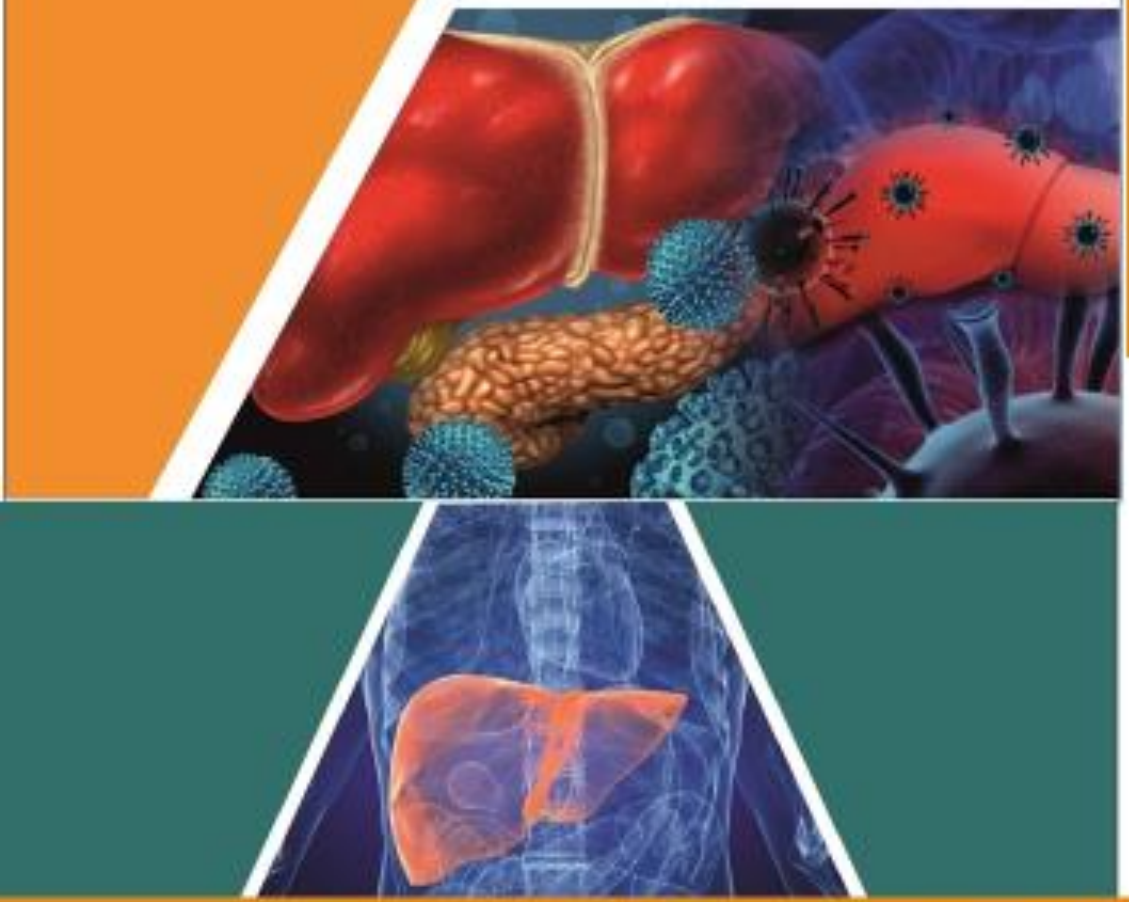
PROJECT PRAKASH

Programmed Approach to Knowledge and Sensitization on Hepatitis

HEPATITIS INDUCTION PROGRAM

FOR DOCTORS



DIAGNOSIS & MANAGEMENT OF VIRAL HEPATITIS B & D

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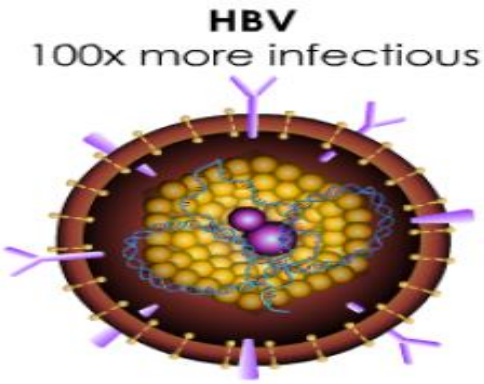
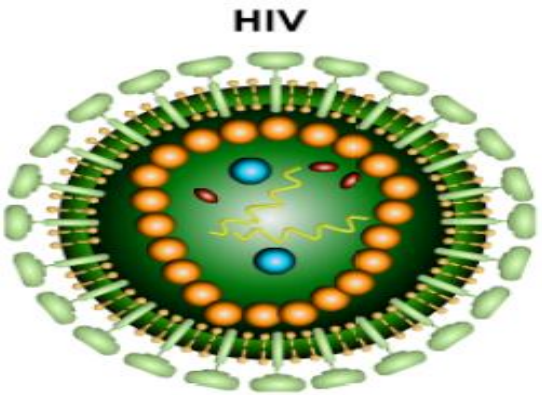
Hepatitis B Virus





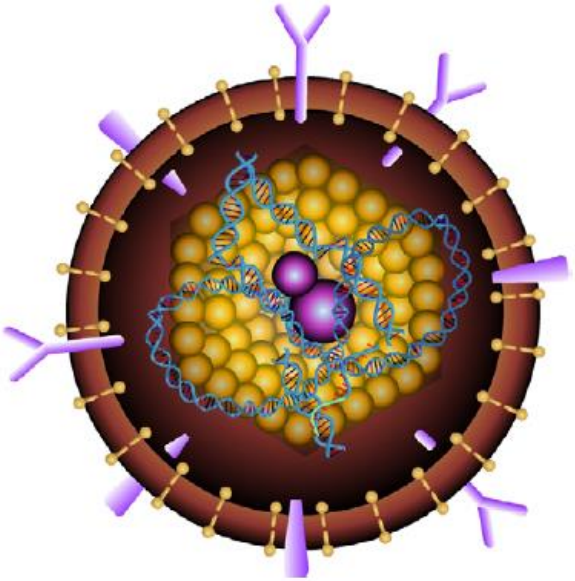
- HBV is 100 times more infectious than HIV.
- HBV can survive outside the body at least seven days at room temperature and still be capable of causing infection.
- Contributors to the infectivity of HBV include the
  - Hardiness of the virus
  - Greater concentration of HBV particles than of HIV particles in the blood of individuals infected with these viruses.

Hepatitis B Virus

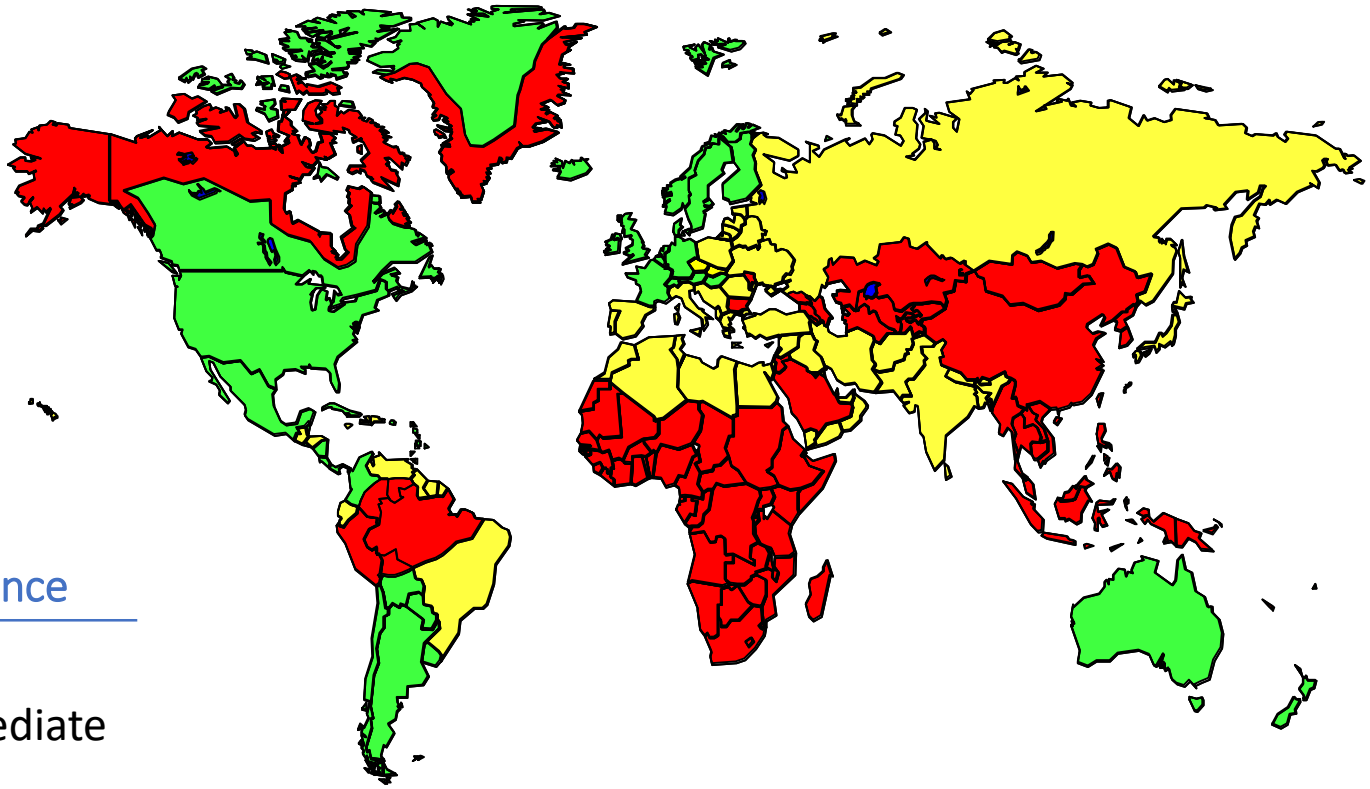
- The hepatitis B virus is a small, double-stranded DNA virus belonging to the Hepadnaviridae family of viruses.

- Hepadnaviridae is a family of hepatotropic DNA viruses, meaning that they have an affinity for hepatocytes.

- They can be found in some birds, small mammals, such as woodchucks and squirrels, as well as primates.



Geographic Distribution of Chronic HBV Infection



HBsAg Prevalence

- ≥8% - High
- 2-7% - Intermediate
- <2% - Low

Centers for Disease Control and Prevention. Viral Hepatitis Slide sets: Hepatitis B 101. http://www.cdc.gov/ncidod/diseases/hepatitis/slideset/hep_b/hep_b.pdf. Accessed November 16, 2007.

Hepatitis – Disease Terminology

Acute hepatitis[1]

Short-term infection with hepatitis B virus which the body's immune system clears within 6 months

Chronic hepatitis[1]

Long-term infection where the body is unable to clear the virus itself. Generally defined as the presence of HBsAg for > 6 months

Severe forms

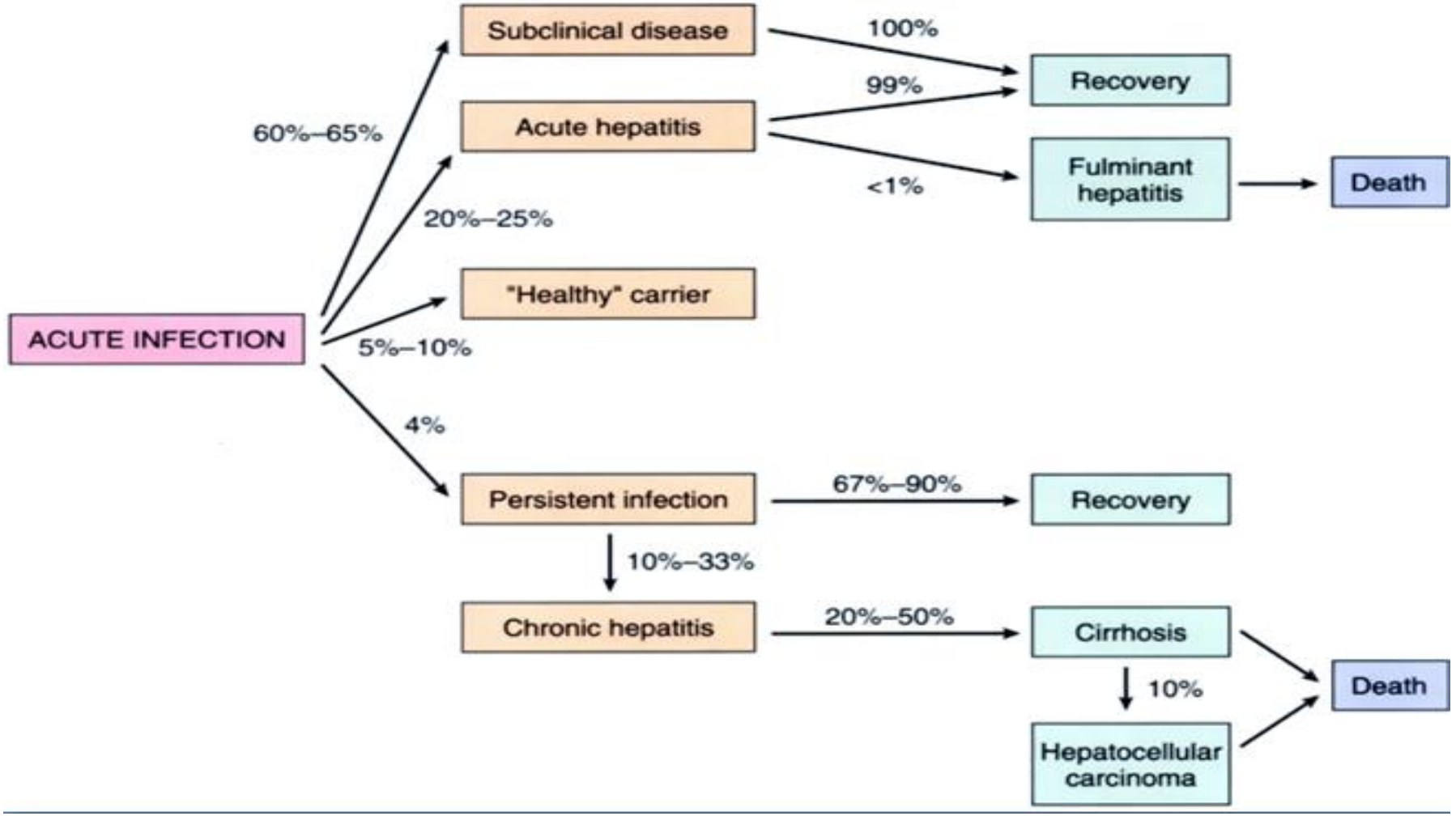
Severe Acute hepatis/ Acute Liver Failure

Acute on Chronic Liver Failure

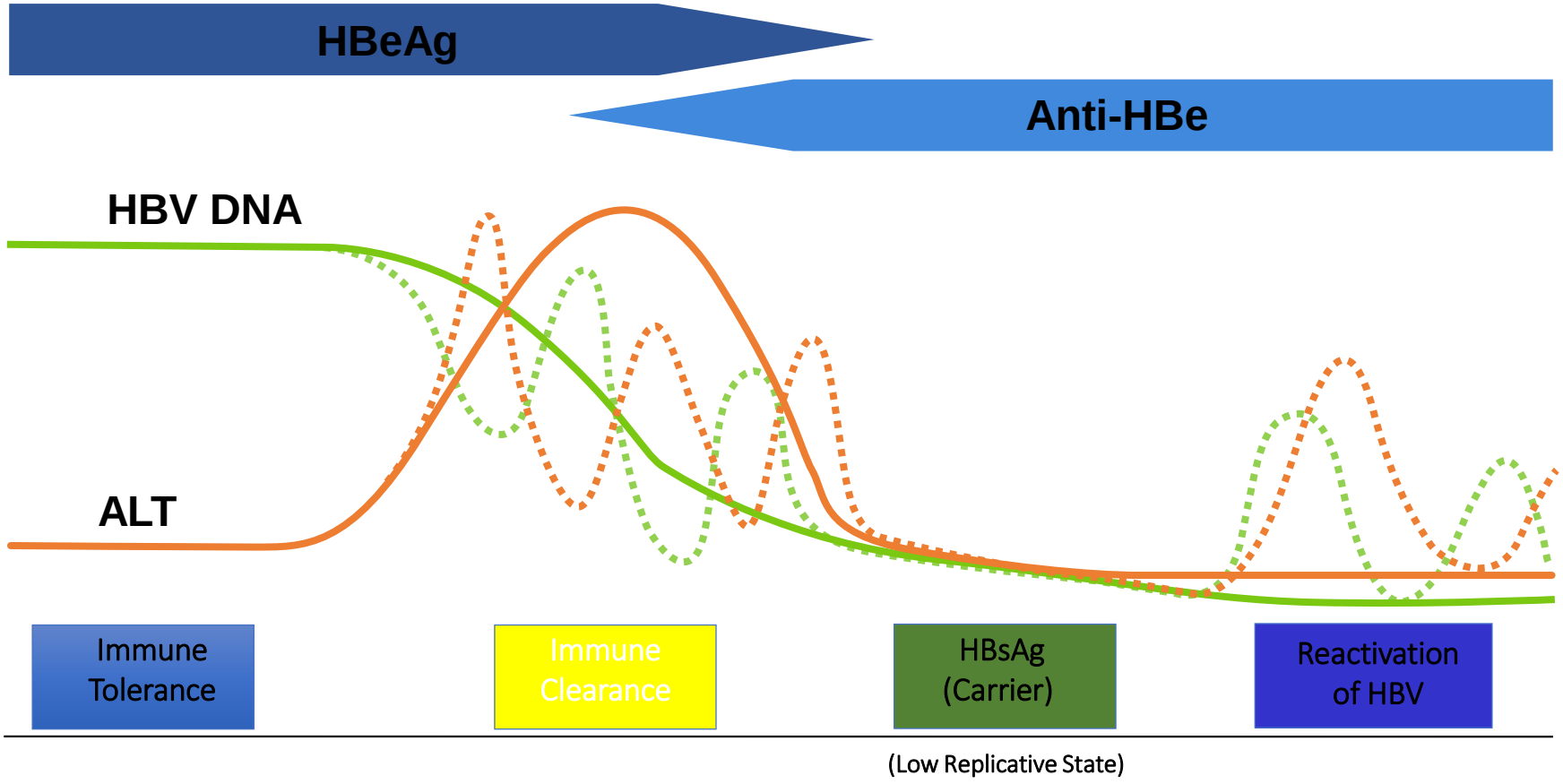
Cirrhosis with decompensation/HCC

[1] Lok A, Hepatology 2001

Natural History of Hepatitis B infection



Phases of Chronic Hepatitis B



Yim HJ and Lok ASF. Hepatology. 2006;43:S173-S181.

Approach for diagnosis of Hepatitis B

- **Careful evaluation** of the patient's **medical history** for hepatitis B risk factors
- Evaluation of the **patient's symptoms**
- Thorough **physical examination** with particular attention given to evaluate signs of chronic liver disease or its complications.
- **Laboratory evaluation** of the blood for markers of disease and/or liver function
- **Biopsy and Transient Elastography**

Signs & Symptoms of HBV Infection

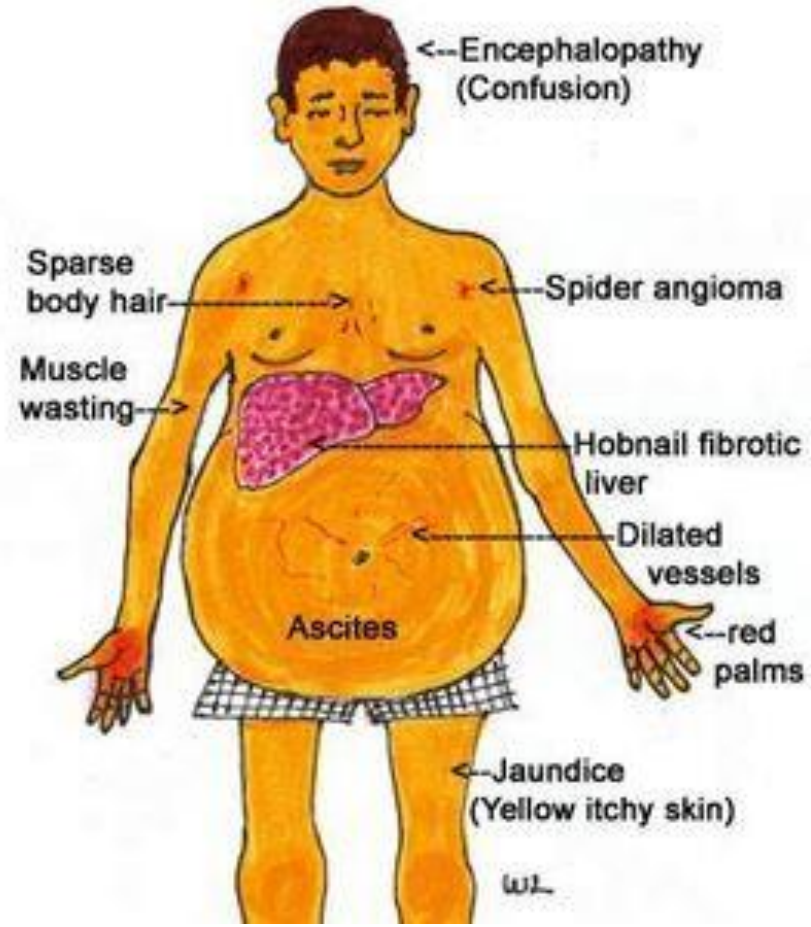
Short-Term Infection

- Tiredness or “flu-like” symptoms
- Nausea or stomach ache
- Diarrhea
- Skin rash
- Yellow eyes/skin (jaundice)
- Light-colored stools
- Dark yellow urine
- Depression
- Taste abnormalities

Long-Term Infection

- Same symptoms as acute
- Muscles and joints ache
- Weakness
- Signs and symptoms of cirrhosis
- Signs and symptoms of liver cancer

Typical presentation in advanced liver disease - Cirrhosis



Laboratory diagnosis

Liver Function Tests

Markers of Hepatocyte Death

- Alanine aminotransferases (ALT)
- Aspartate aminotransferases (AST)

Markers of Cholestasis

- ALP
- GGT

Tests of Liver Function

- Albumin, Prothrombin Time, Bilirubin
  - (Combine with scores for hepatic encephalopathy and ascites to form Child-Turcotte-Pugh Score)
- MELD score calculated with total bilirubin, creatinine, and INR – predictor of mortality

[1] *National Academy of Clinical Biochemistry. 2000*

Transient Elastography

- Transient elastography is a noninvasive test that evaluates the degree of fibrosis by measurement of liver stiffness or elasticity .
- TE –AUROC (F2 stage- 0.81-0.95) and cirrhosis (F4 stage) 0.8–0.98.

- 6.3–7.9-Sig. Fibrosis
- 9.0–13.8 kPa for Cirrhosis

- Pitfalls: Necroinflammation, edema, food intake, and cholestasis

Sarin et al. Hepatol Int (2016) 10:1–98

SEROLOGIC & MOLECULAR TESTING

Hepatitis B markers

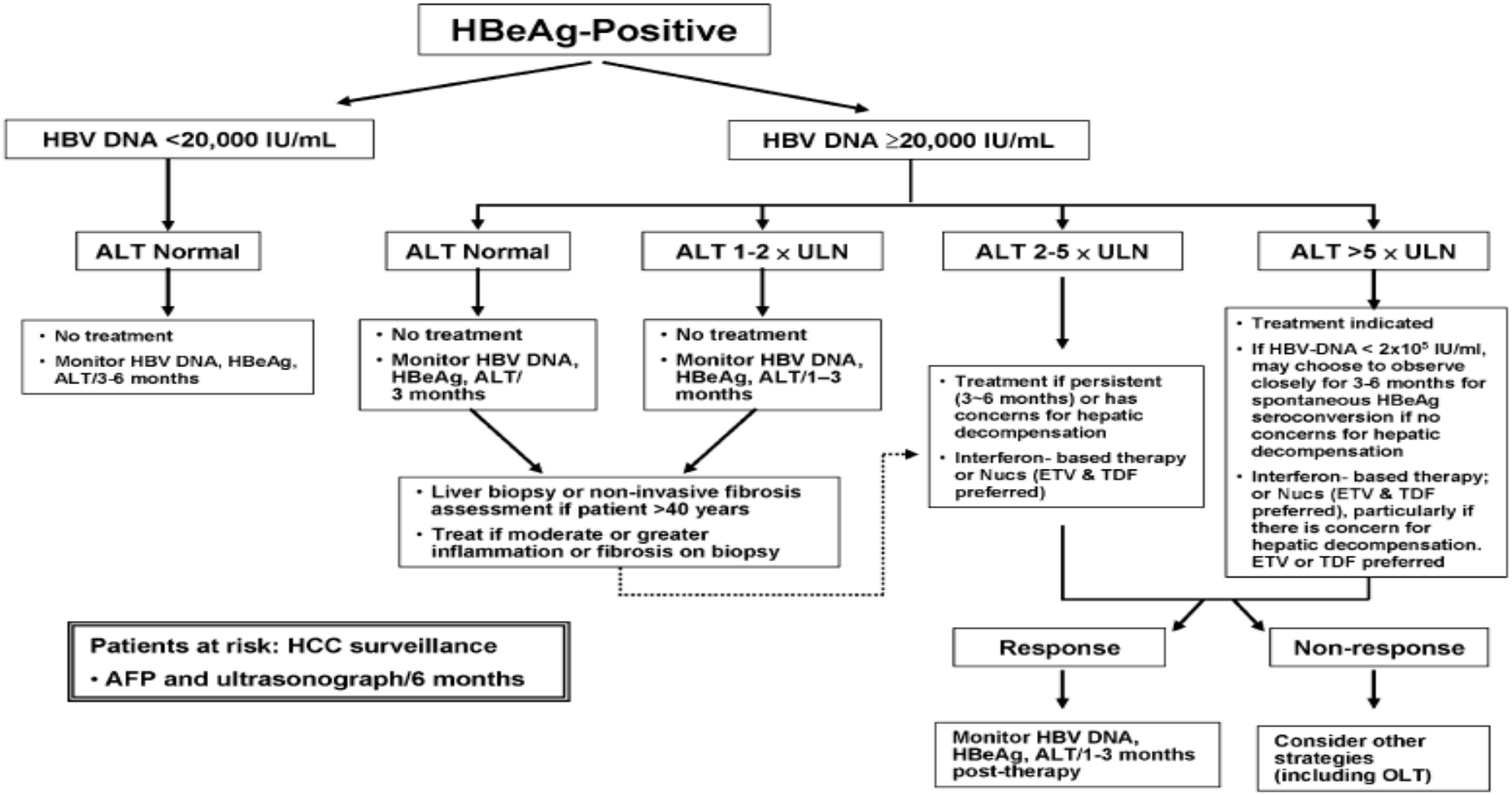
Test	Acute Hepatitis B	Post Exposure (Immunity)	Previous Immunization	Chronic Hepatitis B	Healthy Carrier
HBsAg	+	-	-	+	+
Anti-HBs	-	+	+	-	-
HBeAg	+/-	-	-	+/-	-
Anti-HBe	-	+/-	-	+/-	+/-
Anti-HBc	+	+	-	+	+
IgM anti-HBc	+	-	-	-	-
HBV DNA	+	-	-	+/-	-
ALT	Elevated	Normal	Normal	Elevated / Normal	Normal

Who Should be Treated?

- Ideally all patients
  - If available treatment can eradicate virus
  - Long term viral suppression are safe and affordable

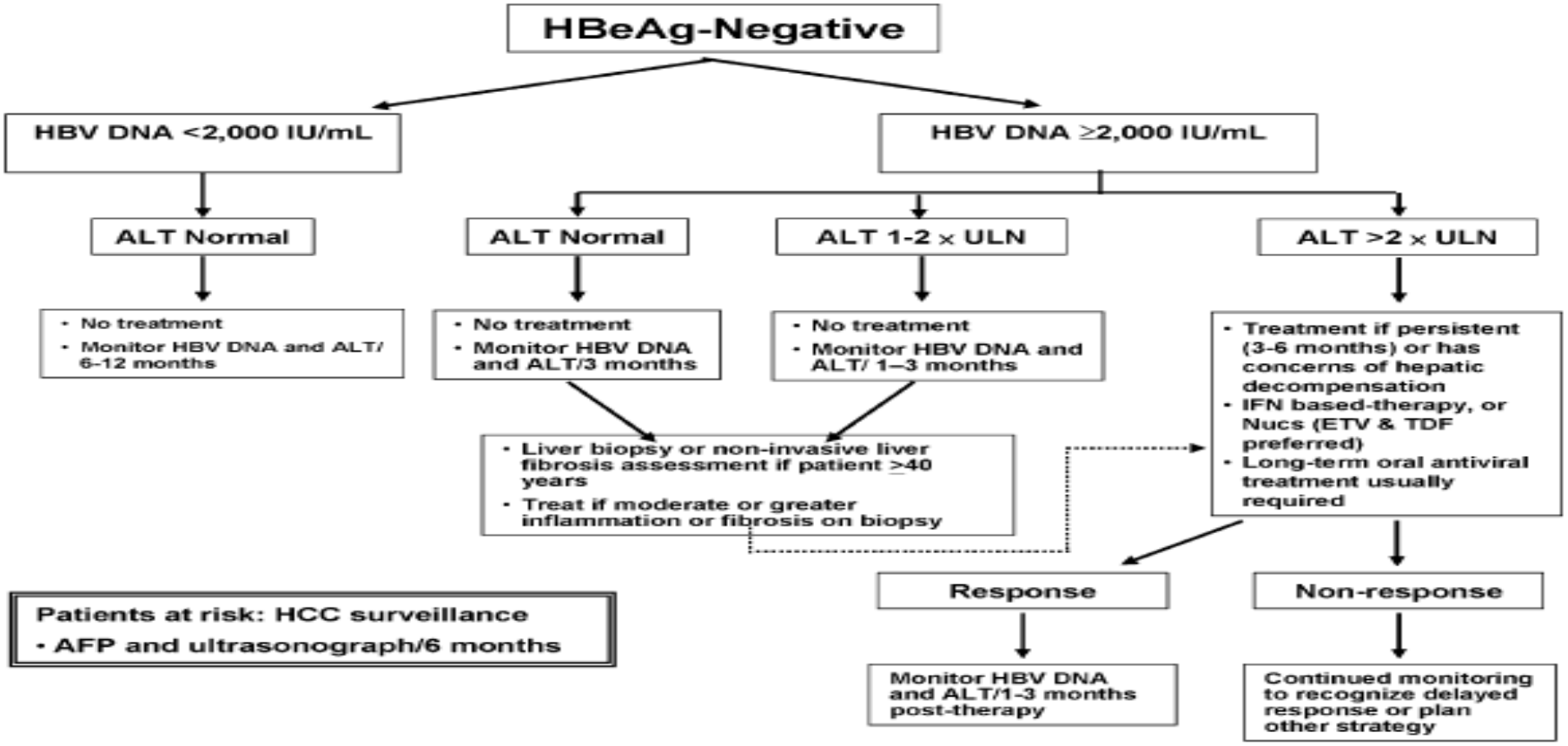
➢ Limitations
  - Drug resistance
  - Long term safety unknown
  - Expensive

Chronic HBV Infection-HBeAg Positive Treatment Indications(APASL guidelines)



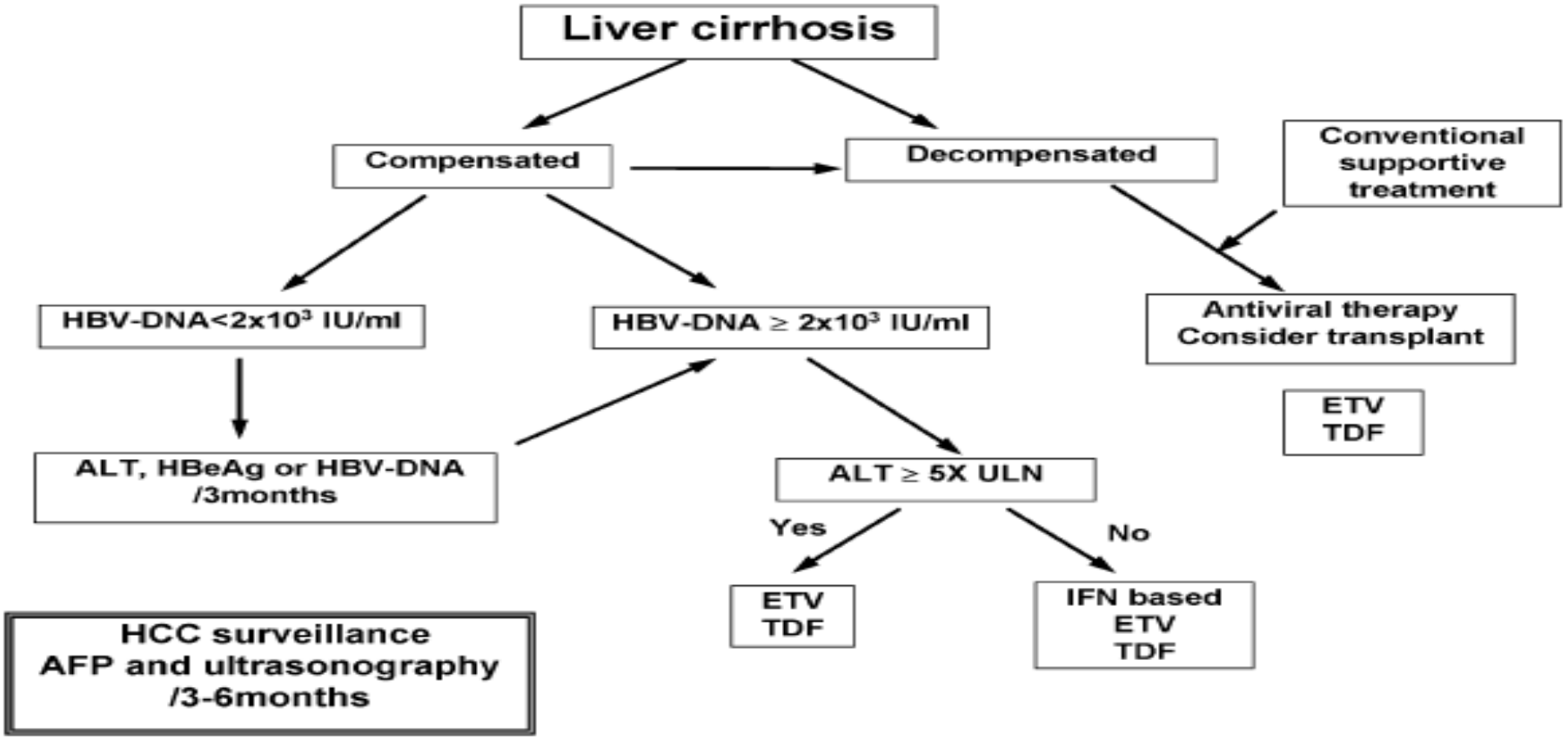
Sarin et al. Hepatol Int (2016) 10:1–98

Chronic HBV Infection-HBeAg -Negative – Treatment Indications(APASL guidelines)



Sarin et al. Hepatol Int (2016) 10:1–98

Treatment Indications(APASL guidelines)- HBV-related Cirrhosis



Sarin et al. Hepatol Int (2016) 10:1–98

Treatment Options

(Peg)-IFNa

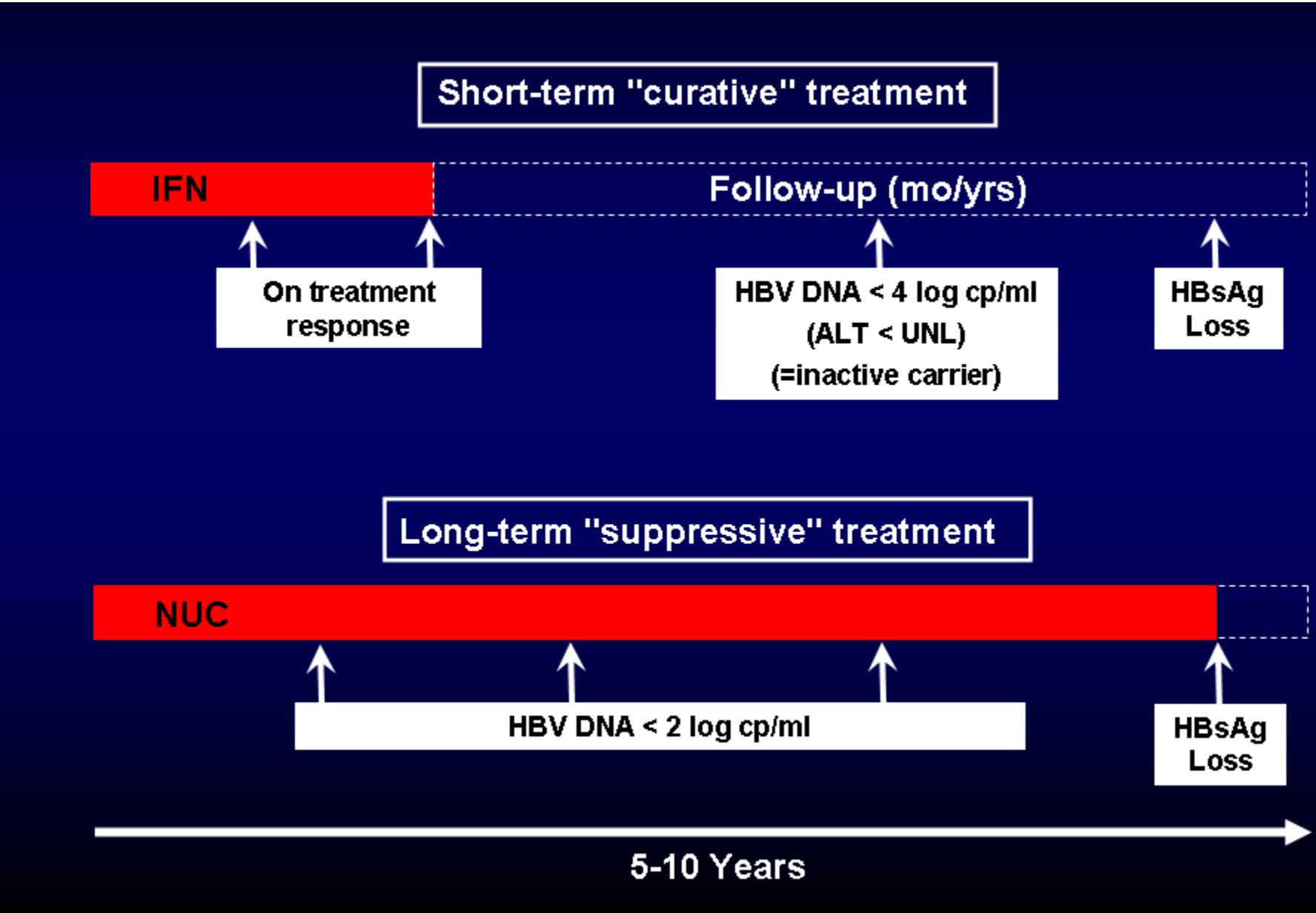
(antiviral+ immunomodulator)

ETV, TDF

TBV, LAM, ADV

(pure antivirals)

Therapeutic strategies for Chronic hepatitis B



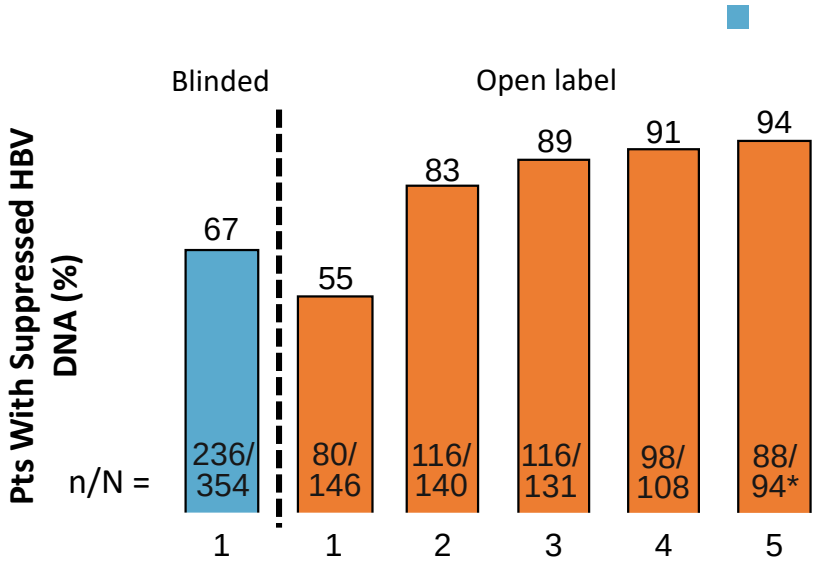
Benefits of Long-term Oral HBV Therapy

- Suppresses HBV DNA[1,2]
- Normalizes ALT[2,3]
- Prevents fibrosis progression[3,4]
- Promotes fibrosis regression, even in cirrhosis[4]
- Prevents and even reverses hepatic decompensation[1]
- ***Reduces, but does not eliminate, the risk of HCC[1,5]***
- ***Long-term therapy is effective . . . but low rates of HBsAg loss[6]***

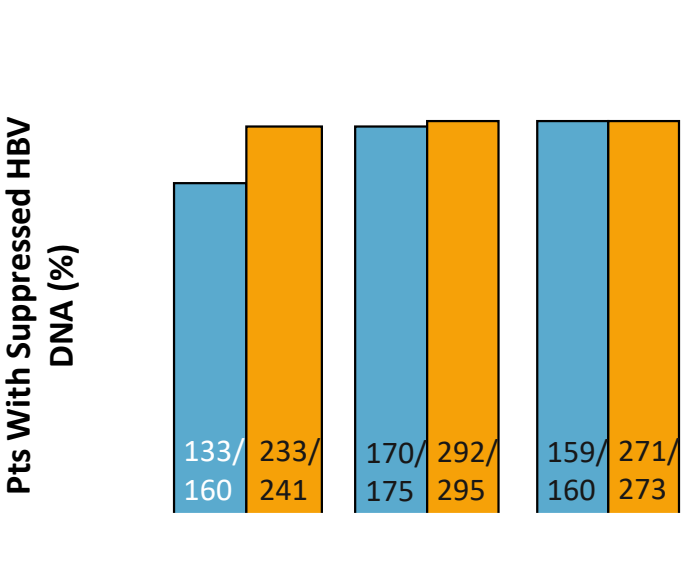
1. Lim YS, et al. Gastroenterology. 2014;147:152-161.2. Chang TT, et al. Hepatology. 2010;51:422-430.
3. Zoutendijk R, et al. Gut. 2013;62:760-765. 4. Marcellin P, et al. Lancet. 2013;381:468-475.
5. Papatheodoridis GV, et al. J Hepatol. 2015;62:363-370. 6. Papatheodoridis GV, et al. Hepatol. 2016;63:1481-1492.

Potent HBV DNA Suppression With Nucleos(t)ide Therapy

Long-term ETV[1]



Long-term TDF



*5 additional pts who remained on treatment at the Yr 5 visit had missing HBV DNA measurements.

Long-term therapy with potent nucleos(t)ides leads to suppression in almost all pts

1. Chang TT, et al. Hepatology. 2010;51:422-430. 2. Marcellin P, et al. N Engl J Med 2008; 359:2442-2455. 3. Marcellin P, et al. Lancet. 2013;381:468-75. 4. Buti M, et al. Dig Dis Sci. 2015;60:1457-1464.

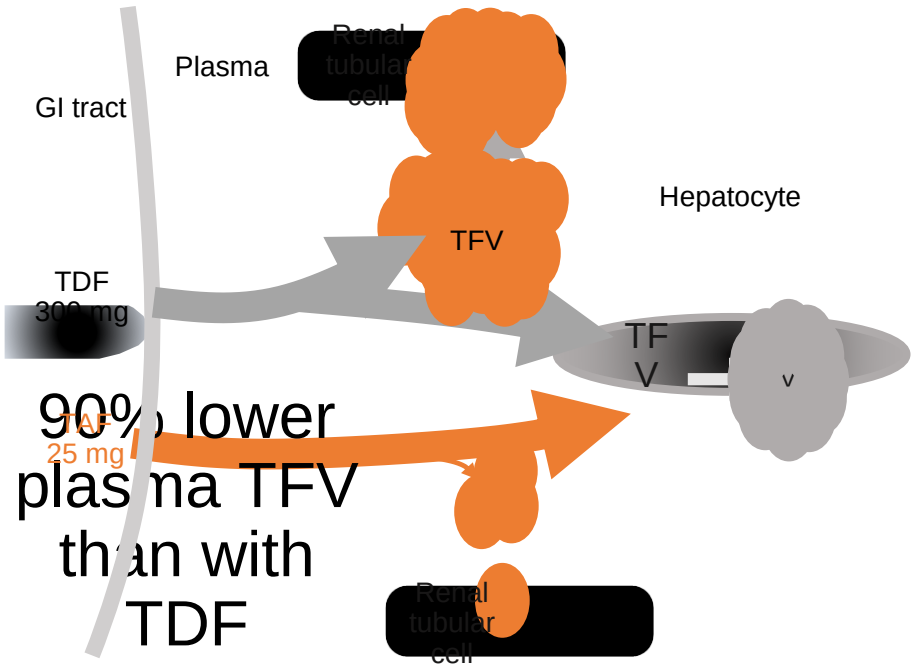
Recommended Nucleos(t)ide Analogues for HBV

Nucleos(t)ide Analogue	Approval in HIV	Approval in CHB	QD Dose	Lowest CrCl Without Dose Adjustment (mL/min)
Entecavir	N/A	2005	0.5 mg	50
Tenofovir disoproxil fumarate	2001	2008	300 mg	50 (no dose recommendation at < 10 without dialysis)
Tenofovir alafenamide	2015 (as part of fixed-dose combination with antiretrovirals)	2016	25 mg	15 (not recommended at < 15 in HBV monoinfection)

Entecavir [package insert]. 2017. Tenofovir disoproxil fumarate [package insert]. 2017. Tenofovir alafenamide [package insert]. 2017.

Slide credit: clinicaloptions.com

TAF vs TDF: Mechanism of Action



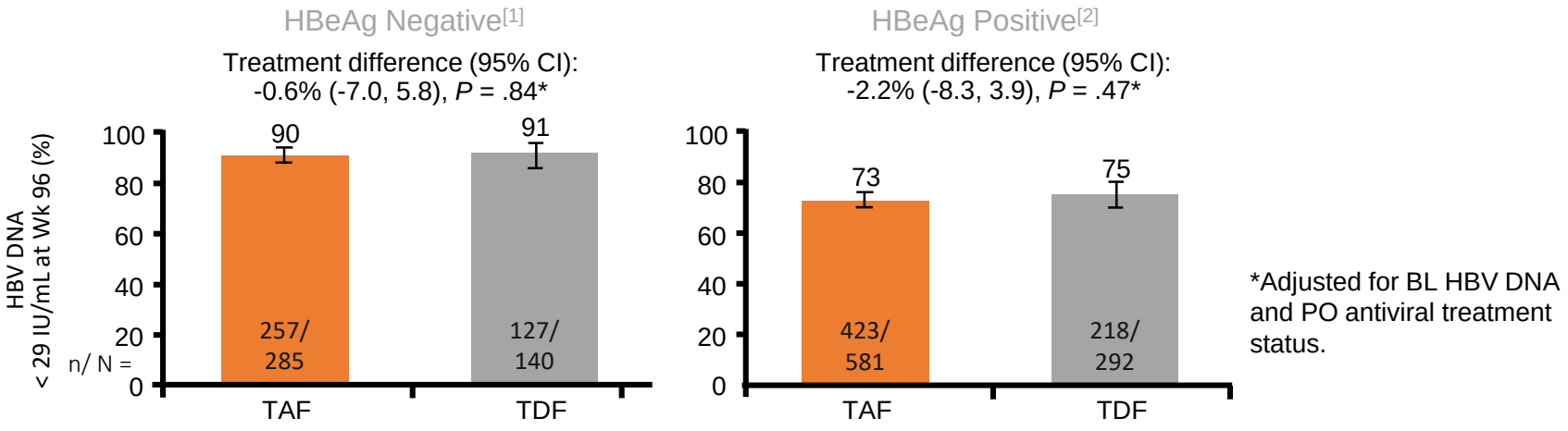
- Tenofovir alafenamide: novel prodrug of tenofovir

TAF: no dose adjustment needed in pts with CrCl > 15 mL/min

Arribas JR, et al. CROI 2017. Abstract 453. Duarte-Rojo A. Therap Adv Gastroenterol. 2010;3:107-119. Murakami E, et al. Antimicrob Agents Chemother. 2015;59:3563-3569. Tenofovir disoproxil fumarate [package insert]. 2017. Tenofovir alafenamide [package insert]. 2017.

TAF vs TDF in Chronic HBV Infection: **Wk** 96 Efficacy

- HBV DNA: TAF noninferior to TDF at Wks 48 and 96 in both studies; no resistance found in any arm



*Adjusted for BL HBV DNA and PO antiviral treatment status.

ALT: significantly greater rate of ALT normalization at Wk 96 with TAF vs TDF

HBeAg-positive pts: higher rate of HBeAg seroconversion at Wk 96 vs Wk 48 with TDF or TAF[2]

HBeAg-negative pts: minimal decline in HBsAg with TDF or TAF for (1 TAF-treated pt with GT A had HBsAg loss and seroconversion)[1]

***Lancet Gastroenterol Hepatol* 2016; 1: 196–206, *Lancet Gastroenterol Hepatol* 2016; 1: 185–95**

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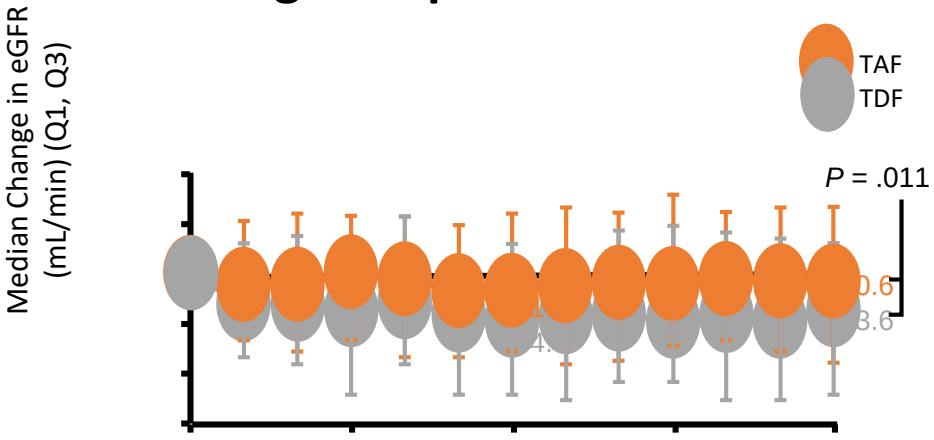
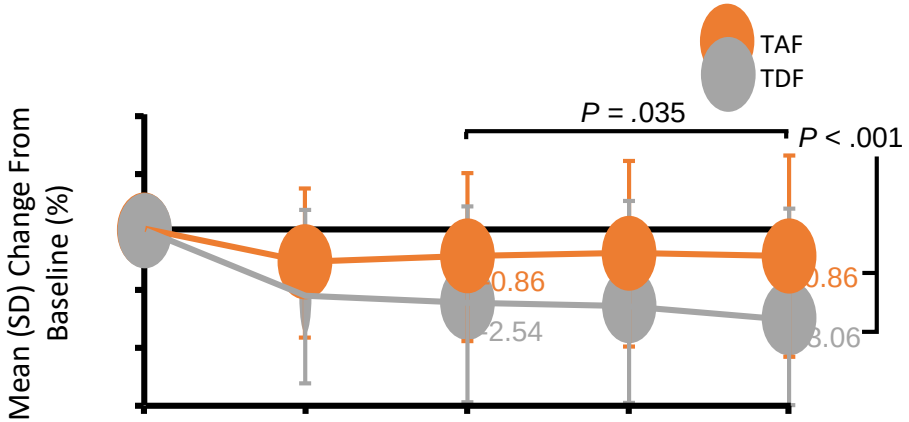
TAF vs TDF in Chronic HBV Infection: Renal and Bone Outcomes

- **Significantly smaller effect on renal function with TAF at Wk 48 and Wk 96 in HBeAg-negative pts[1]**



Significantly smaller effect on spine BMD with TAF at Wk 48 and Wk 96 HBeAg-negative pts[1]



Similar results seen with HBeAg-positive pts[2]

When to stop?


Doctor, for how long should I take the pills ?
Well, let's talk in 2064...

How do u define cure in HBV?

Actual cure

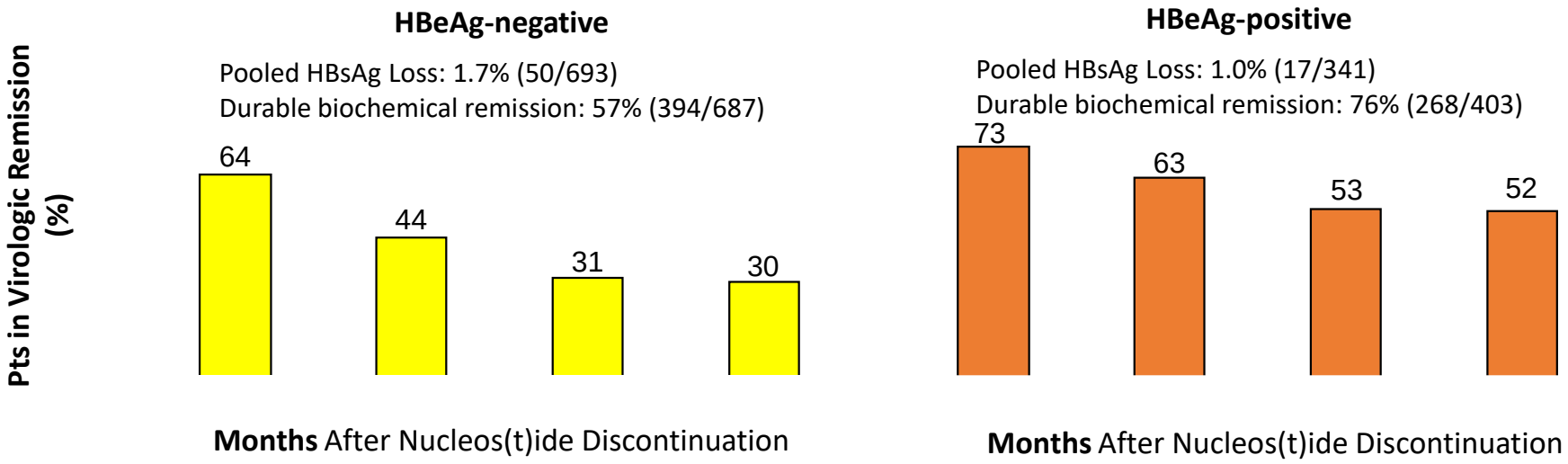
- True cure = all traces of HBV gone from the liver (like HCV)
- VERY difficult (if not impossible) → cccDNA

Functional cure

- Use the markers of pts who do well:
  1. HBsAg loss (ideally with anti-HBs)
  2. Possibly sustained off-treatment inactive disease without HBsAg loss (HBeAg negative, DNA undetectable, normal ALT, normal histology)

Is Long-term HBV Therapy Required?

- Systematic review of stopping nucleos(t)ide therapy in HBeAg-negative (n = 967) and HBeAg-positive (n = 733) pts

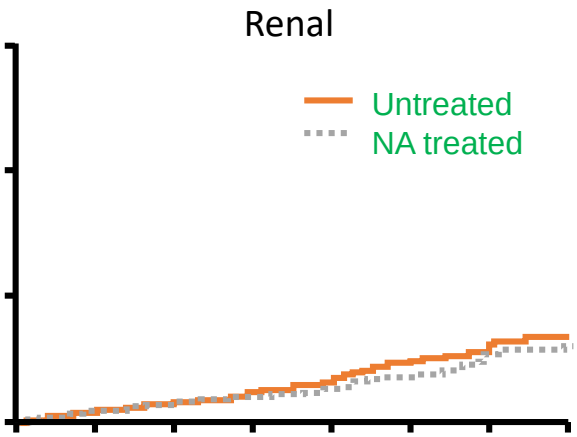


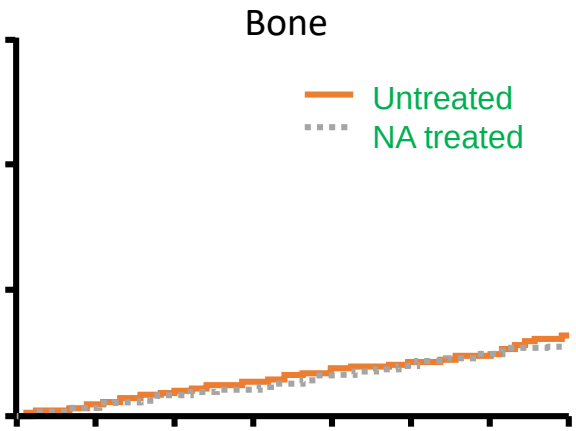
- High rate of relapse to active disease
- Low rate of HBsAg loss…Long-term therapy required

Papatheodoridis GV, et al. Hepatol. 2016;63:1481-1492.

Long term Safety of Nucleos(t)ide Analogues

- Observational study of n = 46,454 untreated vs n = 7046 pts treated with NAs, median follow-up of 4.9 yrs
- Generally very good long-term safety . . . but individual pts may have toxicity

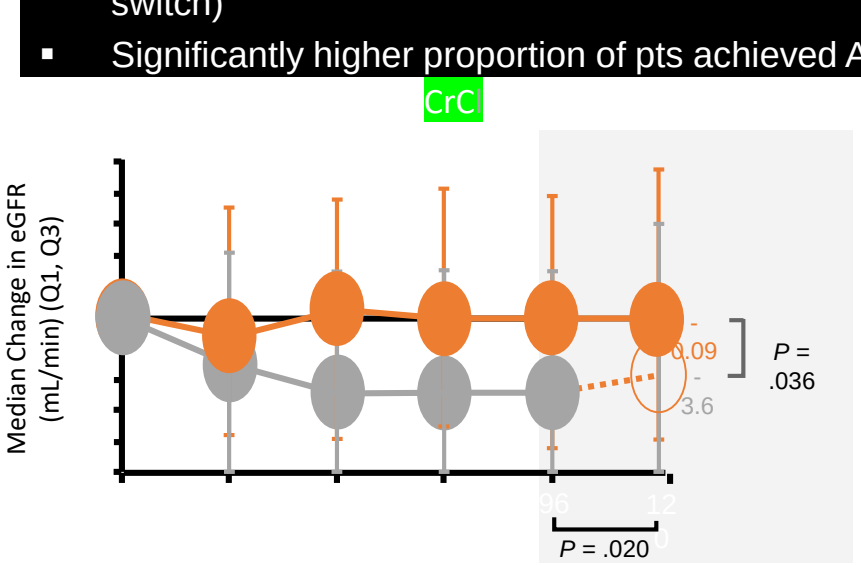


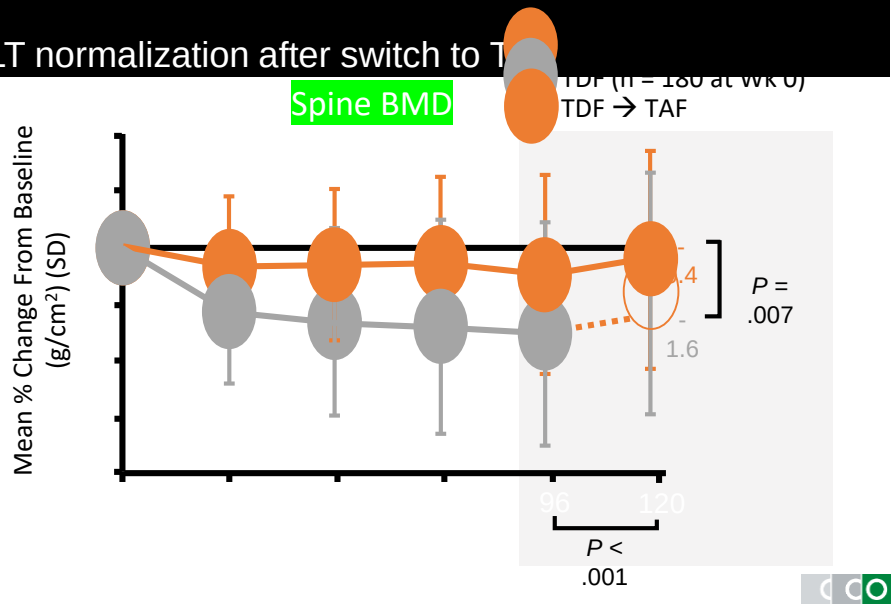


Wong G L-H, et al. Hepatology. 2015;62:684-693.

Switch to TAF vs Continuing TDF in Chronic HBV Infection: Renal and Bone Outcomes

- Analysis of open-label extension data from 2 phase III trials in HBV-infected pts switching from TDF to TAF at Wk 96
- 88% of pts achieved virologic suppression at Wk 96 (preswitch) and maintained to Wk 120 (post switch)
- Significantly higher proportion of pts achieved ALT normalization after switch to T





Chan HLY, et al. EASL 2017. Abstract PS-041.

Slide credit: clinicaloptions.com

Lancet Gastroenterol Hepatol 2016; 1: 196–206, *Lancet Gastroenterol Hepatol* 2016; 1: 185–95
,

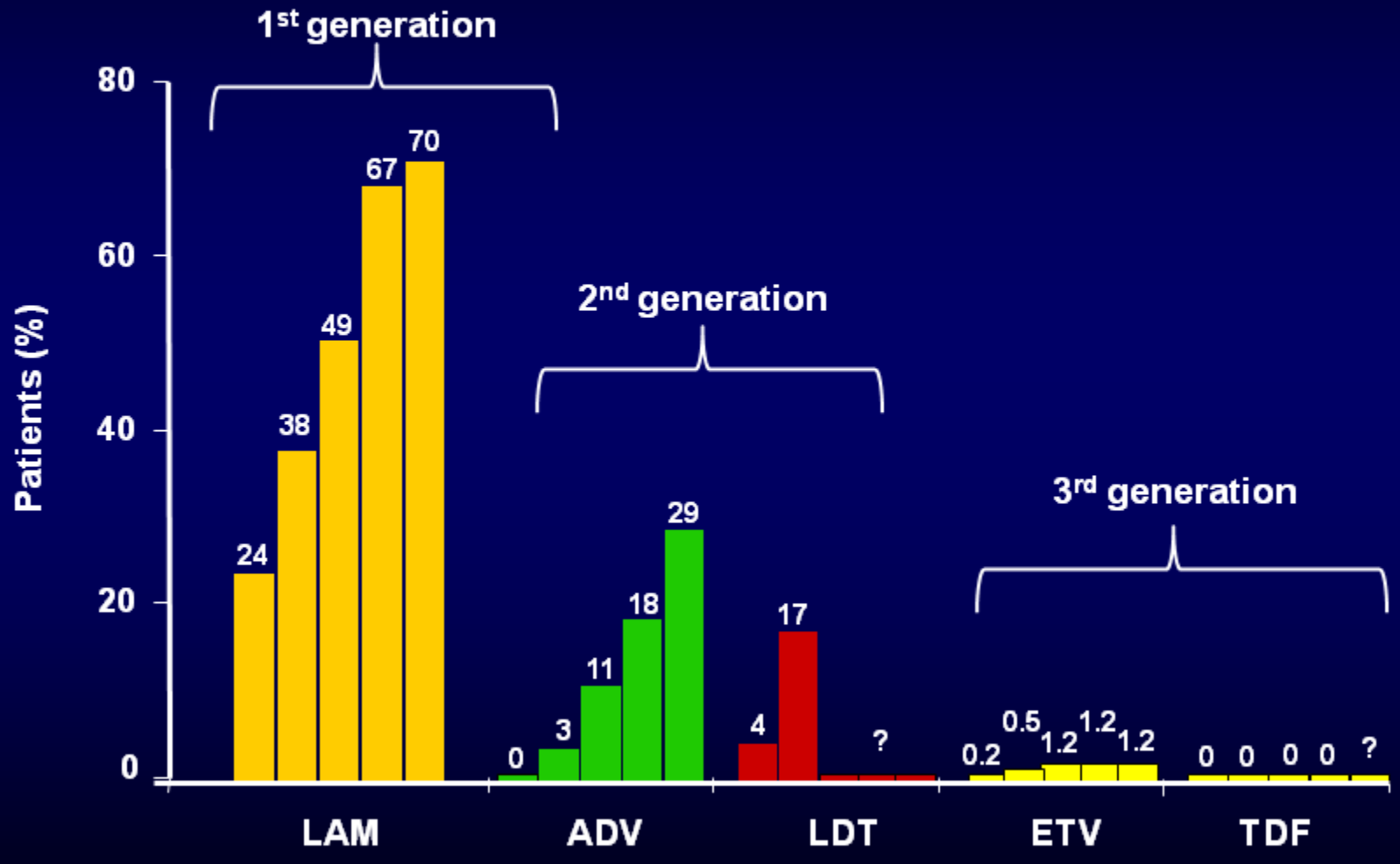
Treatment failures

Primary non-response	Less than 1 $\log_{10}$ IU/mL decrease in HBV DNA level from baseline at 3 months of therapy
Partial virological response	Decrease of HBV DNA of more than 1 $\log_{10}$ IU/mL but detectable HBV DNA by real-time PCR at 24 or 48 weeks of therapy (according to drug potency and genetic barrier to resistance)
Virological breakthrough	Confirmed increase in HBV DNA level of more than 1 $\log_{10}$ IU/mL compared to the nadir
HBV resistance to NUCs	Selection of HBV variants with amino acid substitutions that confer reduced susceptibility to the administered NUC(s)

adapted from EASL HBV Guidelines, J Hepatol 2009

Incidence of Resistance in NUC-naïve Patients

**Collation of currently available data – not from head-to-head studies*



adapted from EASL HBV Guidelines, J Hepatol 2009

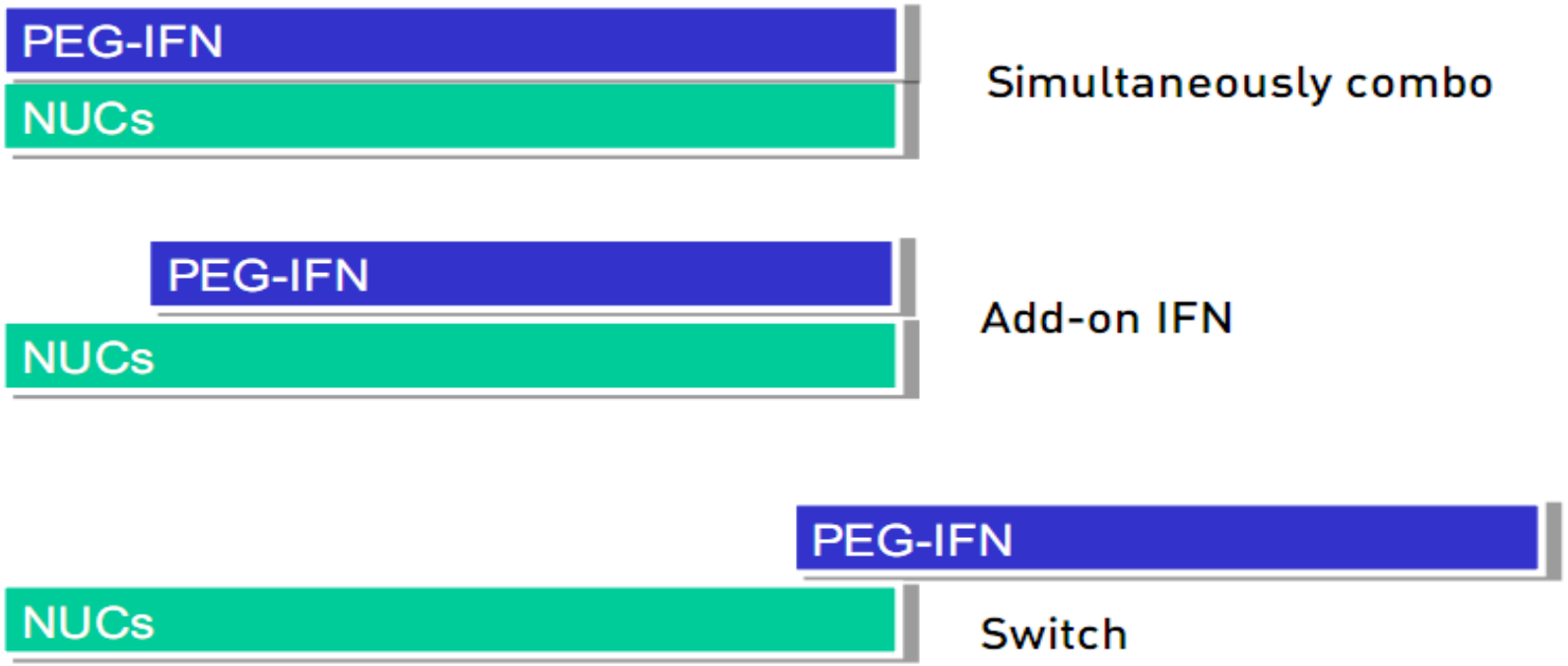
Management of HBV Resistance (Early add-on)

LAM resistance	• Add TDF
LDT resistance	• Add TDF*
ETV resistance	• Add TDF*
ADV resistance	• Switch to TDF and add a second drug ▪ If N236T, add LAM, ETV* or LDT* or switch to Truvada ▪ If A181V/T, add ETV* or switch to Truvada
TDF resistance**	• Add ETV*, LDT*, LAM or switch to Truvada

*the long-term safety of these combinations is unknown
**not seen so far ; do genotyping and phenotyping in an expert lab to determine the cross-resistance profile

adapted from EASL CPG HBV, J Hepatol 2009

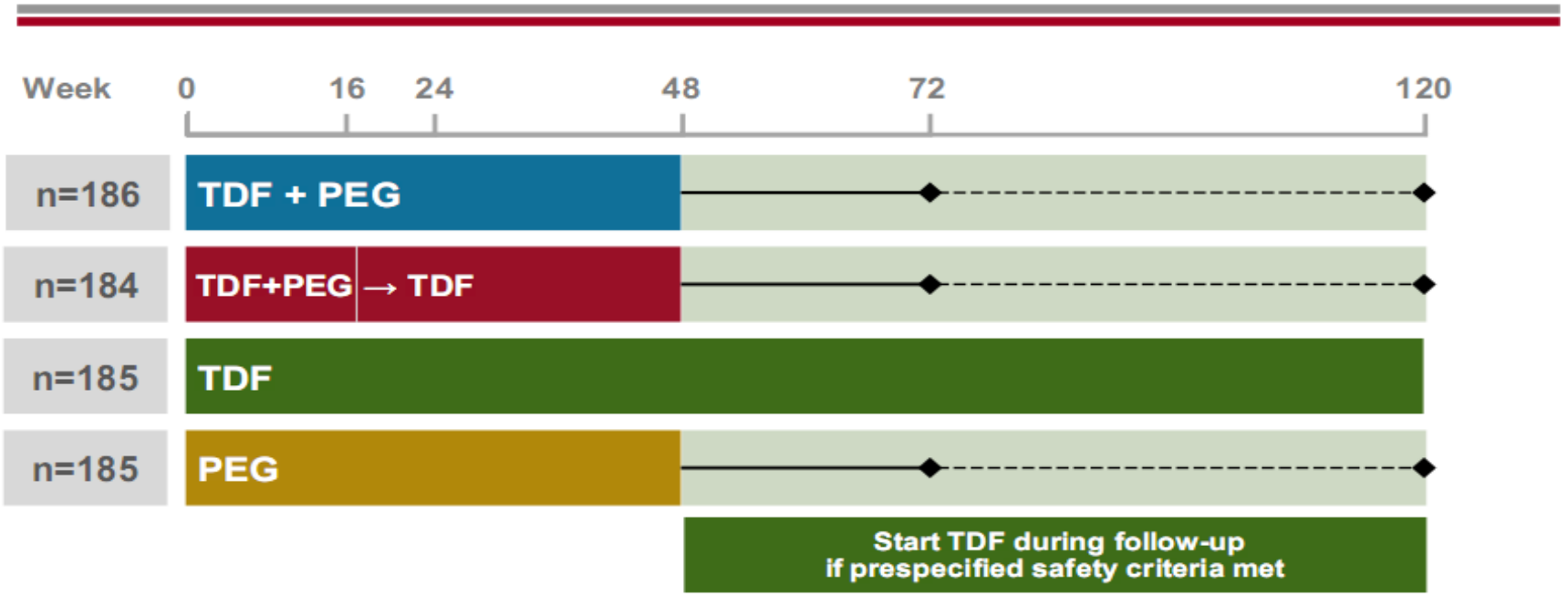
Interferon to enhance HBsAg Loss?



Concepts in Interferon use

- **Simultaneous Initiation**
- Add on Therapy
- Switch Therapy

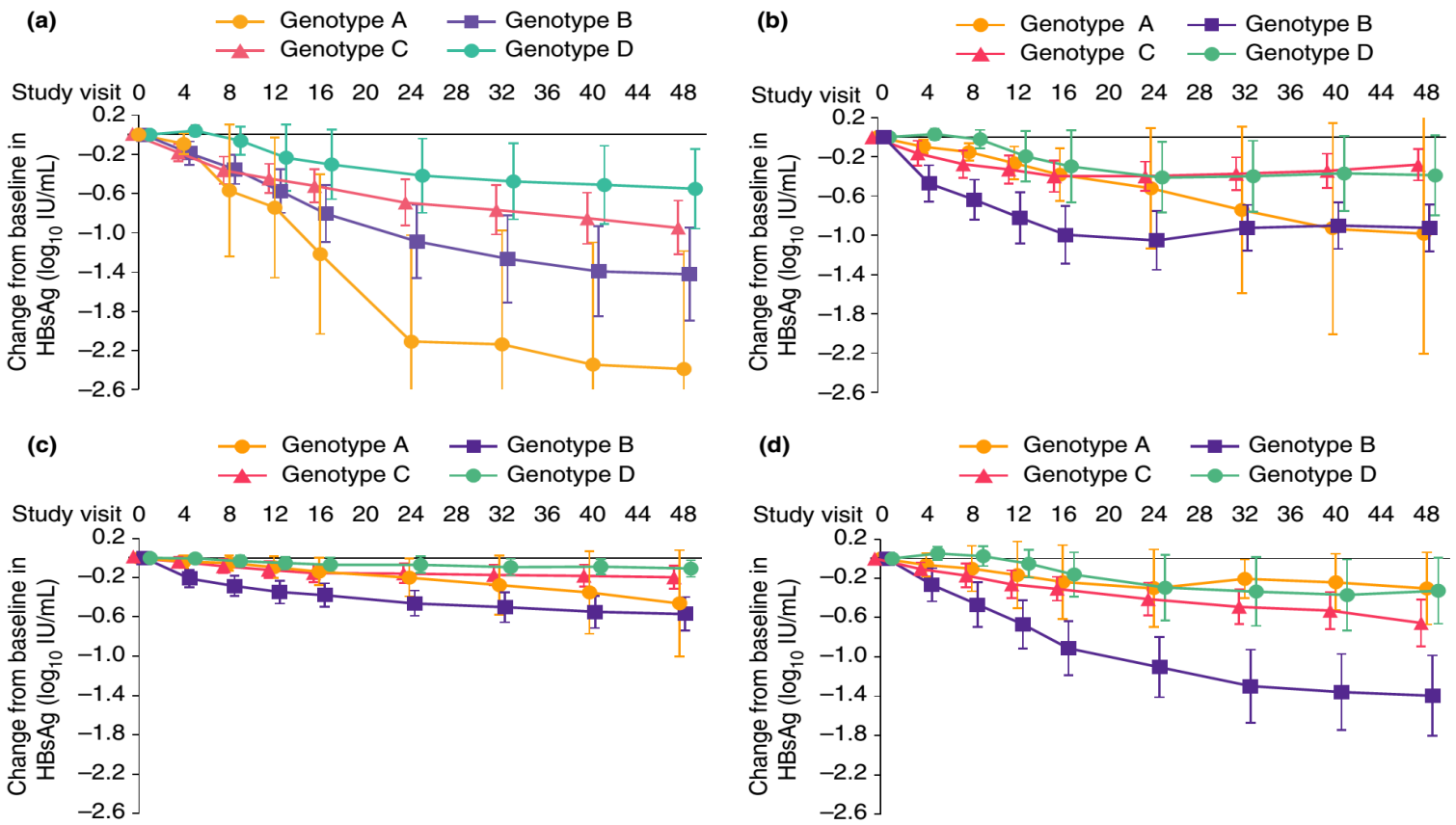
Combination of PegIFN and Tenofovir



- Randomized, controlled, open-label study (N=740)
  - Stratified by screening HBeAg status and HBV genotype
- Inclusion criteria
  - HBeAg+ and HBV DNA ≥20,000 IU/mL; HBeAg- and HBV DNA ≥2,000 IU/mL
  - ALT >54 and ≤400 U/L (men); ALT >36 and ≤300 U/L (women)
  - No bridging fibrosis or cirrhosis on liver biopsy or by transient elastography

Aliment Pharmacol Ther 2016; 44: 957–966

Efficacy HBsAg Loss based on genotype and HBeAg Status



Aliment Pharmacol Ther 2016; 44: 957–966

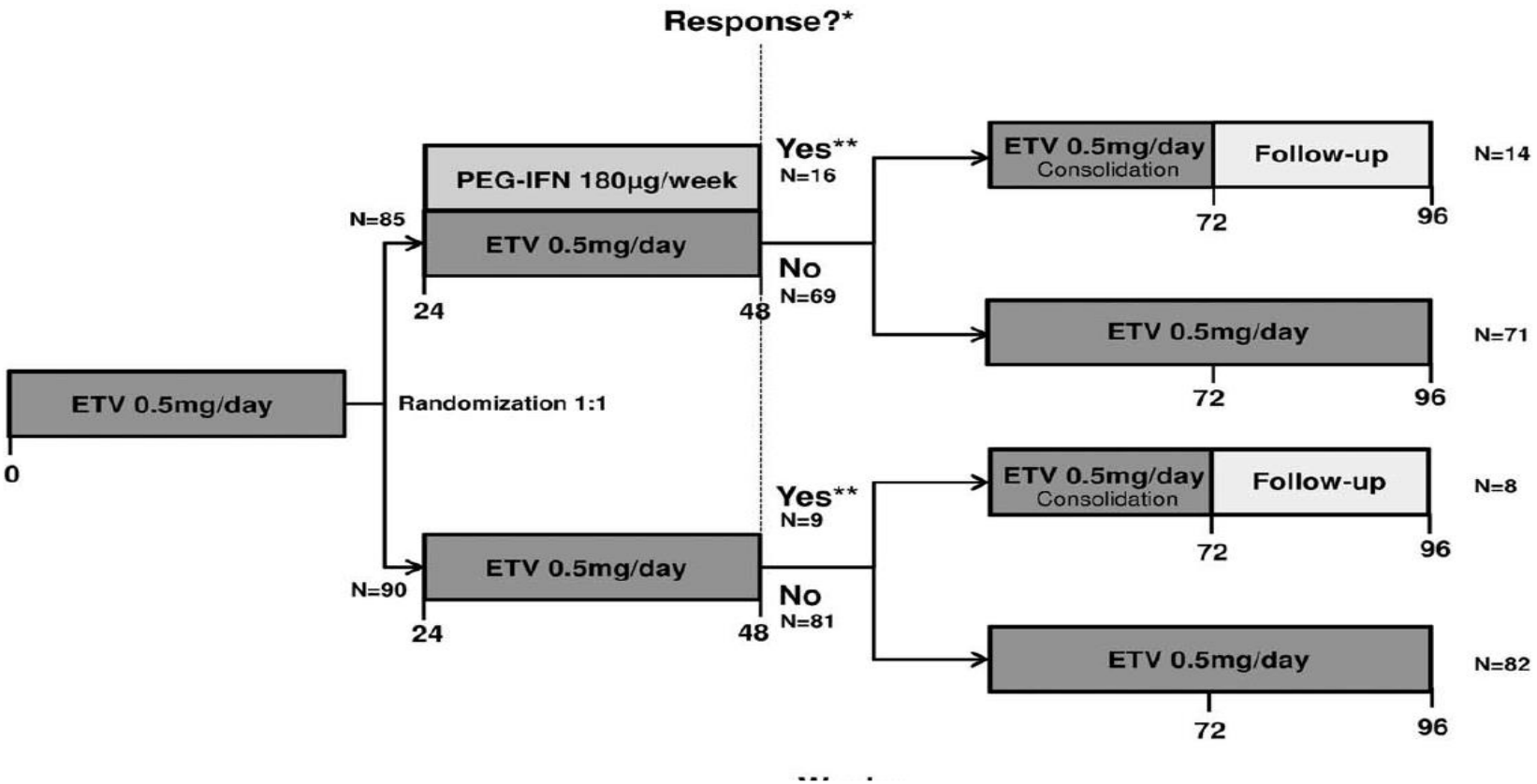
Concepts in Interferon use

- **Add on Therapy**

- Switch Therapy

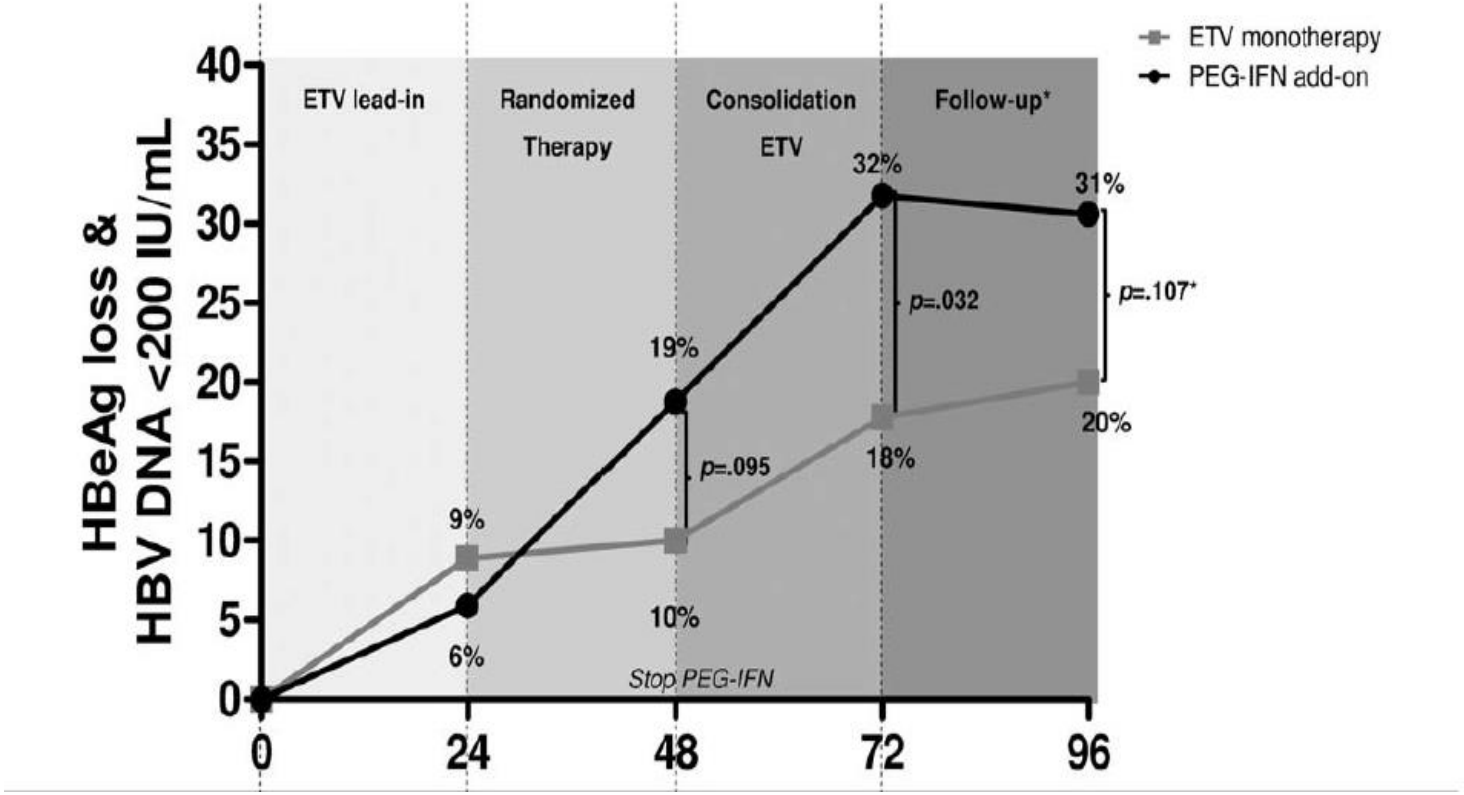
Adding PegIFN to Nucs-ARES Study

Randomized-182 patients



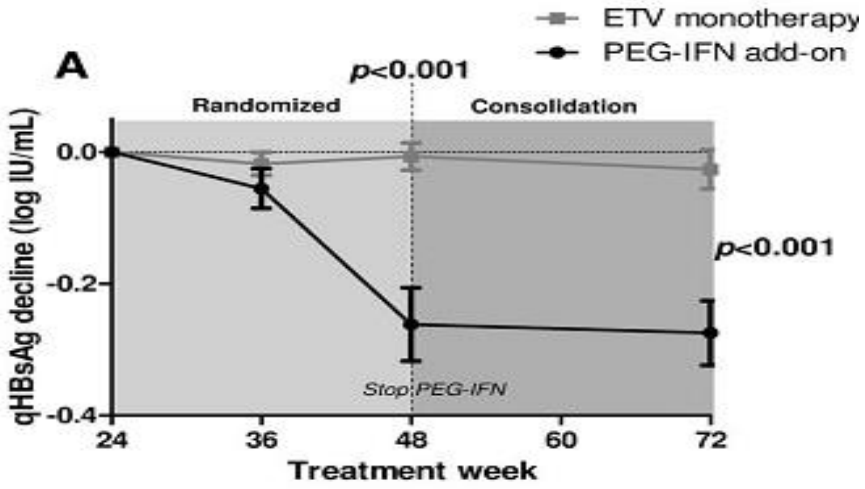
Hepatology. 2015 May;61(5):1512-22.

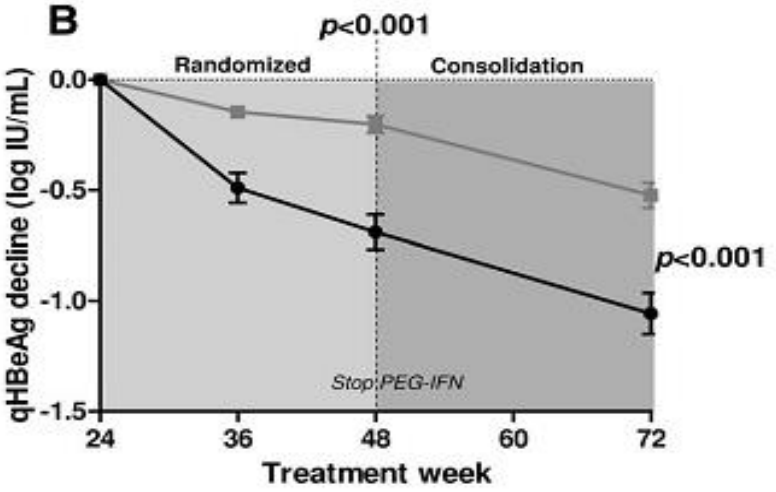
Results-ARES Trial

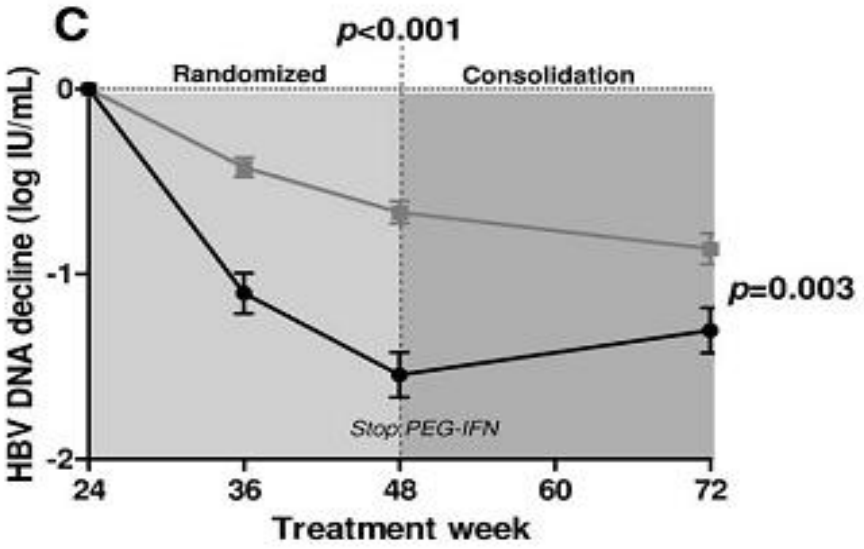


Hepatology. 2015 May;61(5):1512-22.

Decline in HBsAg, HBV DNA and HBeAg- ARES study





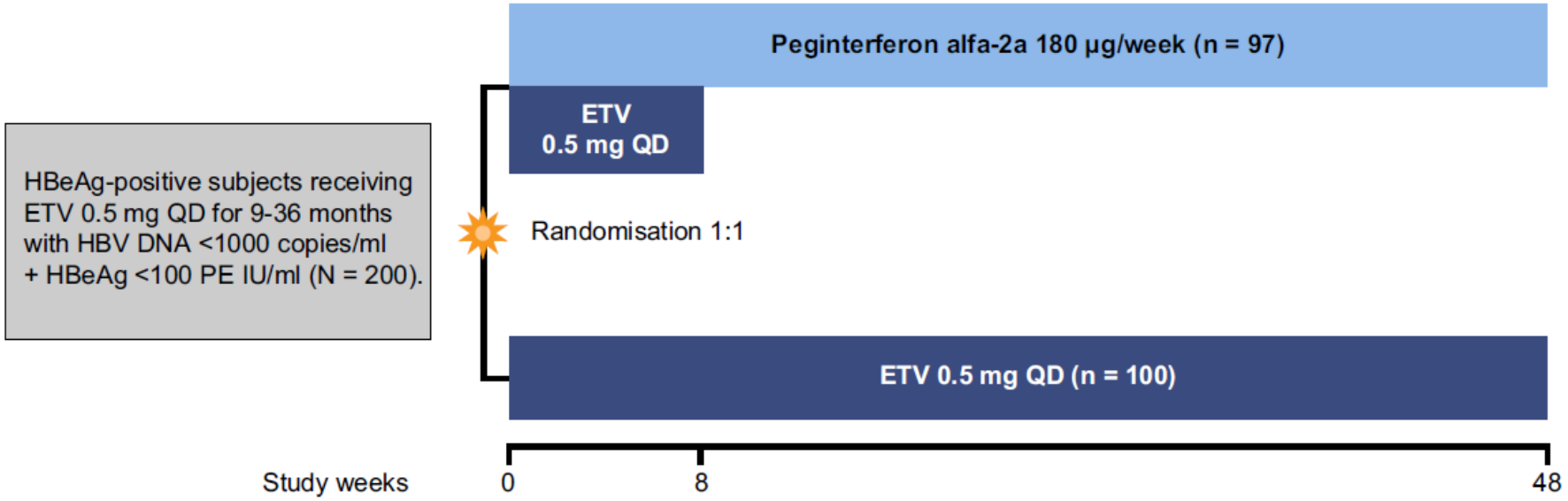


Hepatology. 2015 May;61(5):1512-22.

Switch Therapy (OSST study)

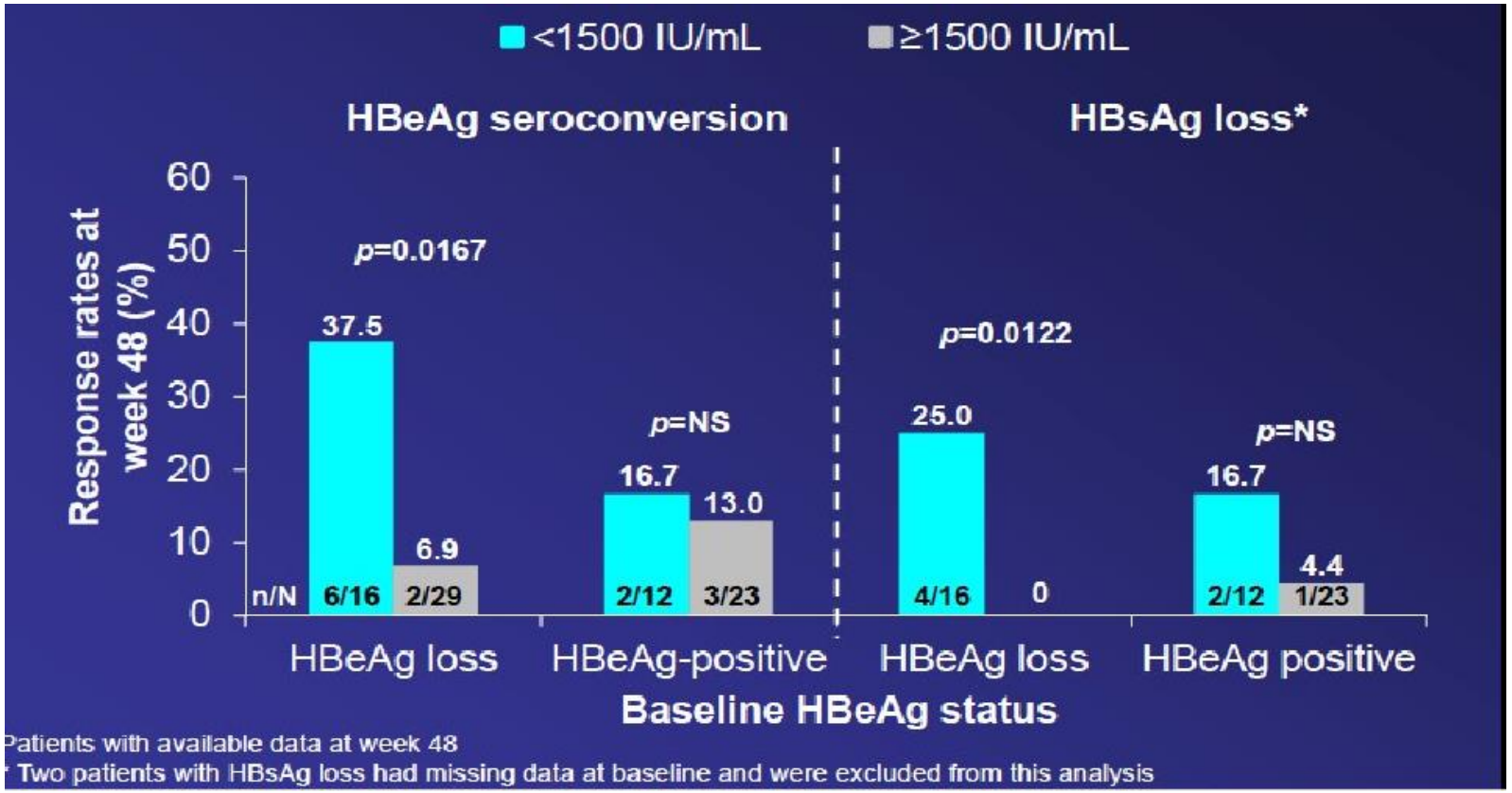
Study design

- Randomized, multicenter, open-label study
- Primary endpoint: HBeAg seroconversion at end of treatment (week 48)
- Secondary endpoint: HBsAg loss at week 48



Ning et al J of Hepatology 2014

HBeAg loss+HBsAg<1500iu/ml was associated with HbeAg Seroconversion(37.5%) and HBsAg loss(25%) at week 48



Concepts in Interferon use

- Add on Therapy
- Switch Therapy
- **Add on Therapy with Extension based on HBsAg Kinetics**

Letters to the Editor

EASL JOURNAL OF HEPATOLOGY

A response-guided approach based on HBsAg kinetics may identify patients with the greatest chance of success

N=10

Loss Of HBsAg -60%

Persistence of loss greater than 18 months of therapy

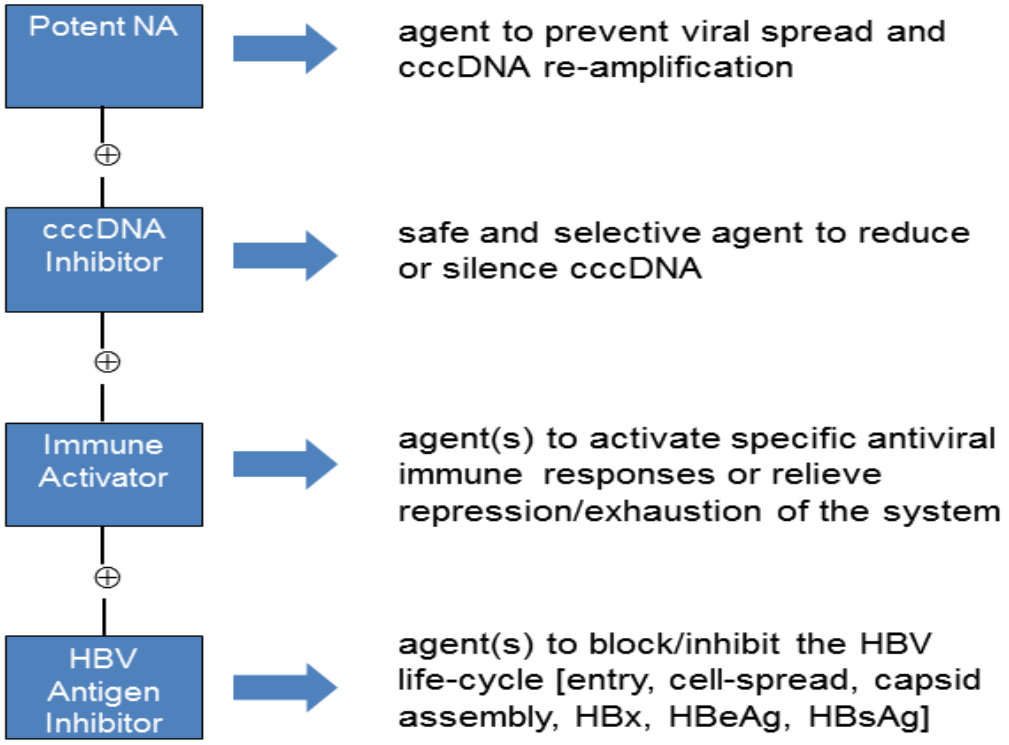
Seroconversion in 40%

Loss of HBsAg –Predicts loss of HBsAg

Duration of interferon treatment

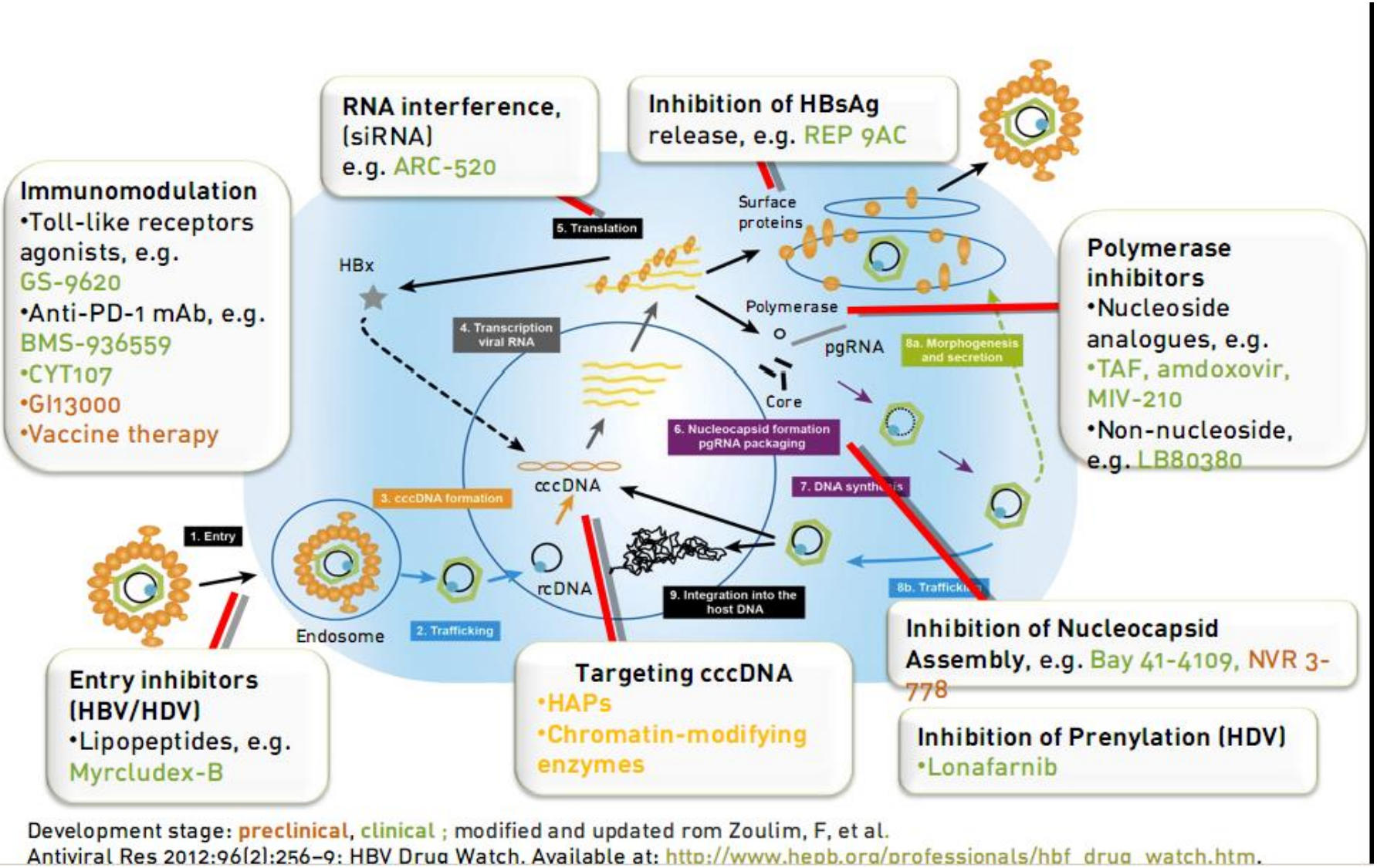
Halfon P et al J of Hepatology 2014

Future of Hep B:What would a curative regimen look like ?



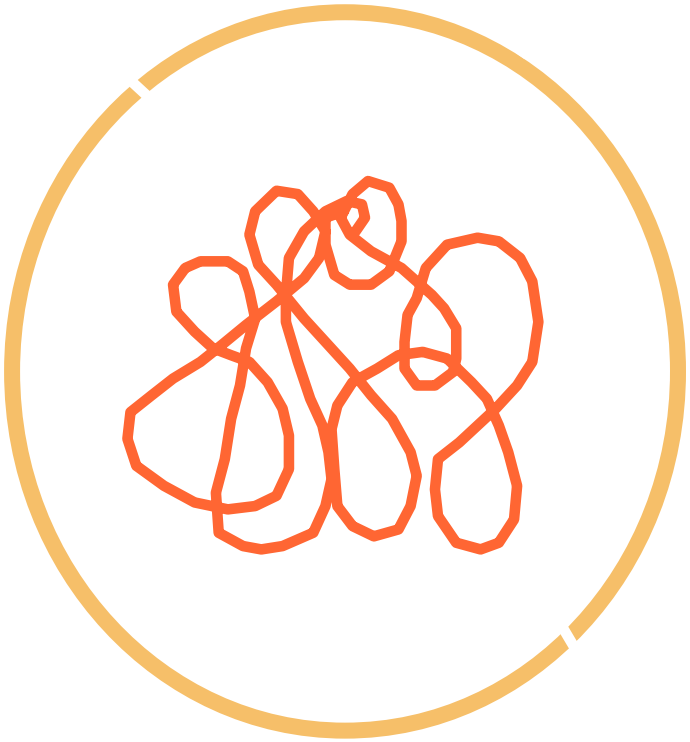
Courtesy S Locarnini

Emerging Targets for Hepatitis B-Future

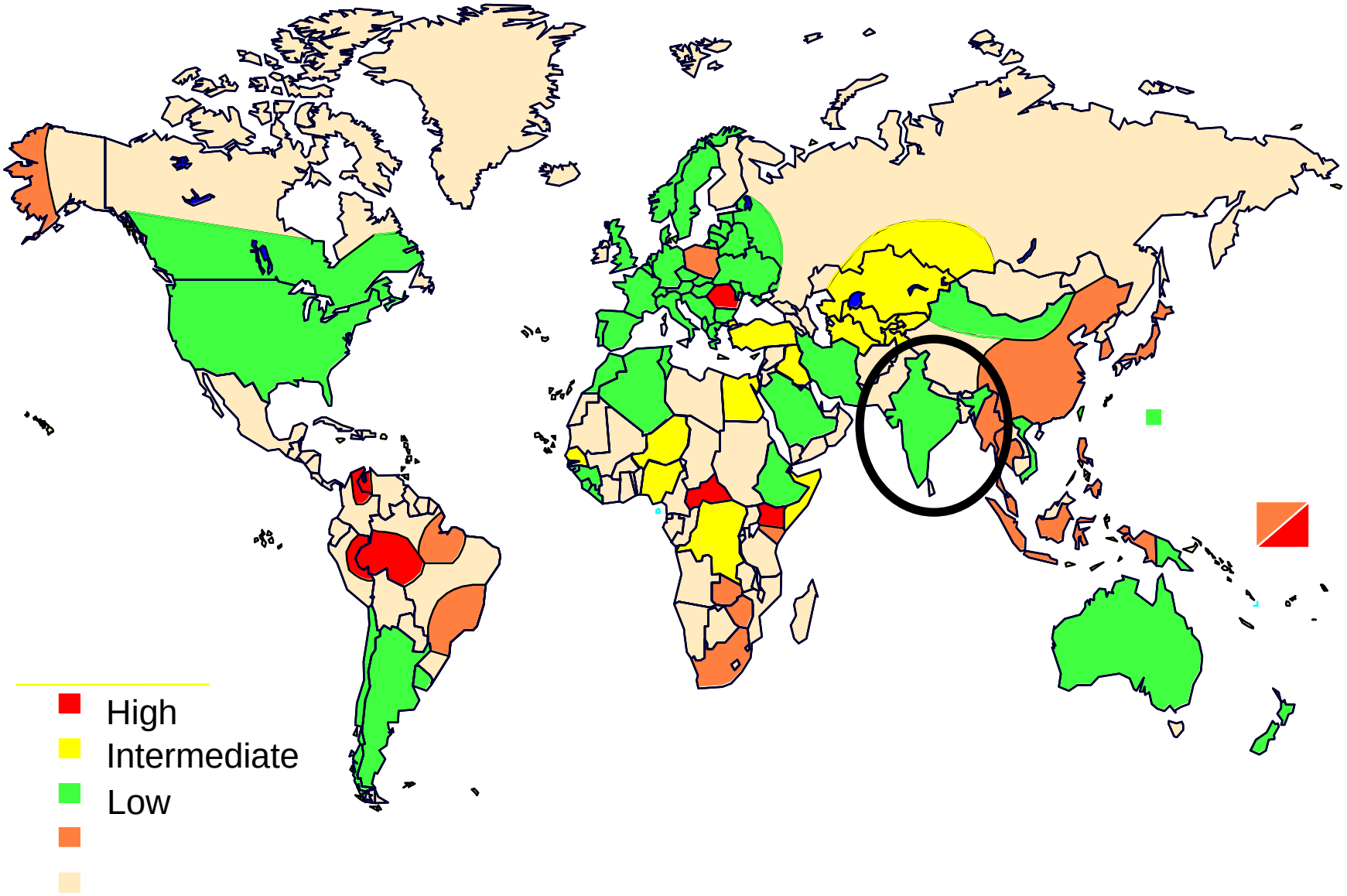


Development stage: preclinical, clinical ; modified and updated rom Zoulim, F, et al. Antiviral Res 2012;96(2):256–9; HBV Drug Watch. Available at: http://www.hepb.org/professionals/hbf_drug_watch.htm.

Hepatitis D (Delta) Virus



Geographic Distribution of HDV Infection



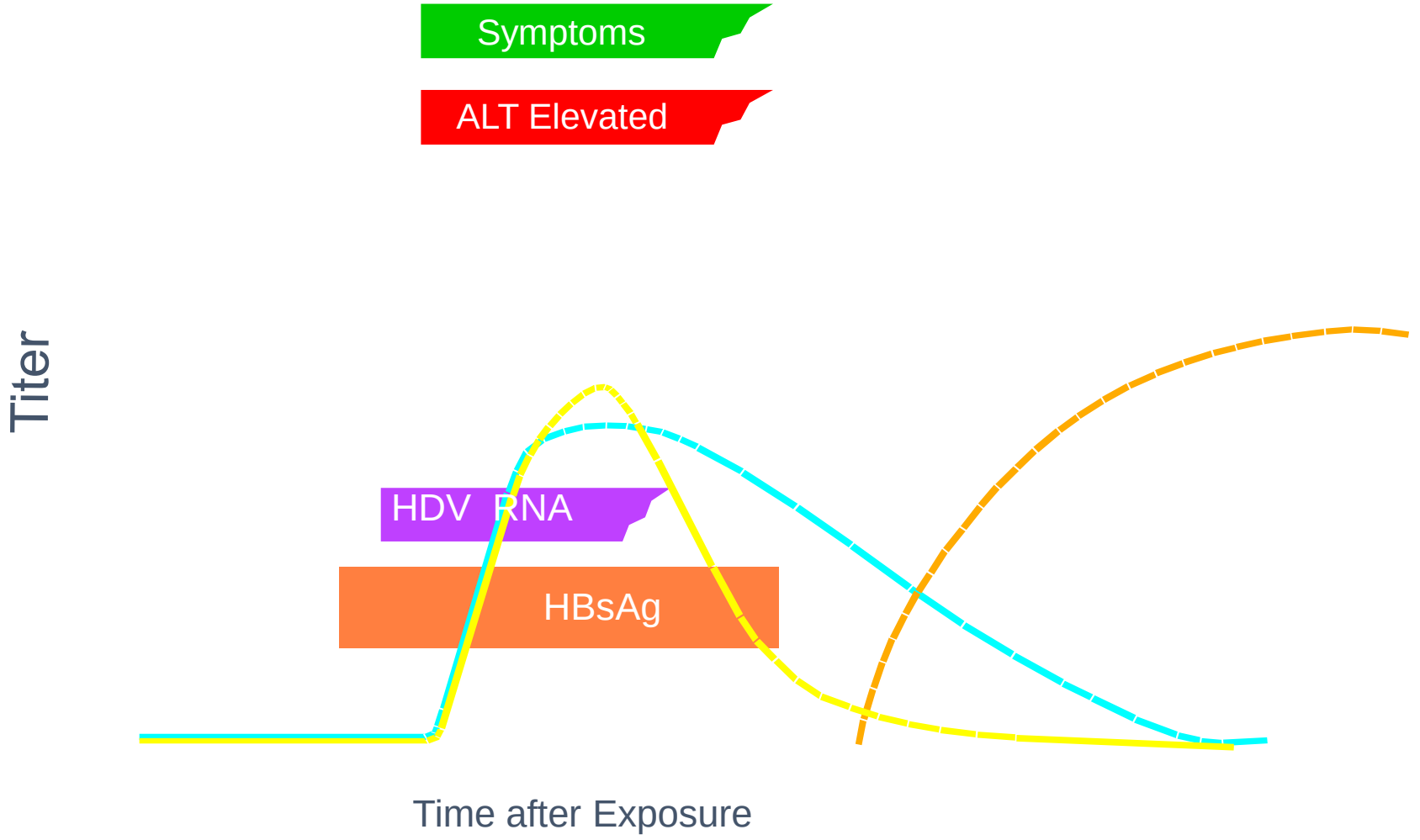
Hepatitis D - Clinical Features

Coinfection with HBV

Superinfection on top of chronic HBV

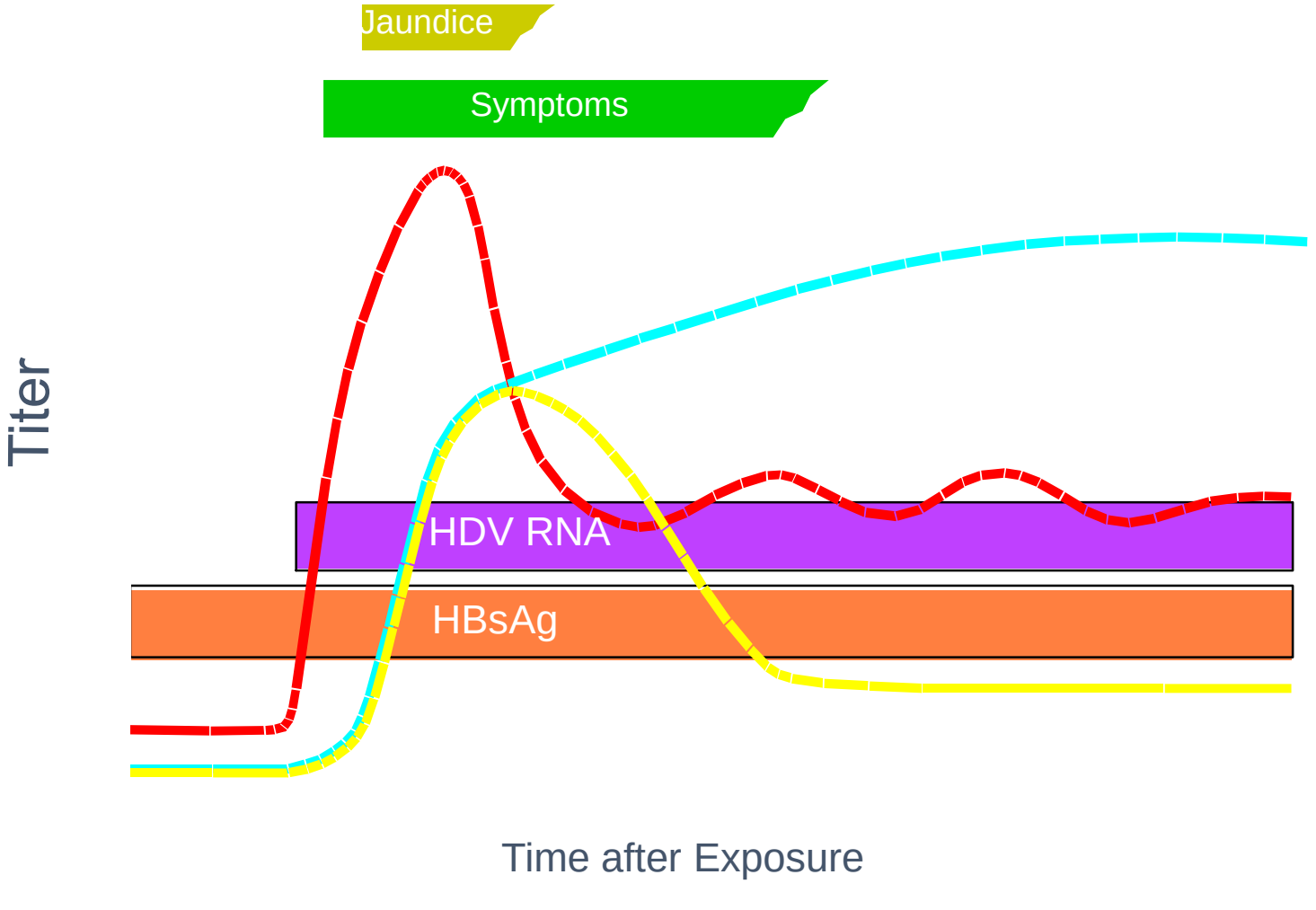
HBV – HDV Coinfection

Typical Serological Course



HBV – HDV Super-infection

Typical Serological Course



Hepatitis D Virus
Modes of Transmission

- Percutanous exposures
- Permucosal exposures

Hepatitis D – Prevention

HBV-HDV Coinfection

- Pre or postexposure prophylaxis to prevent HBV infection (HBIG and/or Hepatitis B vaccine)

HBV-HDV Superinfection

- Education to reduce risk behaviors among persons with chronic HBV infection

Hepatitis D – Treatment

- **Acute –No treatment , Foscarnet shown benefit**

- **Chronic – Standard Interferon (High Dose -9 mu thrice weekly x 12)**
  Pegylated Interferon (little data)
  Peg Interferon + Adefovir
  Tenofovir (HBV-HDV-HIV coinfected)

Experimental therapies – Prenylation and Entry inhibitors

Nat Rev Gastroenterol Hepatol. 2010 Jan;7(1):31-40.

Thank You!