
# Hepatitis B

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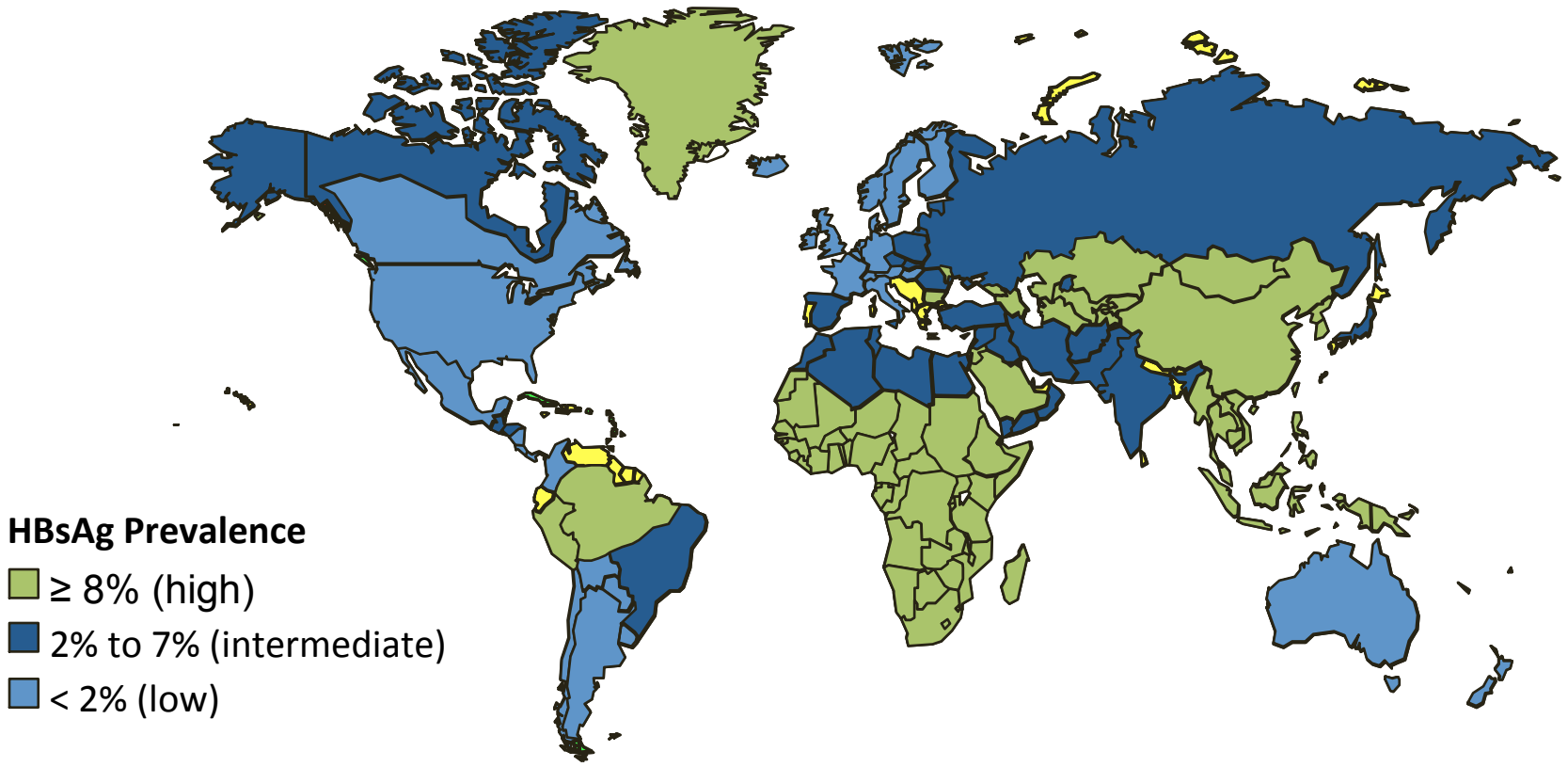
GreenShoots FOUNDATION

# Overview

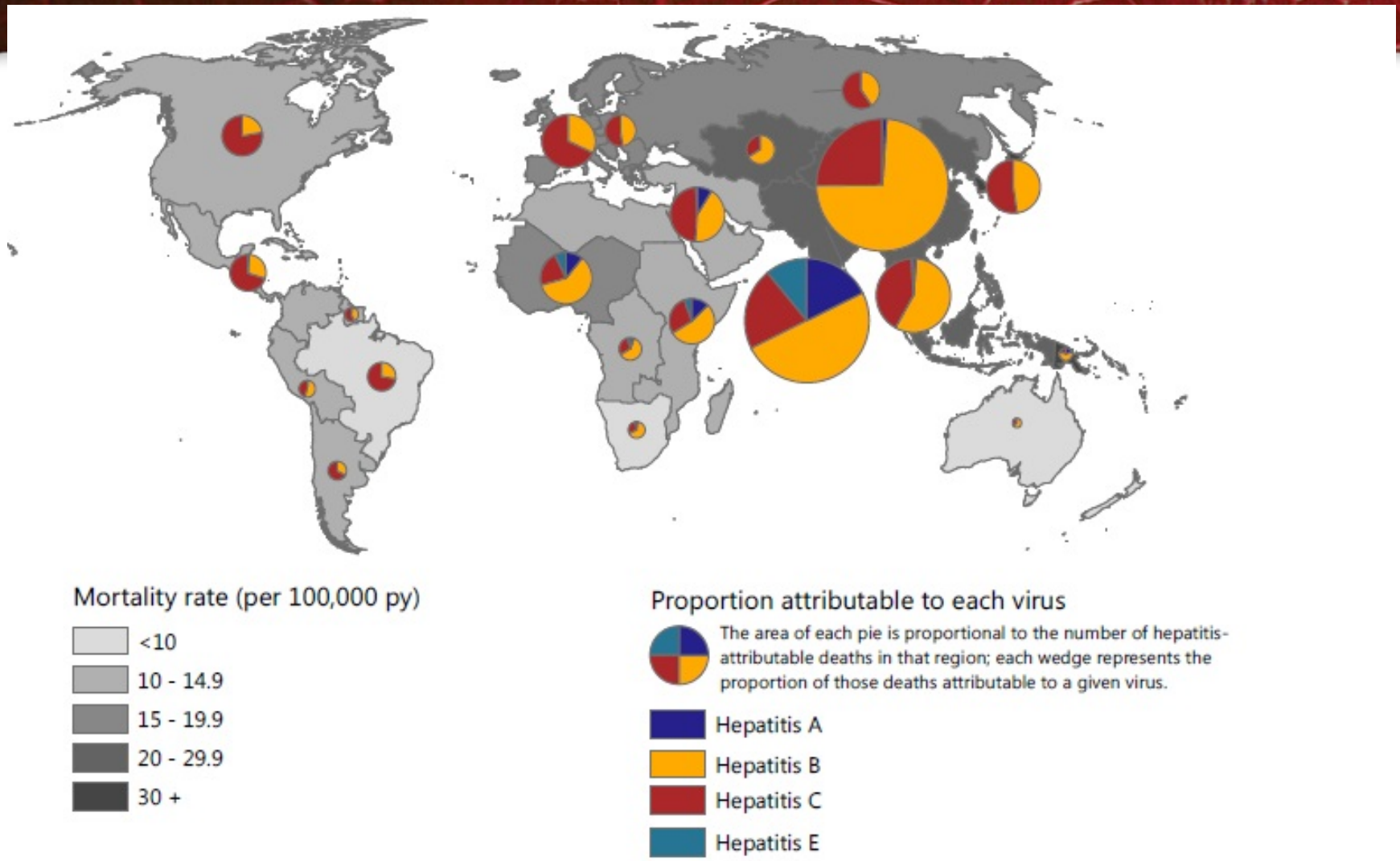
- Epidemiology
- Virology and life-cycle of HBV
- Natural history, disease and staging
- Treatment
- Treatment-related outcomes
- Preventing MTCT of HBV
- Re-activation with immune suppression therapy

# HBV - a global problem

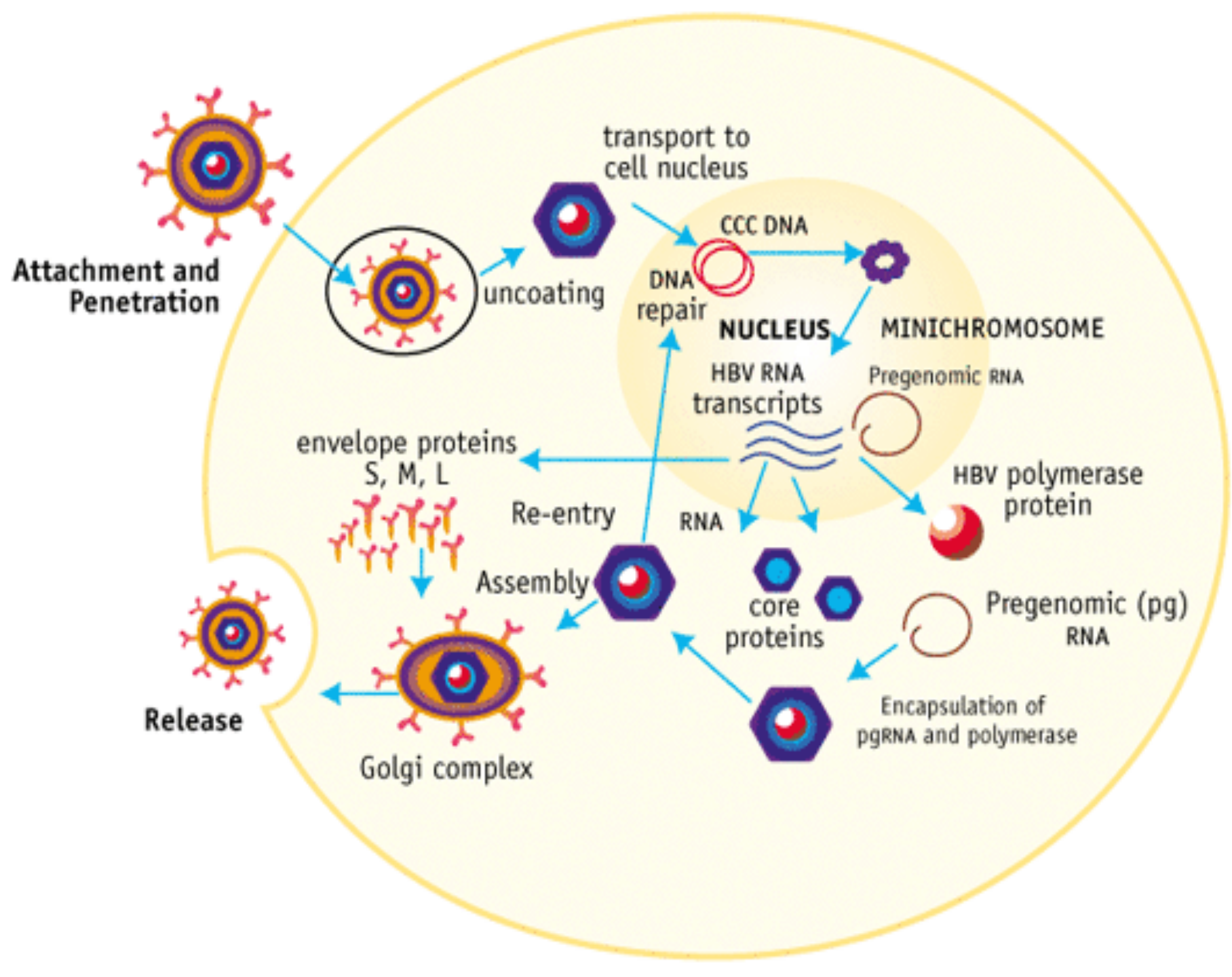



Weinbaum CM, et al. MMWR Recomm Rep. 2008;57(RR-8):1-20.

# Global mortality from viral hepatitis




(Cooke et al submitted)


Attachment and Penetration
uncoating
transport to cell nucleus
CCC DNA
DNA repair
NUCLEUS
MINICHROMOSOME
HBV RNA transcripts
Pregenomic RNA
envelope proteins S, M, L
Re-entry
RNA
HBV polymerase protein
Assembly
core proteins
Pregenomic (pg) RNA
Encapsulation of pgRNA and polymerase
Release
Golgi complex

# HBV Genotypes: Epidemiology

- HBV classified into 8 well-documented genotypes (A-H)
  - A: North America, Western Europe, and Africa
  - B and C: Asia
  - D: Southern Europe, Africa, and India
  - E: West Africa
  - F: Central and South America and Alaska
  - G: United States, France, and Germany
  - H: Central America
- Genotype B associated with less active disease, slower progression, and lower incidence of HCC than genotype C
- Genotypes A and B respond better to IFN than genotypes C and D

Kramvis A, et al. J Viral Hepat. 2005;12:456-464.

# Geographical distribution of HBV genotypes A to H

North Europe & USA - A

Mediterranean basin - D

Africa A, D&E

India A

Far East B & C

**Rare types:**

F – Latin America

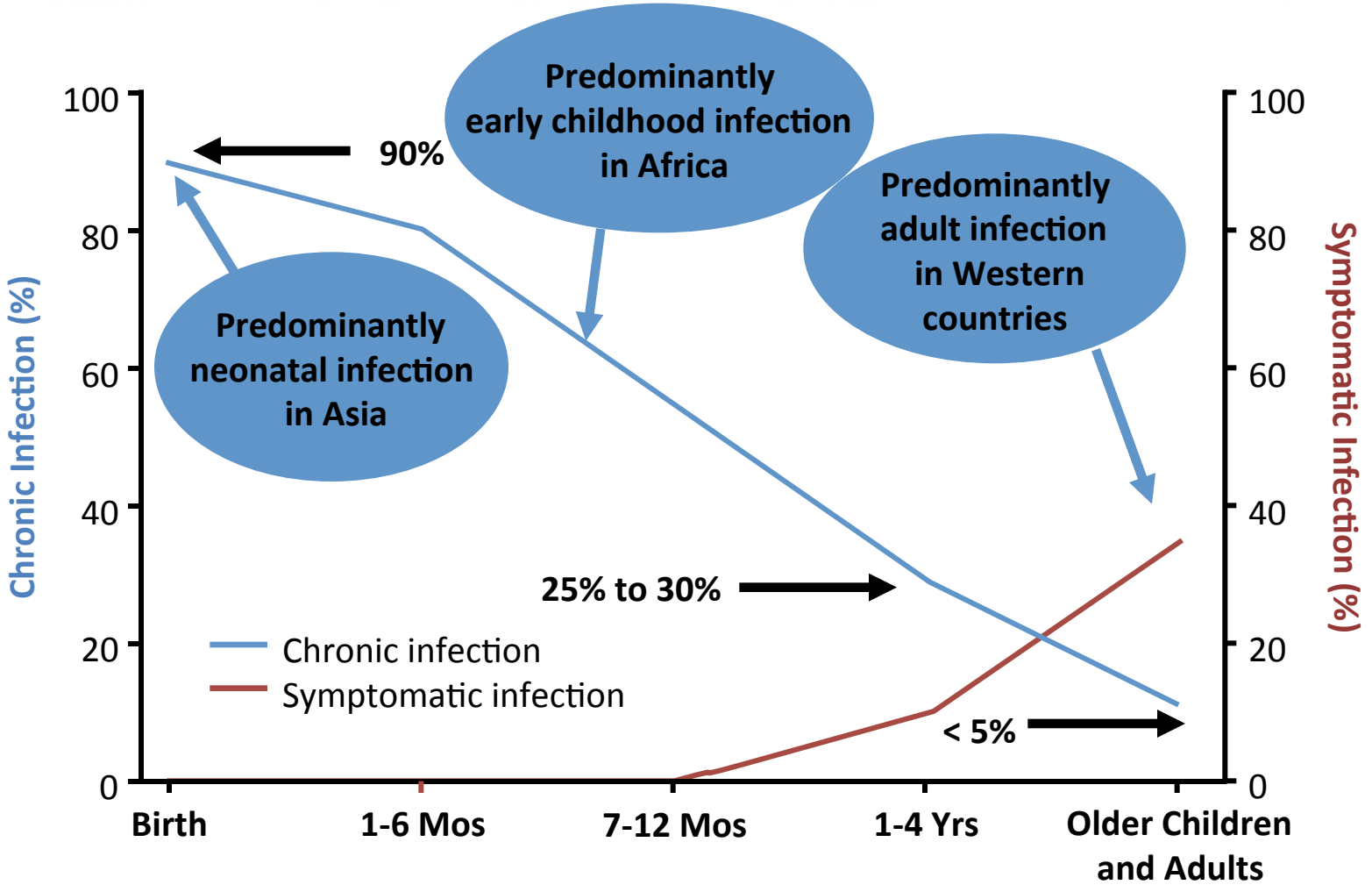
G –France, USA

H –Mexico, Latin America

# Modes of HBV Transmission

- Spread via exposure to blood and bodily fluids
- Need a break in skin or mucus membrane
- Found in semen, saliva, vaginal mucus, and tears but at levels 1000-fold lower than in serum
- Not found in urine, sweat, or stool

# Outcome of HBV Infection by Age of Transmission



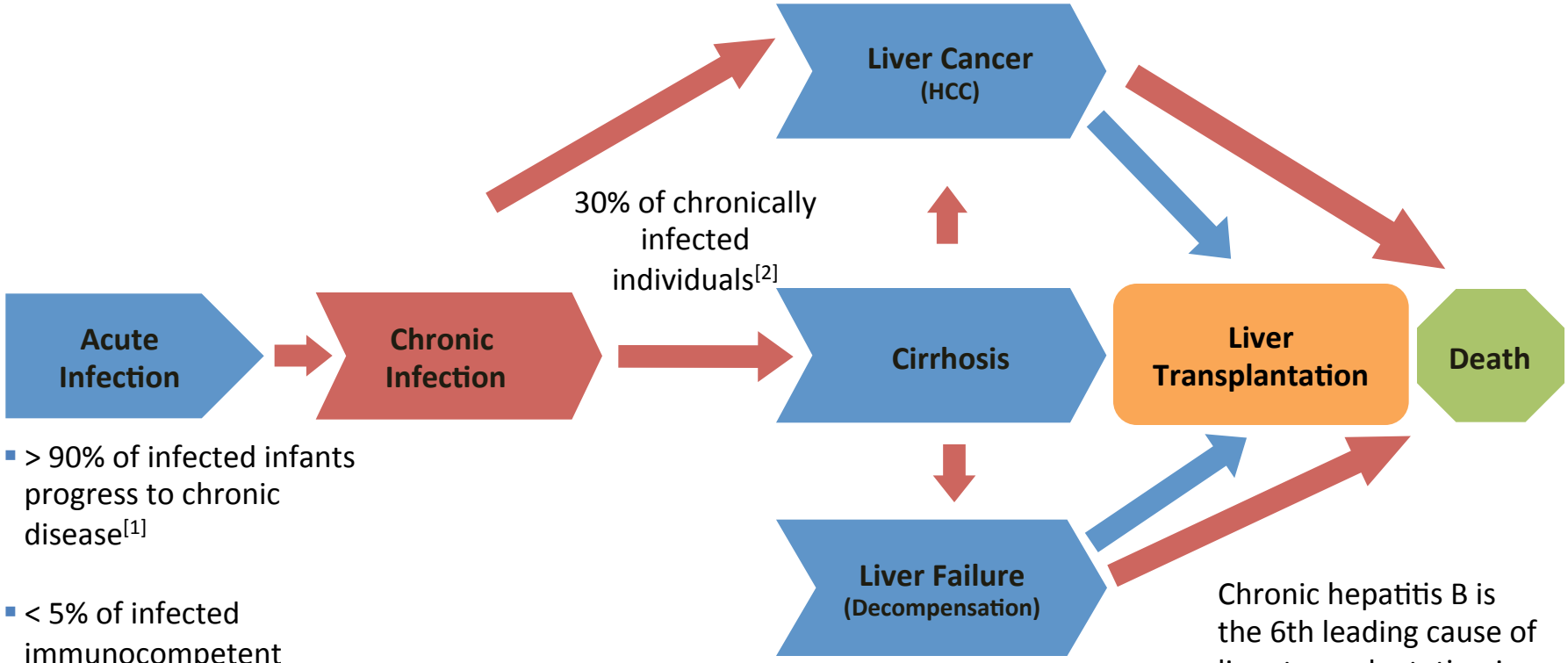

Adapted from Stanford Asian Liver Center. 2007 physician's guide to hepatitis B: a silent killer.

# Geographic Differences in Epidemiologic and Clinical Characteristics

| Characteristic | Asia/Sub-Saharan Africa | N America/W Europe |
|---|---|---|
| Endemicity | High | Low |
| Age of infection | Birth, toddler | Early adulthood |
| Primary mode of transmission | Perinatal, horizontal | Percutaneous, sexual |
| Chronicity | Common | Rare |
| Risk of cirrhosis | High | Low |
| Risk of HCC | High | Low |

Mast EE, et al. MMWR Recomm Rep. 2006;55:1-33.
Custer B, et al. J Clin Gastroenterol. 2004;38(10 suppl):S158-S168.

# Hepatitis B Disease Progression




- > 90% of infected infants progress to chronic disease[1]
- < 5% of infected immunocompetent adults progress to chronic disease[1]

23% of patients decompensate within 5 yrs of developing cirrhosis[3]

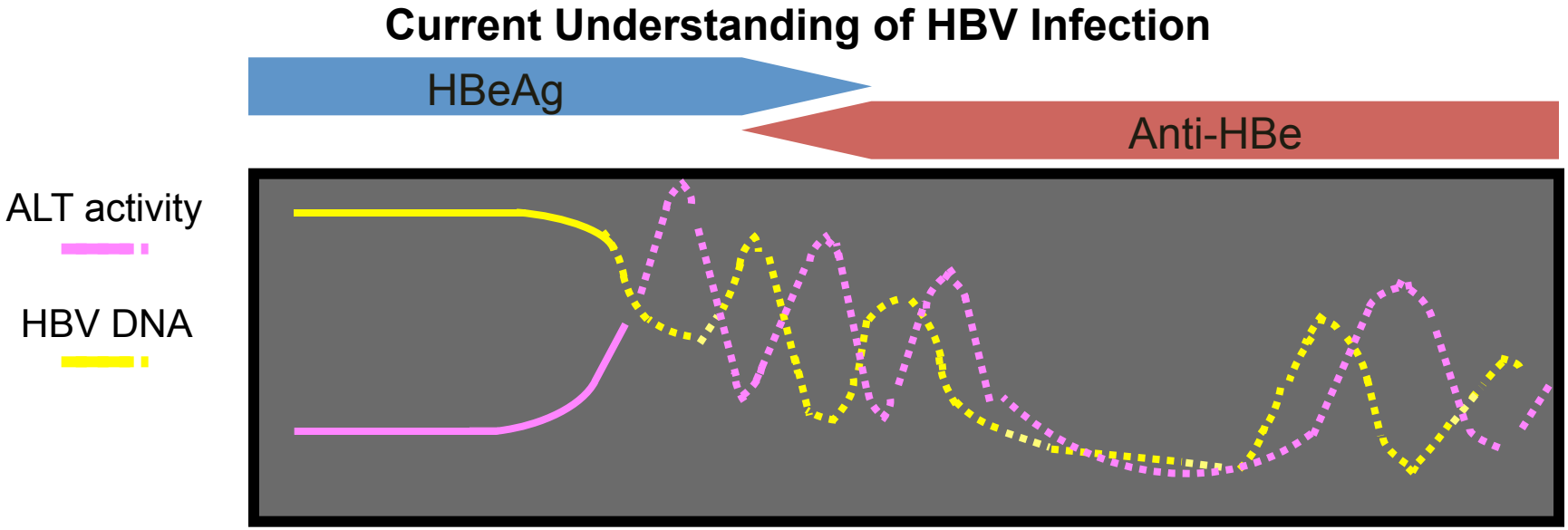
Chronic hepatitis B is the 6th leading cause of liver transplantation in the US[4]

1. CDC. HBV FAQs for health professionals. 2. Torresi J, et al. Gastroenterology. 2000;118(2 suppl 1):S83-S103. 3. Fattovich G, et al. Hepatology. 1995;21:77-82. 4. Seaberg EC, et al. Clin Transpl. 1998:17-37.

# Blood/serum markers in HBV Infection

- HBsAg
  - Marker of chronic hepatitis B when found in serum > 6 months
- Anti-HBs
  - Marker of immunity
- HBeAg
  - An index of active viral replication and high infectivity
  - Only produced by Wild Type HBV (pre-core/core-promotor mutants lose ability produce ‘e’Ag)
- Anti-HBe
  - Appears in recovery phase and is present/absent in reactivation phase
- Anti-HBc
  - Marker of past and possibly current infection
  - IgM anti-HBc – marker of recent infection
- HBV DNA
  - Reported in IU/ml (5 copies/ml = 1 IU/ml)

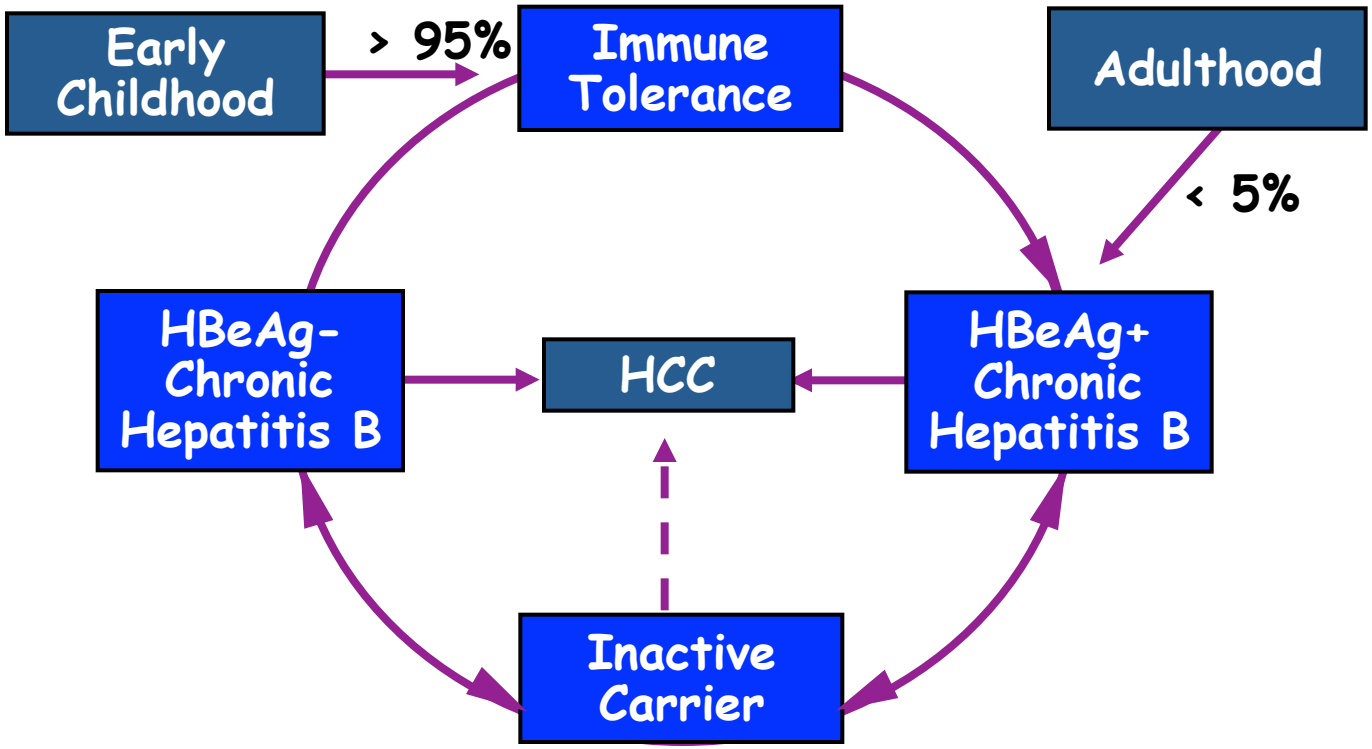
# 4 Phases of Chronic HBV Infection




| Phase | Immune Tolerant | Immune Clearance | Inactive Carrier State | Reactivation |
|---|---|---|---|---|
| Liver | Minimal inflammation and fibrosis | Chronic active inflammation | Mild hepatitis and minimal fibrosis | Active inflammation |

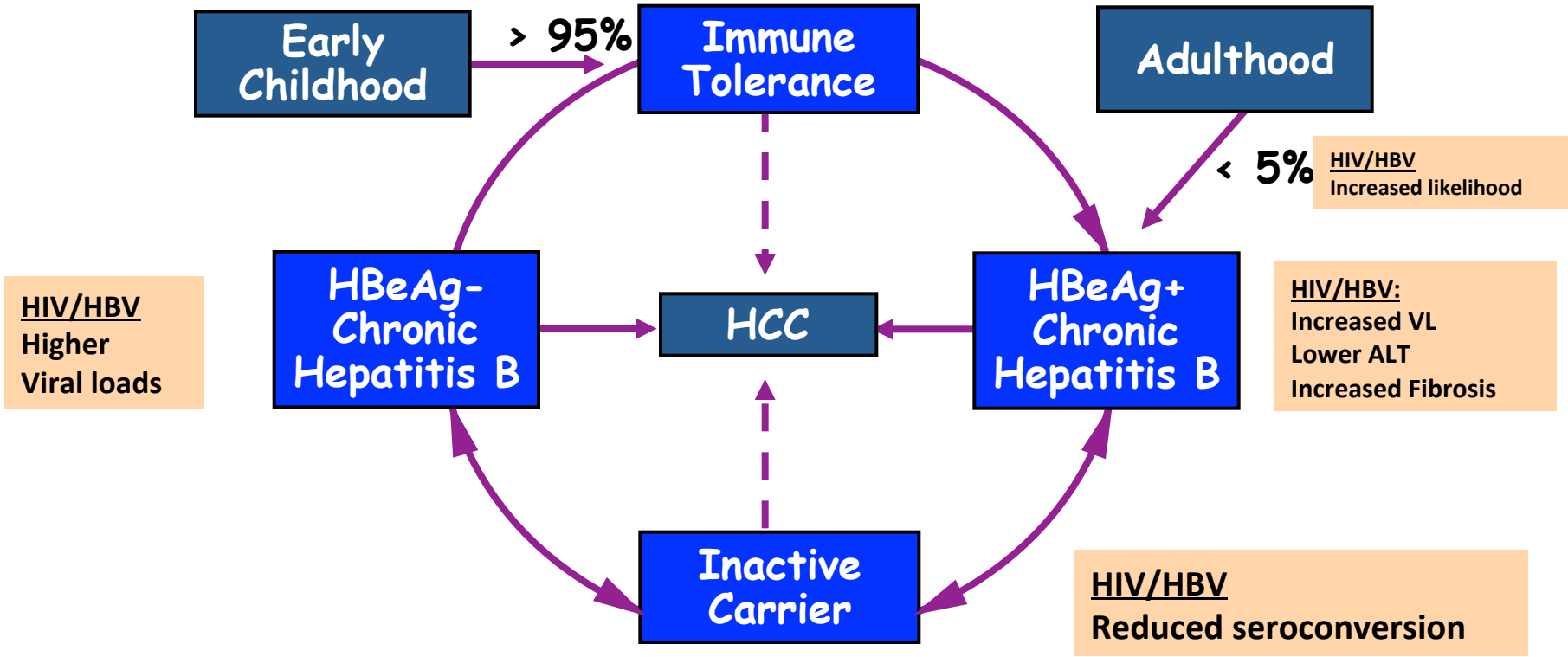
Yim HJ, et al. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology. 2006;43:S173-S181. 

# Natural history of HBV infection – a continuum of interplay between host/virus




Chen DS, *et al. J Gastroenterol Hep.* 1993;8:470–475; Seeff L, *et al. N Engl J Med.* 1987;316:965–970

# Natural history of HBV infection – where does HIV co-infection fit in?




Chen DS, *et al. J Gastroenterol Hep.* 1993;8:470-475; Seeff L, *et al. N Engl J Med.* 1987;316:965-970

# Treatment of HBV - aims

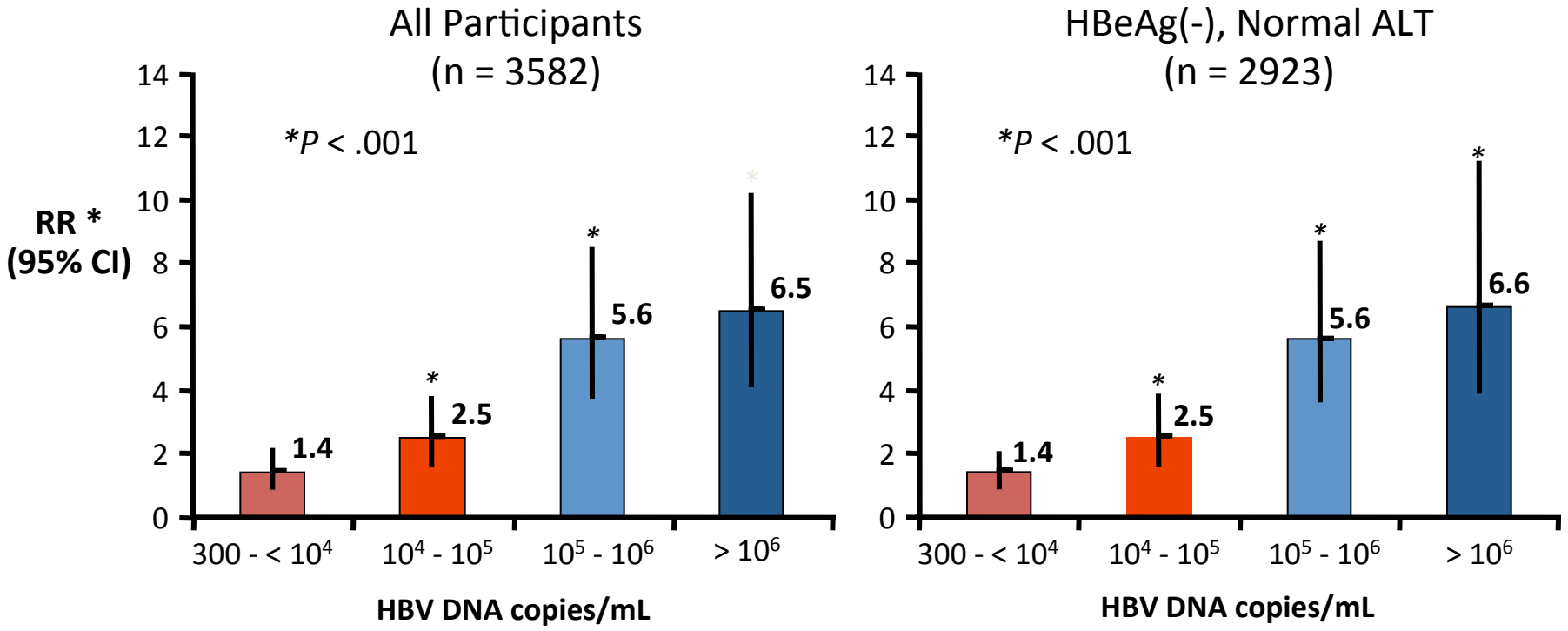
- Ultimate aims
  - Prevent progression to ESLD/death
  - Prevent HCC
  - Prevent transmission of HBV (NB: Vaccination also available)

# When do we need to Rx HBV?

- Everybody with detectable HBV DNA?
- Based on HBV DNA levels?
- Those with evidence of significant liver disease?
  - Based on abnormal ALTs?
  - Histological activity/Fibrosis scores?

# Level of HBV DNA (c/ml) at entry & progression to cirrhosis in *population-based cohort studies*

**3582 HBsAg untreated asian carriers**
**mean follow-up 11 yrs → 365 patients newly diagnosed with cirrhosis**

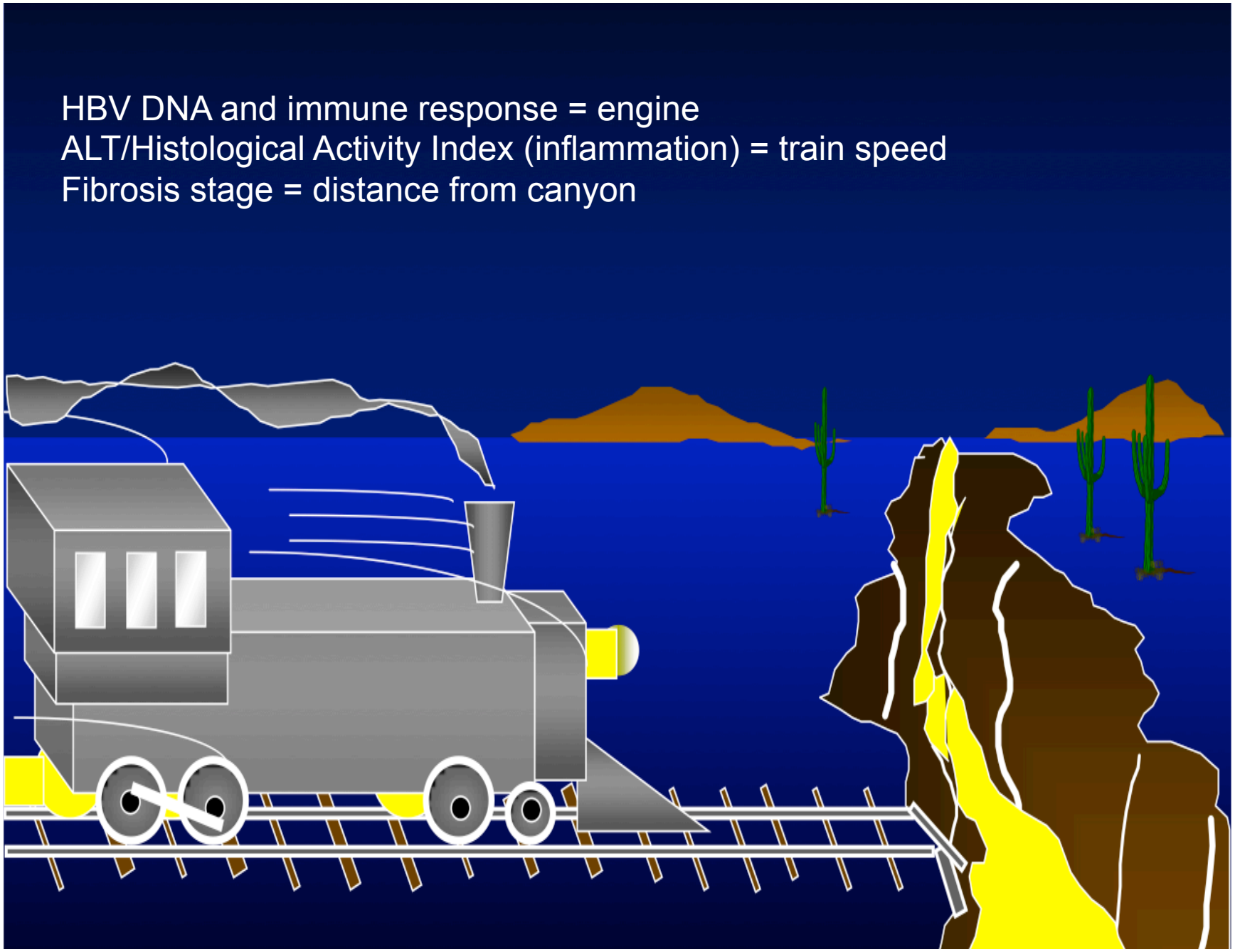



* Adjusted for age, sex, cigarette smoking, and alcohol consumption.

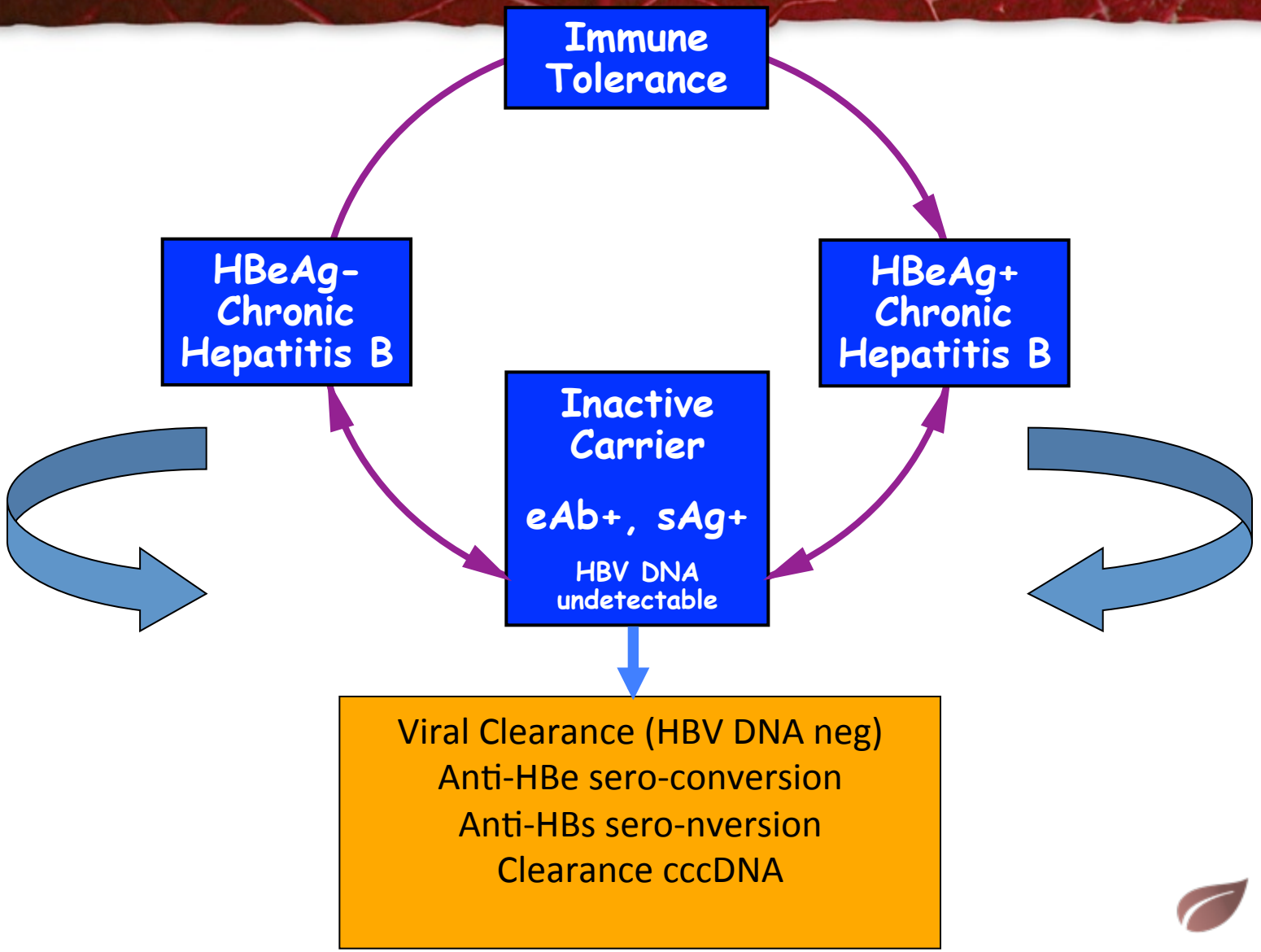
HBV-DNA viral load (> $10^4$ cp/ml) strongest predictor of progression to cirrhosis independent of ALT and HBeAg status

Iloeje UH, Gastroenterology 2006; 130: 678-686

HBV DNA and immune response = engine
ALT/Histological Activity Index (inflammation) = train speed
Fibrosis stage = distance from canyon



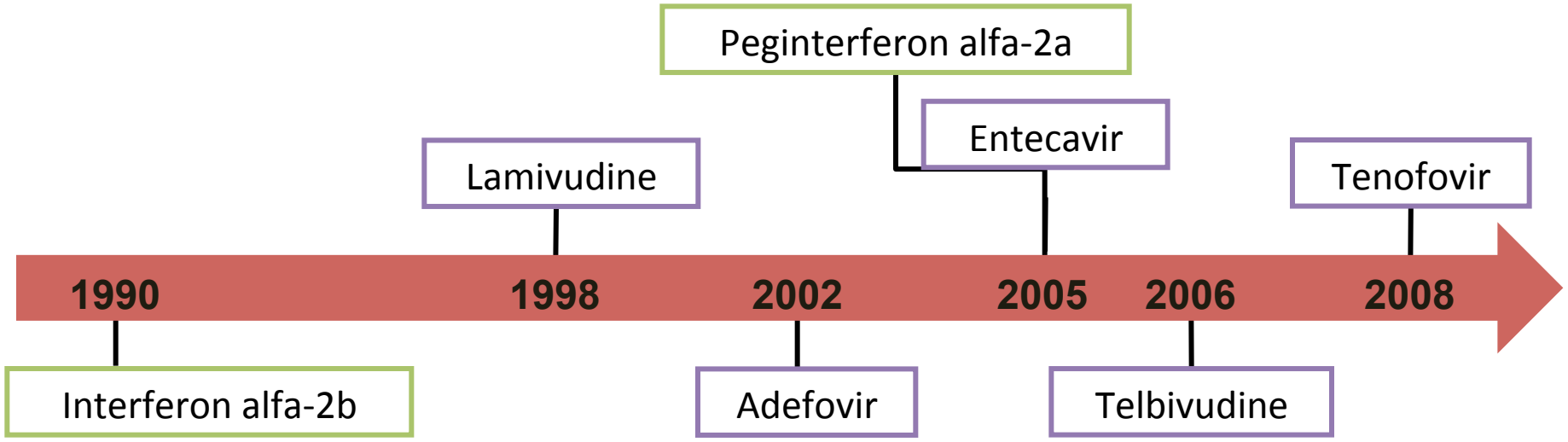
# What does Rx aim to achieve?



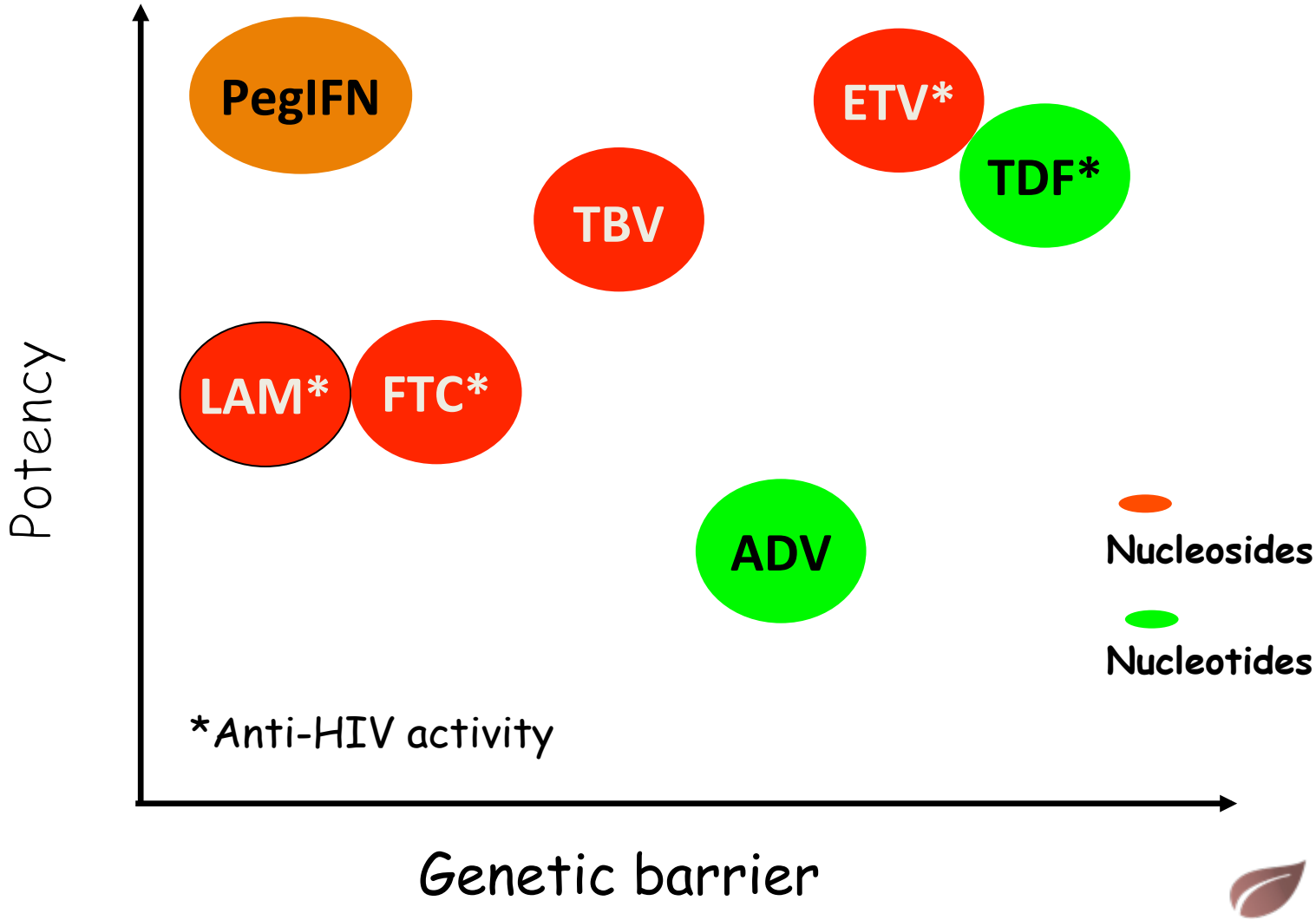
# End-points of HBV Treatment

- Primary
  - HBV DNA suppression
- Secondary
  - Normalisation of ALT
  - Improvement in histology
  - Anti-HBe sero-conversion (for HBeAg+)
  - HBsAg loss and anti-HBs sero-conversion

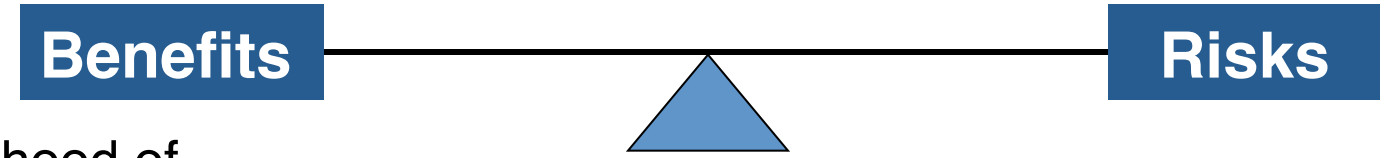
# HBV Treatment Landscape



# Anti-HBV drugs



# When to Start HBV Treatment?




Likelihood of
- Adverse outcome without treatment
- Long-lasting response

Patient's age and preference
Costs

Adverse effects
Drug resistance

**Likelihood of adverse outcome without treatment**

**Activity and stage of liver disease at presentation**

**Risk of cirrhosis/HCC in the next 10-20 yrs**

**Likelihood of long-term benefit with treatment**

# Three key inter-linked factors in the decision to treat

- Age
  - <30yrs vs. >30yrs
  - FH of HCC
- Level of fibrosis/inflammation
  - Cirrhosis
  - F2+ fibrosis
  - Abnormal liver enzymes
- HBV DNA levels
  - >20 000 IU/ml

# Determining Treatment Candidacy for Chronic Hepatitis B: Guidelines

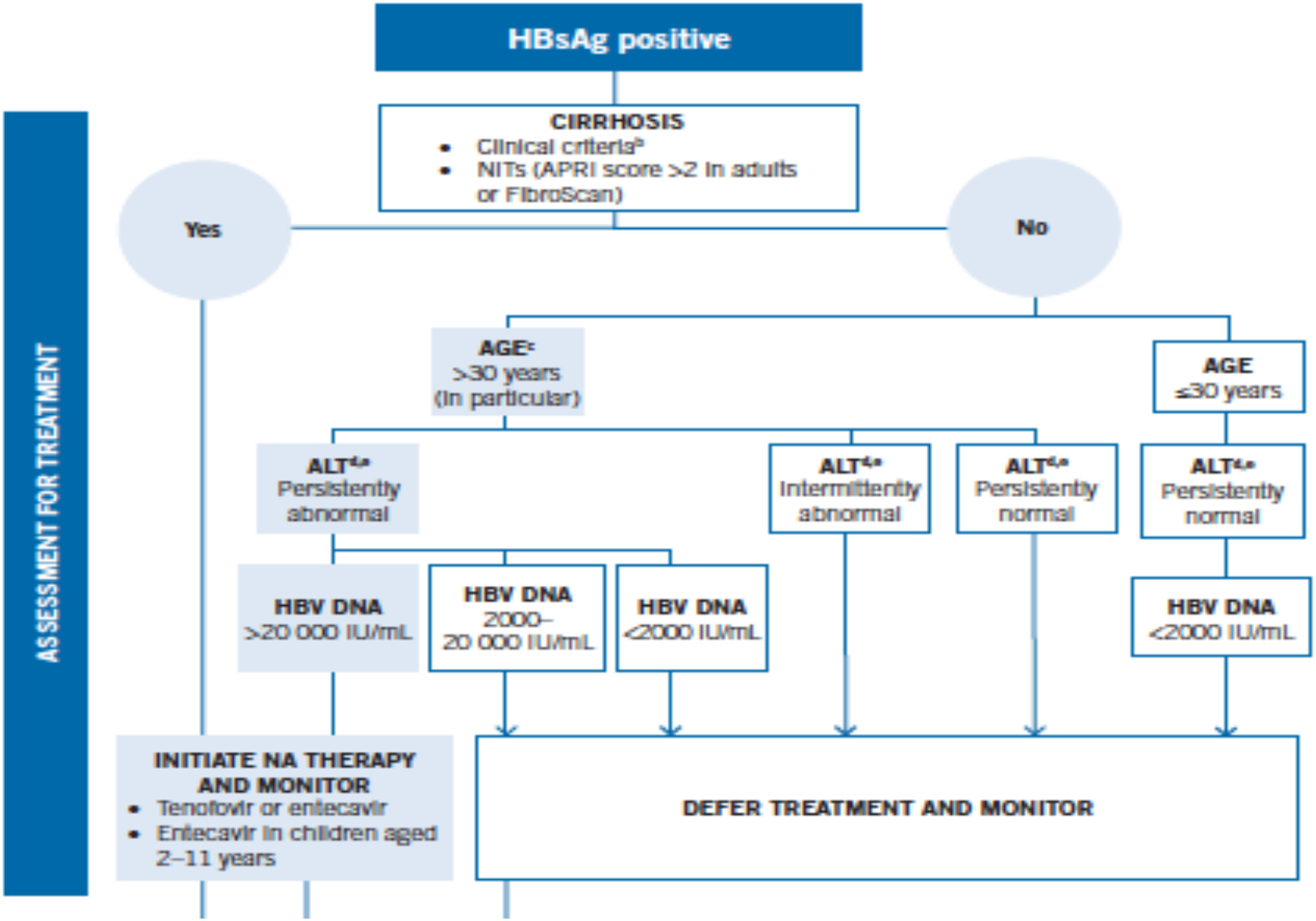
| Guidelines | HBeAg Positive | | HBeAg Negative | |
|---|---|---|---|---|
| | HBV DNA, IU/mL | ALT | HBV DNA, IU/mL | ALT |
| AASLD 2009[1] | > 20,000 | > 2 x ULN or positive biopsy* | ≥ 20,000 | ≥ 2 x ULN or positive biopsy* |
| EASL 2009[2] | > 2000 | > ULN | > 2000 | > ULN |
| APASL 2008[3] | ≥ 20,000 | > 2 x ULN | ≥ 2000 | > 2 x ULN |
| NIH Consensus Conference 2009[4] | > 20,000 | > 2 x ULN or positive biopsy* | ≥ 20,000 | ≥ 2 x ULN or positive biopsy* |

*Moderate/severe inflammation or significant fibrosis.

- Expert guidelines also published with recommendations specific for HBV management in US[5] and more recently for Asian Americans[6]
  - Some key differences between these guidelines

1. Lok AS, et al. Hepatology. 2009;50:661-662. 2. EASL. J Hepatol. 2009;50:227-242. 3. Liaw YF, et al. Hepatol Int. 2008;3:263-283. 4. Degerekin B, et al. Hepatology. 2009;S129-S137. 5. Keeffe EB, et al. Clin Gastroenterol Hepatol. 2006;6:1315-1341. 6. Tong MJ, et al. Dig Dis Sci. 2011;56:3143-3162.

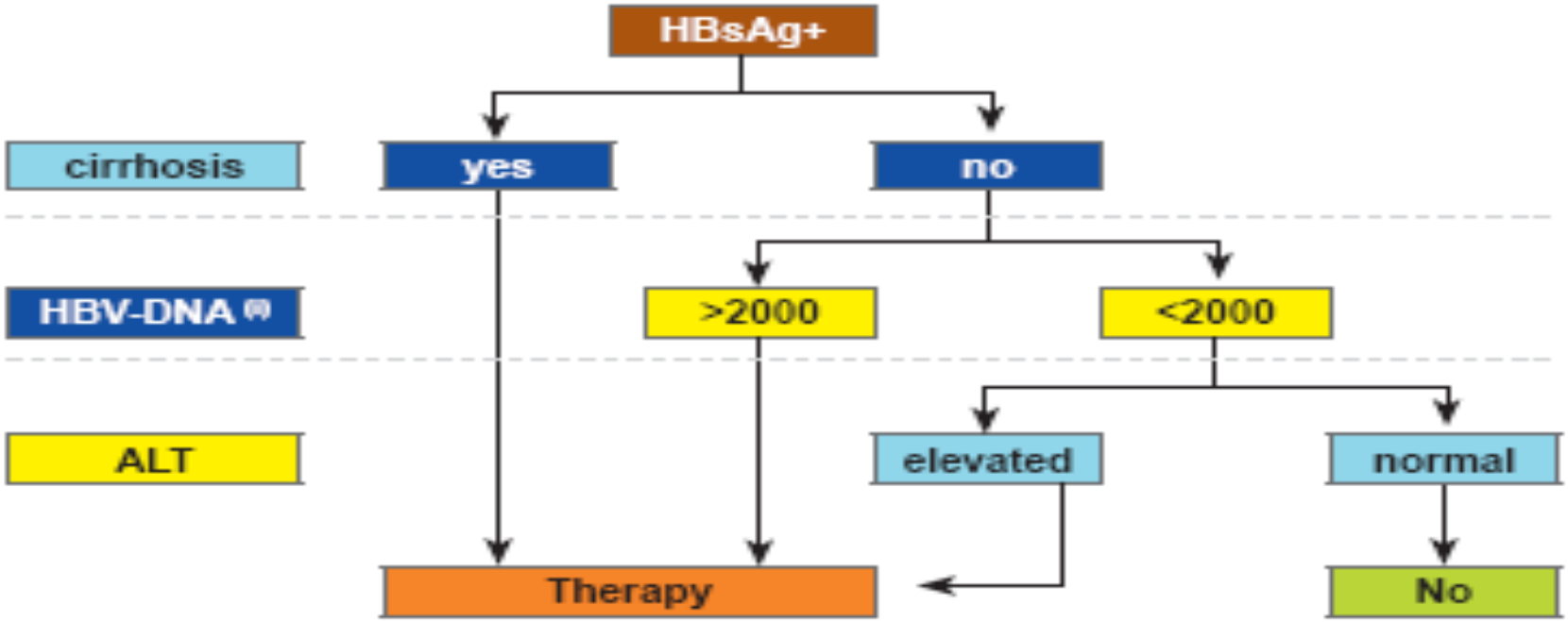
## ALGORITHM OF WHO RECOMMENDATIONS ON THE MANAGEMENT OF PERSONS WITH CHRONIC HEPATITIS B INFECTION[a]




WHO Guidelines 2015

# EACS Guidelines 2014 – HBV in HIV+

## Assessment of treatment indication for HBV infection in HIV-positive individuals




**Note:** In patients with significant liver fibrosis (F2-F3), anti-HBV treatment might be considered even when serum HBV-DNA is below 2000 IU/mL and liver enzymes are not elevated.

# Current Guideline Recommendations for First-line Therapy

- Peginterferon alfa-2a
  - Exceptions: pregnancy, chemotherapy prophylaxis, decompensated cirrhosis, acute infection
- Entecavir
- Tenofovir

EASL. J Hepatol. 2009;50:227-242. Liaw YF, et al. Hepatol Int. 2008;2:263-283.
Lok AS, et al. Hepatology. 2009;50:661-662.

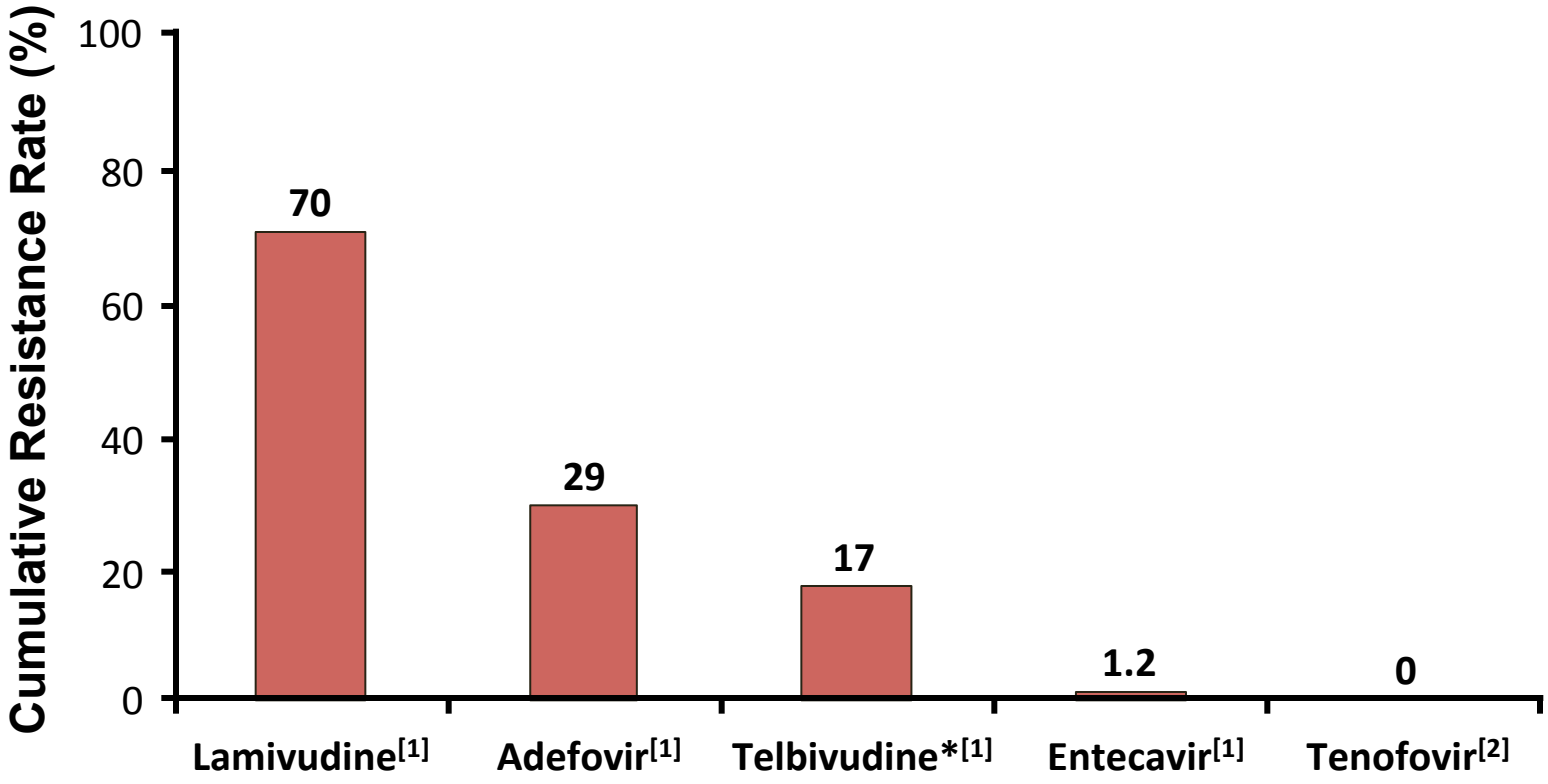
# PegIFN vs. Nucleos(t)ide Analogues

| PegIFN | | Nucleos(t)ide Analogues | |
|---|---|---|---|
| **Pro** | **Con** | **Pro** | **Con** |
| ▪ Finite course of therapy<br>▪ No resistance<br>▪ Higher rate of HBeAg loss in 1 yr<br>▪ Higher rate of HBsAg loss with short duration therapy* | ▪ SC administration<br>▪ Frequent AEs<br>▪ Contraindicated in patients with cirrhosis, in pregnancy, with acute hepatitis B, and who are immunosuppressed | ▪ PO administration<br>▪ Infrequent AEs<br>▪ Safe at all stages of disease, including decompensated cirrhosis<br>▪ Safe in immuno-compromised populations<br>▪ Selected drugs probably safe in pregnancy | ▪ Need for long-term or indefinite therapy<br>▪ Potential for drug resistance |

*Particularly for HBeAg-positive patients with genotype A infection.

Lok AS, et al. Hepatology. 2007;45:507-539. Lok AS, et al. Hepatology. 2009;50:661-662. Lok AS. Hepatology. 2010;52:743-747. Buster EH, et al. Gastroenterology. 2008;135:459-467. Lange CM, et al. Hepatology. 2009;50:2001-2006.

# 5-Yr Rates of Resistance With Oral Agents in Nucleos(t)ide-Naive Patients



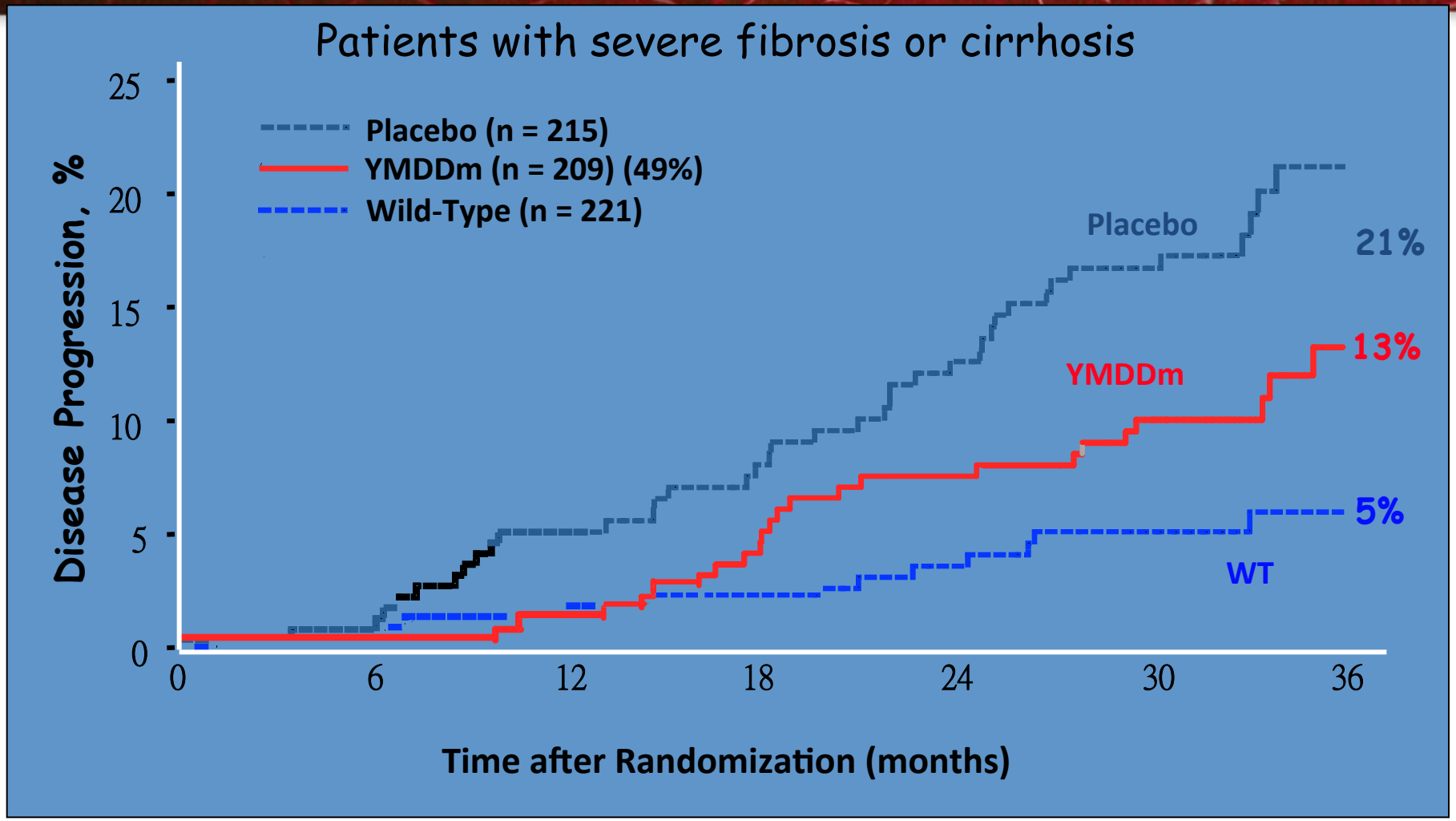

*Telbivudine rate determined at Yr 2.

1. EASL. J Hepatol. 2009;50:227-242. 2. Marcellin P, et al. AASLD 2011. Abstract 1375.

# Genetic Barrier

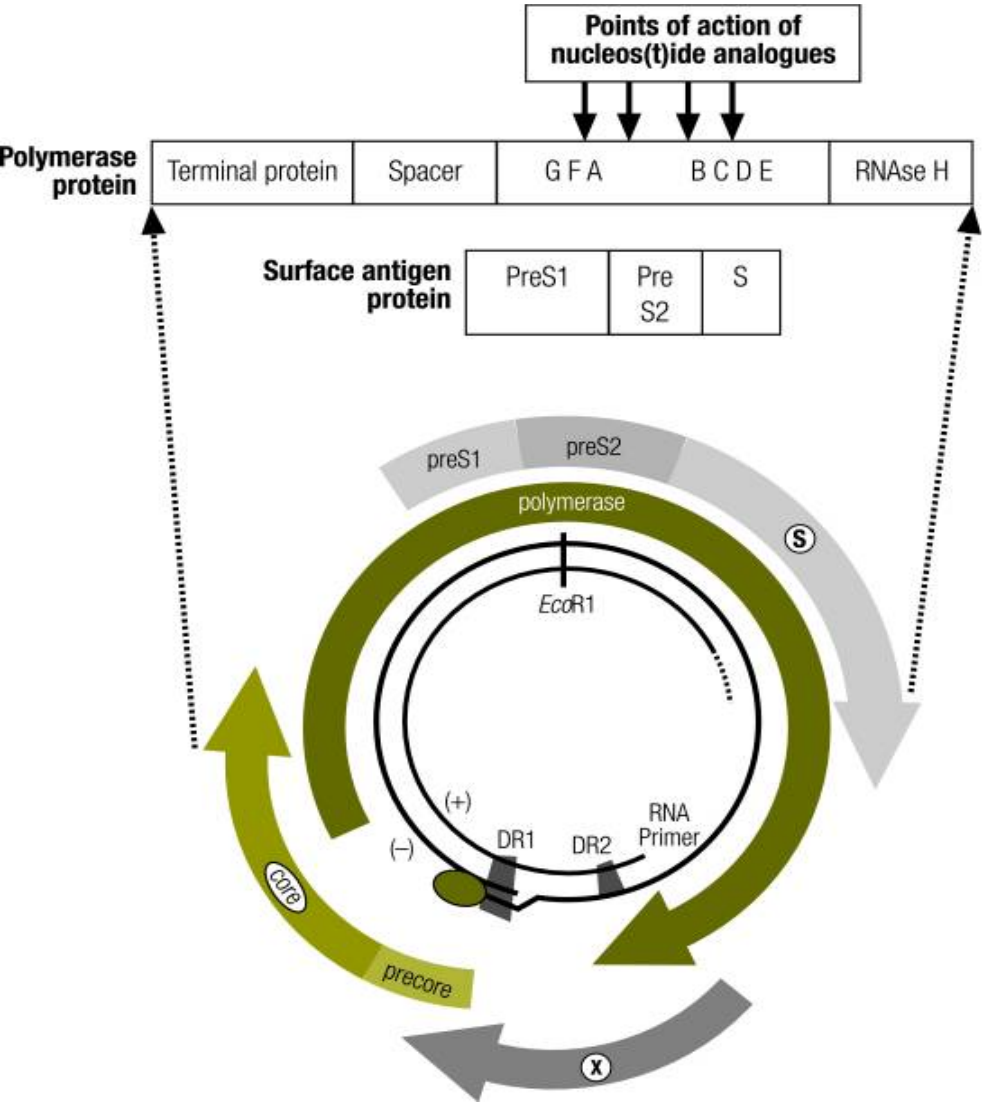
- The number of substitutions needed for primary antiviral drug resistance
  - LAM/TBV: rtM204V/I
  - ADV: rtN236T
- Combination of low genetic barrier drugs: at least 2 mutations required
- ETV: at least 3 mutations required:
  - rtL180M + rtM204V + one of
  - rtT184 or rtS202 or rtM250 change

# Impact of lamivudine resistance on progression of liver disease



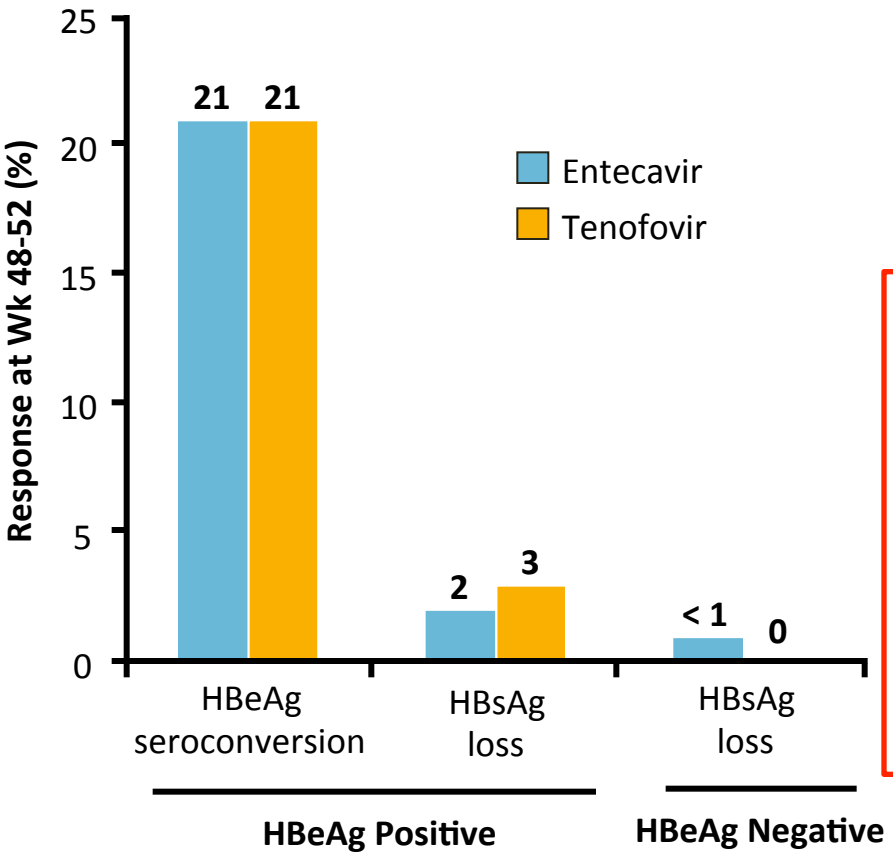

Liaw, N Engl J Med. 2004

# More than just ‘drug resistance’




- Overlapping Pol and S
- Mutations in Pol – changes in S
- ADASMs – Antiviral Drug-Associated S mutations
- ADAPVEMS – Antiviral Drug Associated Potentially Vaccine (and detection) Escape Mutations
- Associated with L-nucleosides and Entacavir, possibly with adefovir

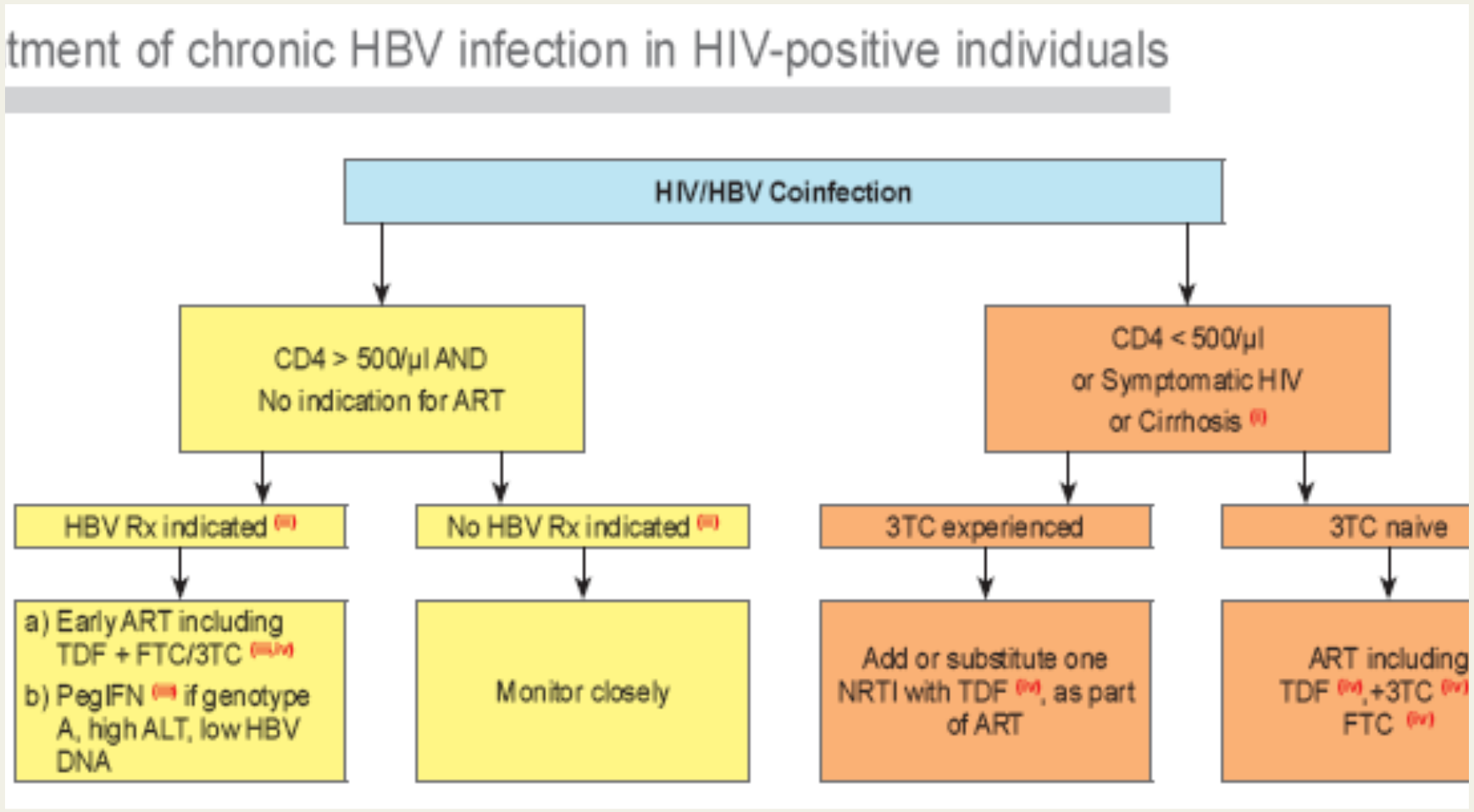
# Selection of Entecavir vs Tenofovir: Either Is an Excellent Choice for Most Patients




| Parameter | Entecavir | Tenofovir |
|---|---|---|
| Log HBV DNA ↓ at Wk 48-52 | | |
| ▪ HBeAg positive | 6.9 | 6.2 |
| ▪ HBeAg negative | 5.0 | 4.6 |
| Genotypic resistance, % | | |
| ▪ NA naive | 1.2 (Yr 5) | 0 (Yr 3) |
| ▪ Lamivudine experienced | 51 (Yr 5) | NR |
| Pregnancy rating | Class C | Class B |
| AEs | None | Renal toxicity; ↓ BMD |

Lok AS. Hepatology. 2010;52:743-747.

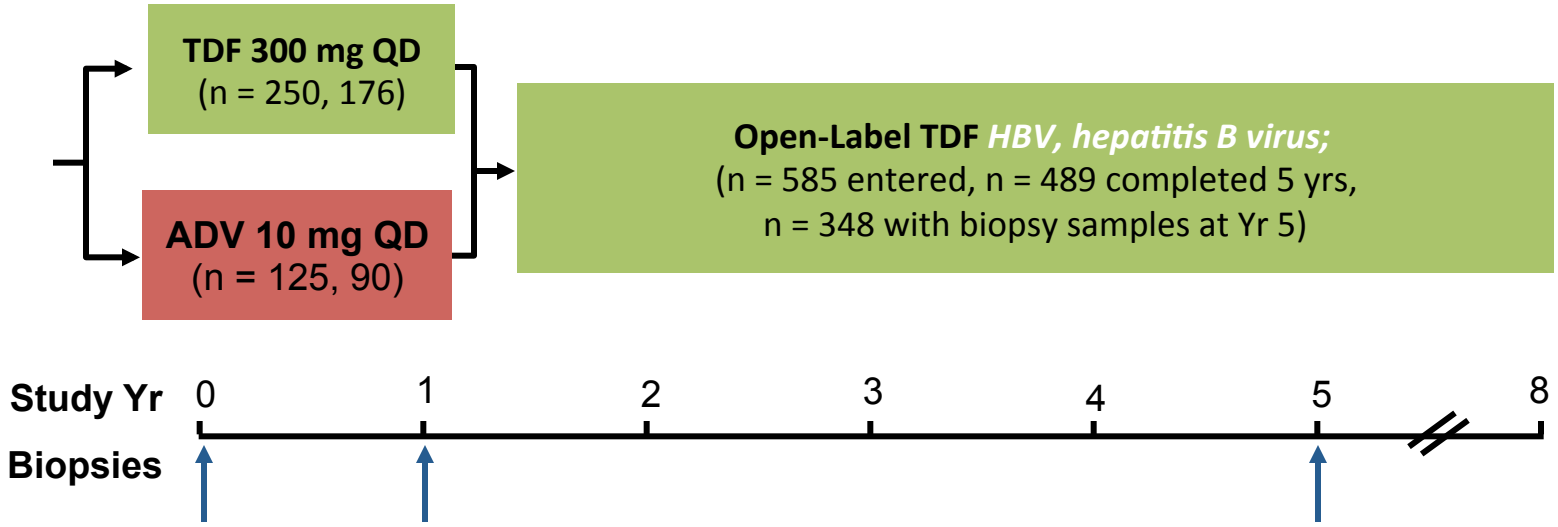
# Management options for HIV/HBV co-infection




EACS Treatment Guidelines 2014

# Studies 102/103: Long-term Histology Study During Open-Label Follow-up

- 2 randomized, double-blind, placebo-controlled phase III trials
- All pts received open-label TDF after Yr 1 for a total study duration of 8 yrs*
- Liver biopsies obtained at baseline, Yr 1, and Yr 5 (nonmandatory)




*FTC could be added for confirmed viremia on/after Wk 72.

13. Marcellin P, et al. Lancet. 2013;381:468-475.

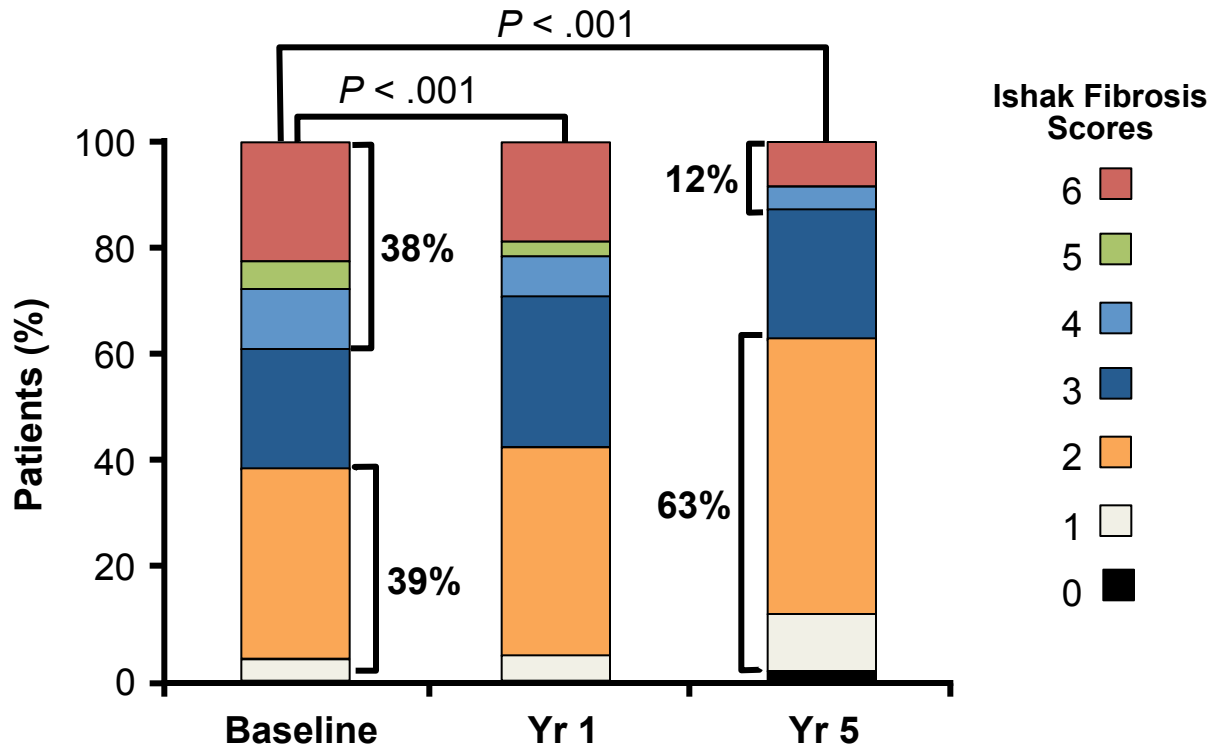
# Non-histologic Efficacy Results at Yr 5

| On Treatment Response, % (n/N)[14] | HBeAg- Patients | HBeAg+ Patients |
|---|---|---|
| HBV DNA < 400 copies/mL | 99 (292/295) | 97 (170/175) |
| ALT ≤ 1 x ULN | 85 (236/277) | 73 (124/169) |
| HBeAg loss | -- | 49 (81/165) |
| HBsAg loss | 0 | 10* (6.8-14.7) |

Marcellin P, et al. Lancet. 2013;381:468-475. Marcellin P. et al. AASLD 2013. Abstract 926.

# 96% of Pts Treated With Tenofovir Had Stable or Improved Fibrosis at Yr 5

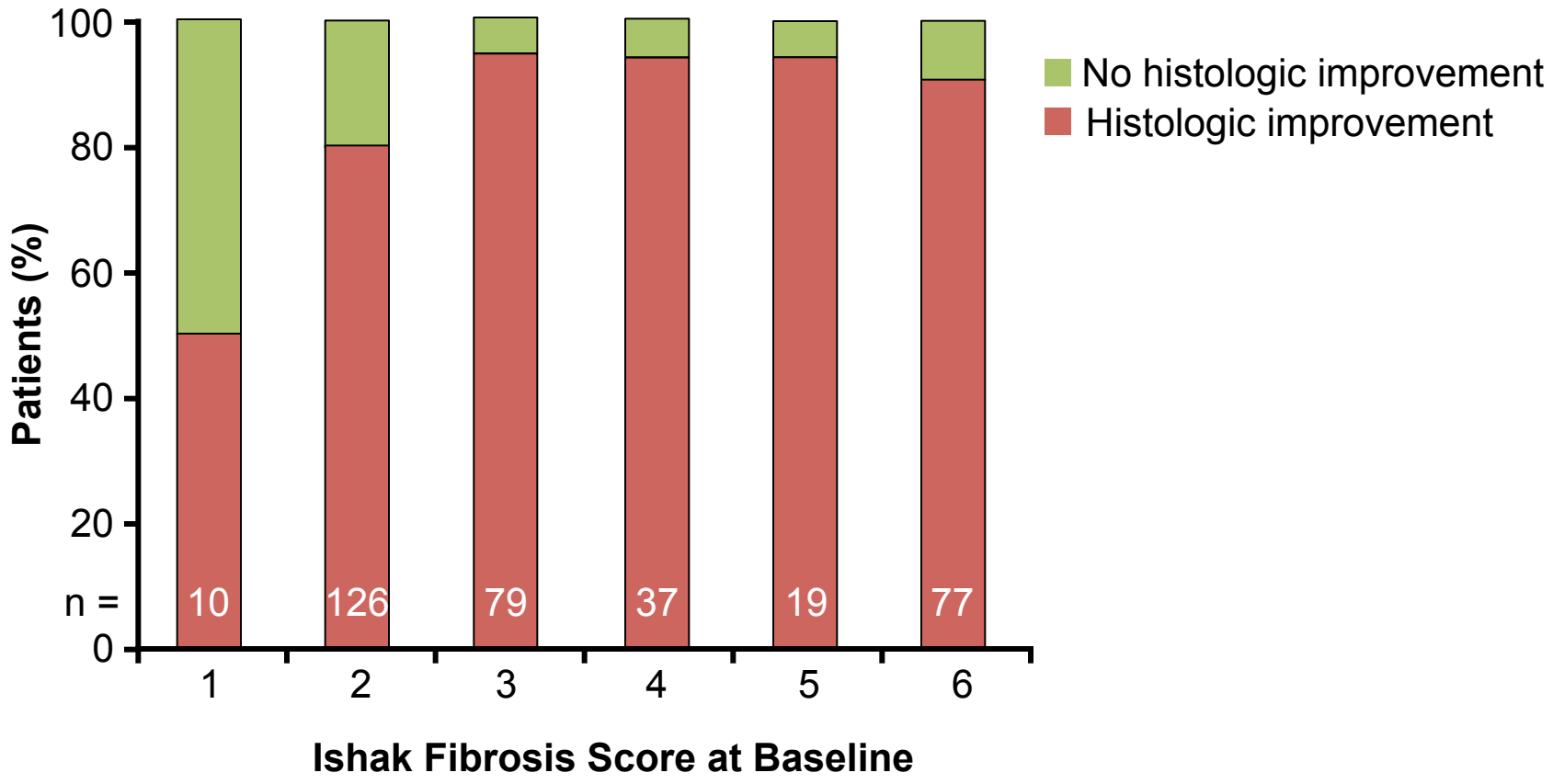
- Pts with Ishak score ≥ 4: 38% at baseline, 12% at Yr 5
- Pts with cirrhosis (Ishak score ≥ 5): 28% at baseline, 8% at Yr 5 (n=96)




N = 348 matched biopsies

Marcellin P, et al. Lancet. 2013;381:468-475.

# Fibrosis Improvement at Yr 5 by Baseline Ishak Fibrosis Score

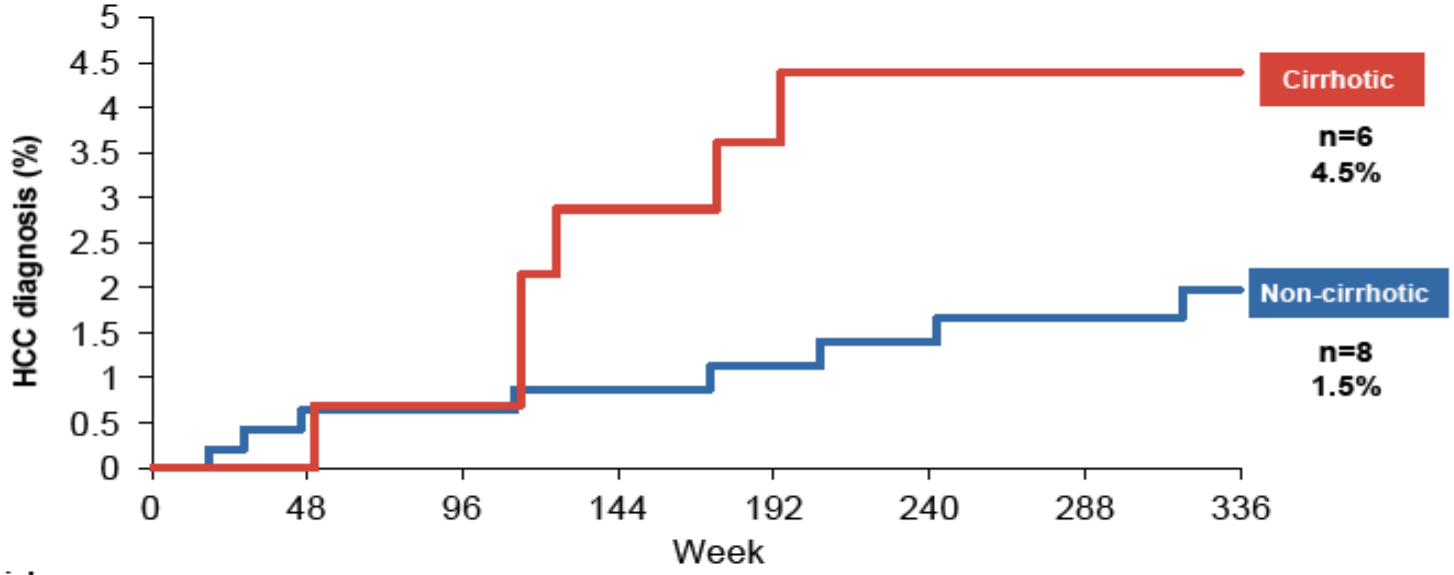



Marcellin P, et al. Lancet. 2013;381:468-475.

# Success in clinical end-points

## Tenofovir Studies 102/103

## HCC Incidence Based on Cirrhosis Status at Baseline



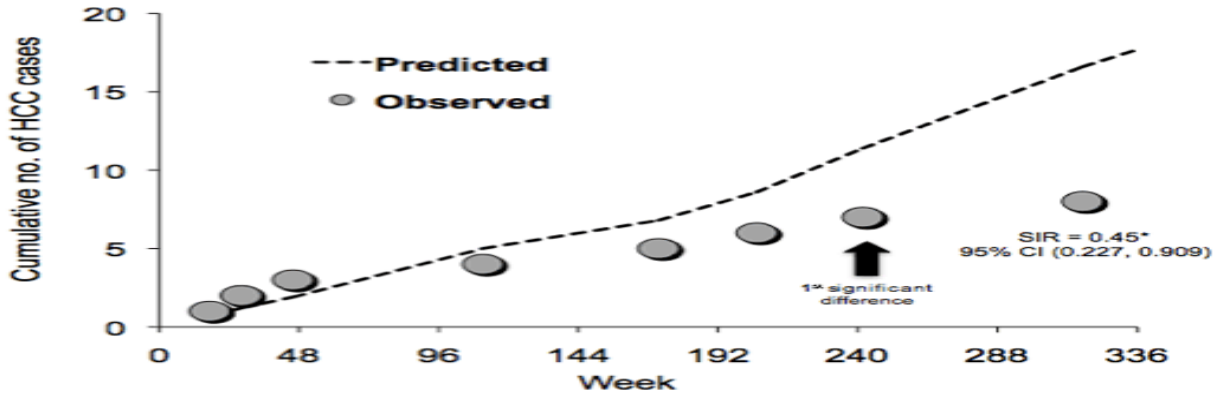

| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Non-cirrhotic | 482 | 453 | 425 | 396 | 377 | 360 | 343 | 324* |
| Cirrhotic | 152 | 146 | 137 | 132 | 126 | 120 | 115 | 109* |

*Patients completing 336 weeks in study as defined by protocol
Kim WR, et al. J Hepatol 2013 Supp 1;58(43):S19 - Oral#43

REACH-B is a risk calculator developed in non-cirrhotic pts so
It may underestimate the risk

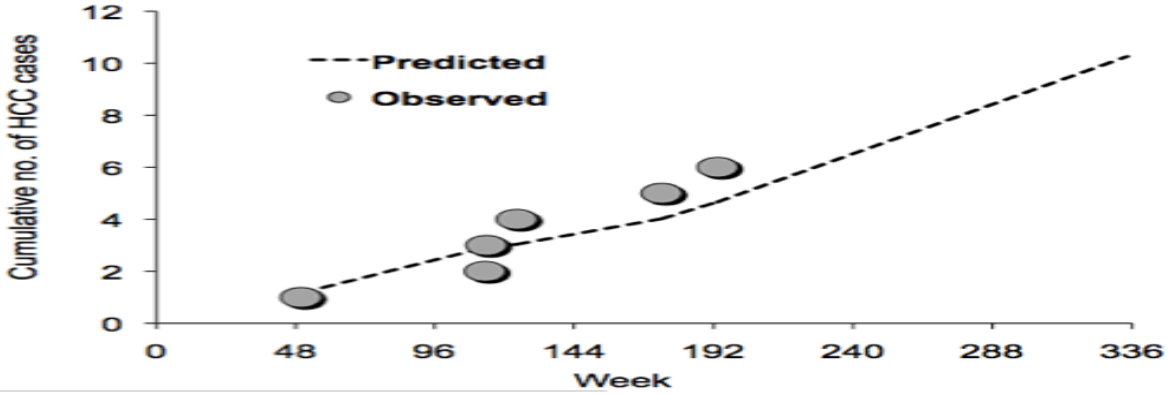
# However, cirrhotics remain ‘at risk’

## Observed vs Predicted HCC Cases: Noncirrhotics



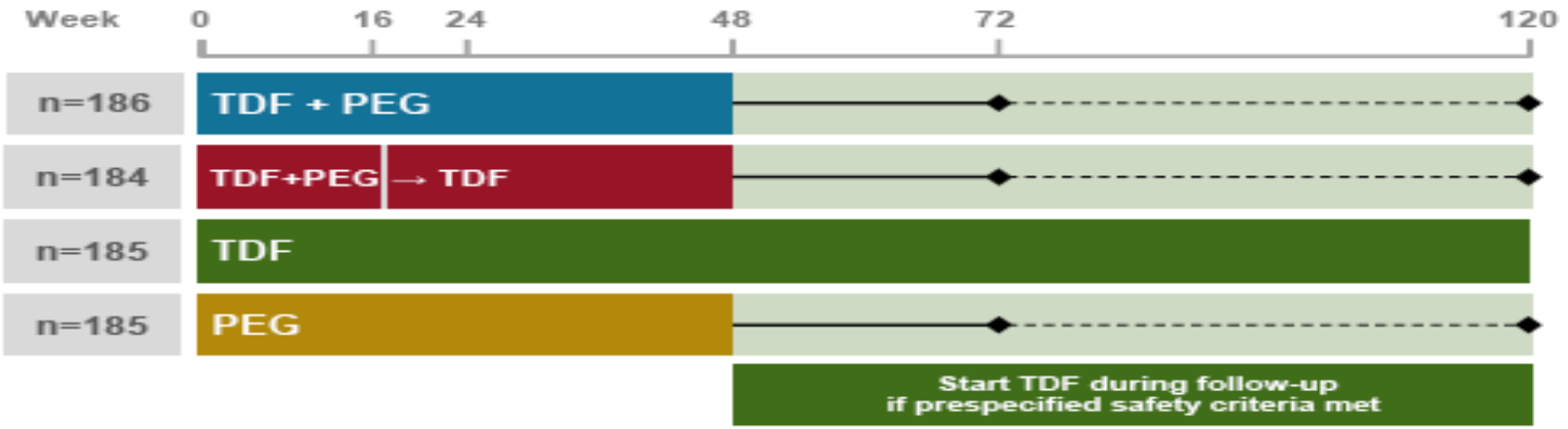

*Statistically significant at nominal α-level of 0.05.
CI, confidence interval; SIR, standardized incidence ratio.

## Observed vs Predicted HCC Cases: Cirrhotics



# Combining Nuc + PegIFN

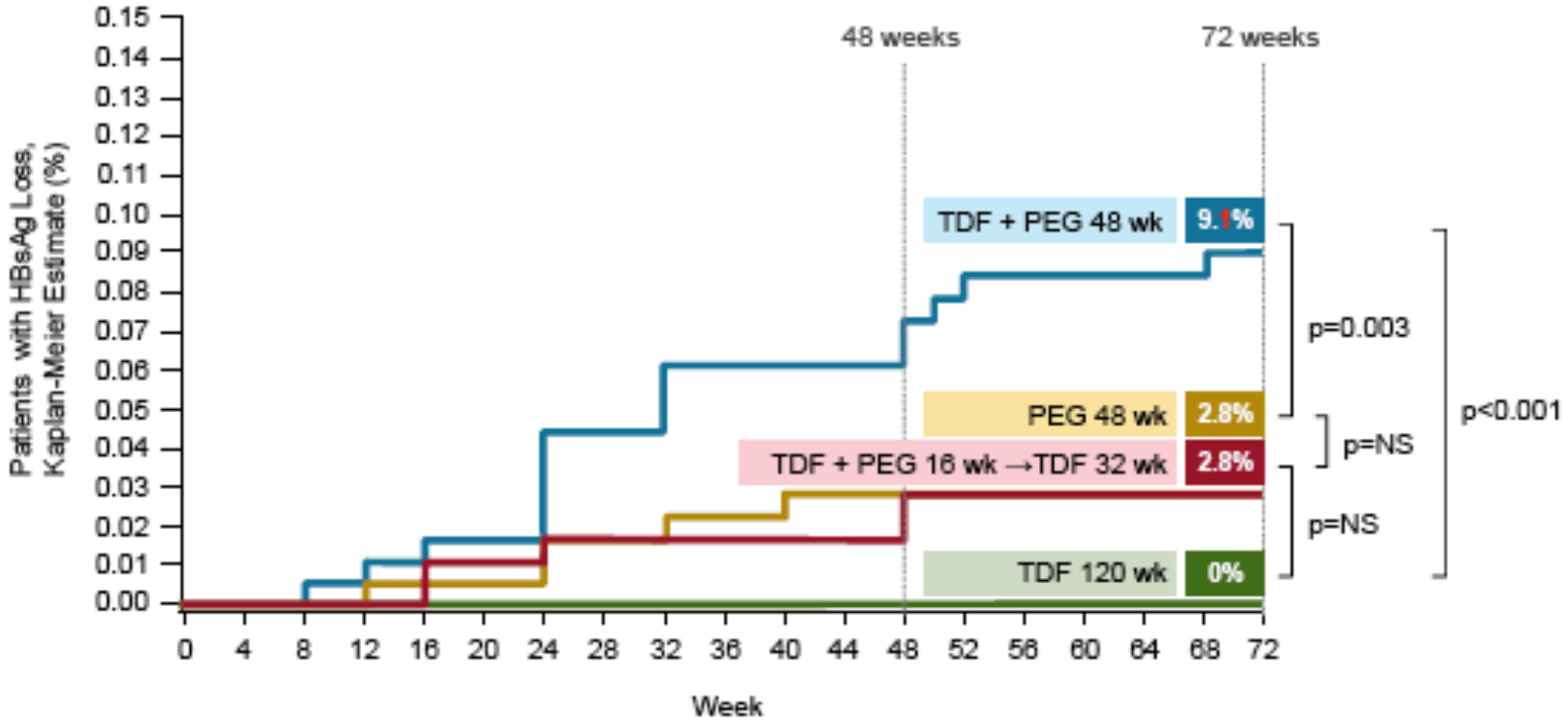
## Study Design




- 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

Marcellin, et al. APASL, March 2015

# HBsAg loss at week 72

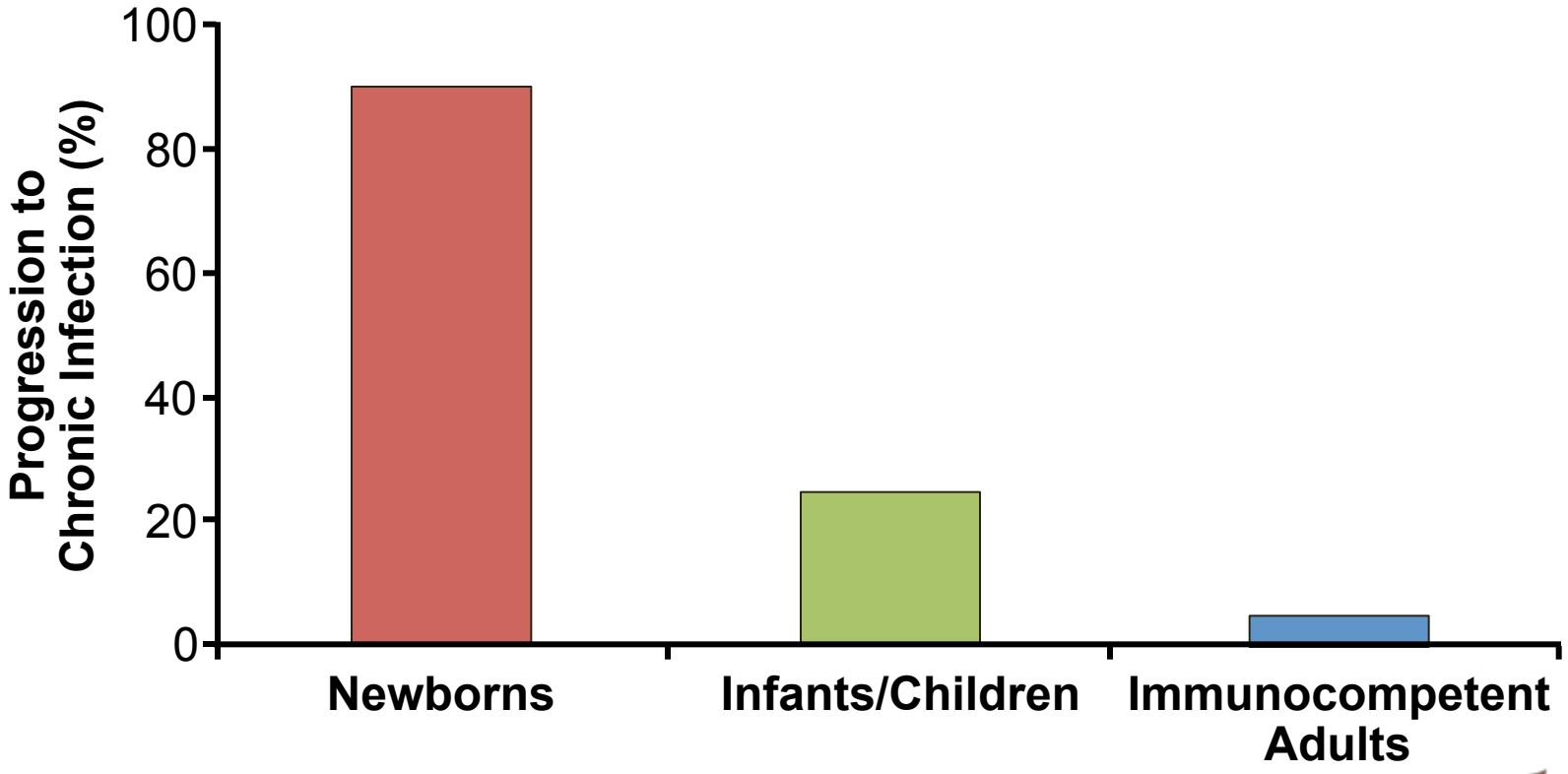



- 7 patients had HBsAg seroreversion on or after Week 48 (4 [TDF + PEG 48 wk], 3 [TDF + PEG 16 wk →TDF 32 wk])

Marcellin, et al. APASL, March 2015

# Preventing Perinatal HBV Transmission: Why Is It So Important?

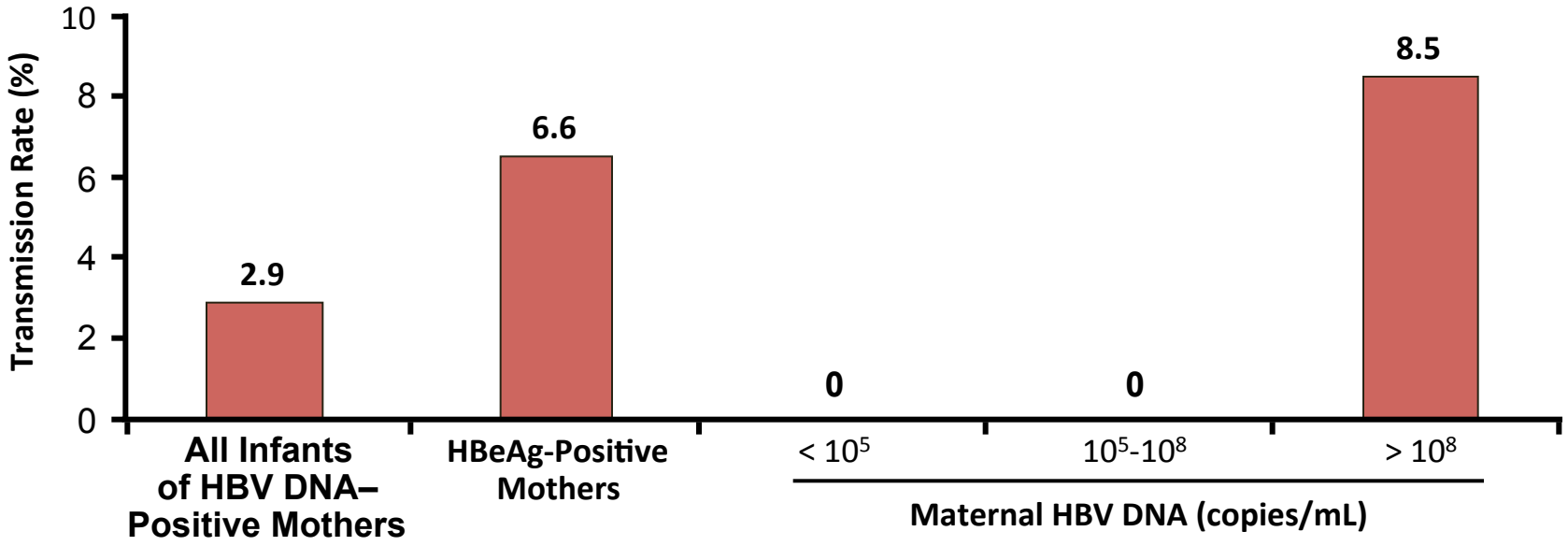
- Risk of progression to chronic infection is inversely related to age at infection




Lok AS, et al. Hepatology. 2009;50:661-662.

# Risk of Perinatal Transmission Associated With HBV DNA Level and HBeAg Positivity

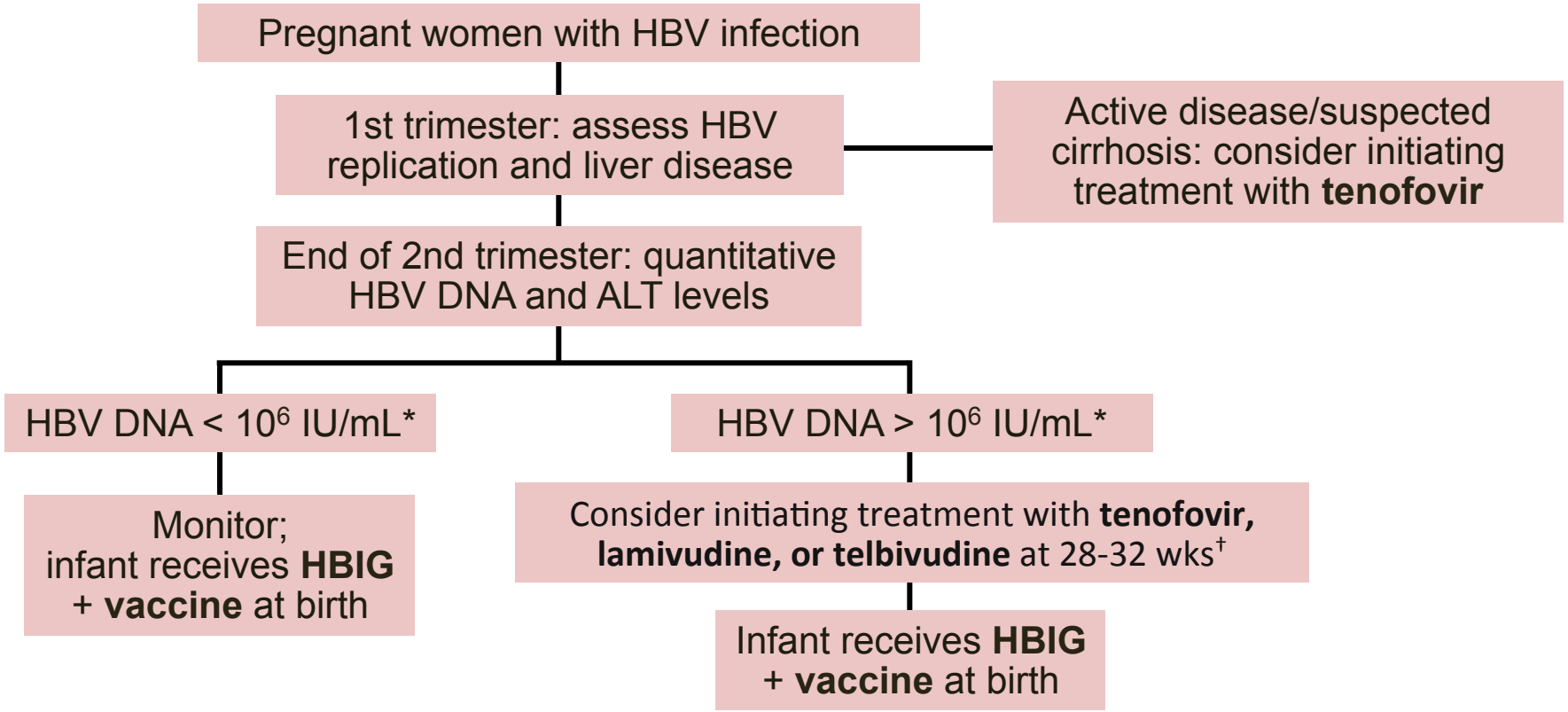
- 213 pregnant HBsAg-positive women with detectable HBV DNA; 138 infants tested at 9 mos of age
- 2.9% (4/138) of infants were HBsAg positive
- In all 4 cases of transmission, mothers were HBeAg positive and had very high HBV DNA (> 8 $\log_{10}$ copies/mL)




Infants received HBIG 100 IU within 12 hrs of birth and HBV vaccination at 0, 2, 4, and 6 mos of age

Wiseman E, et al. Med J Aust. 2009;190:489-492

# Algorithm for HBV Management in Women During Pregnancy




*The cut-off level of maternal HBV DNA level for initiation of therapy is unclear, and HBV DNA from 6-8 $\log_{10}$ IU/mL can be considered for therapy based on physician and patient preference.

†Tenofovir is preferred if treatment is expected to be > 12 weeks or if treatment is expected to continue while breastfeeding.

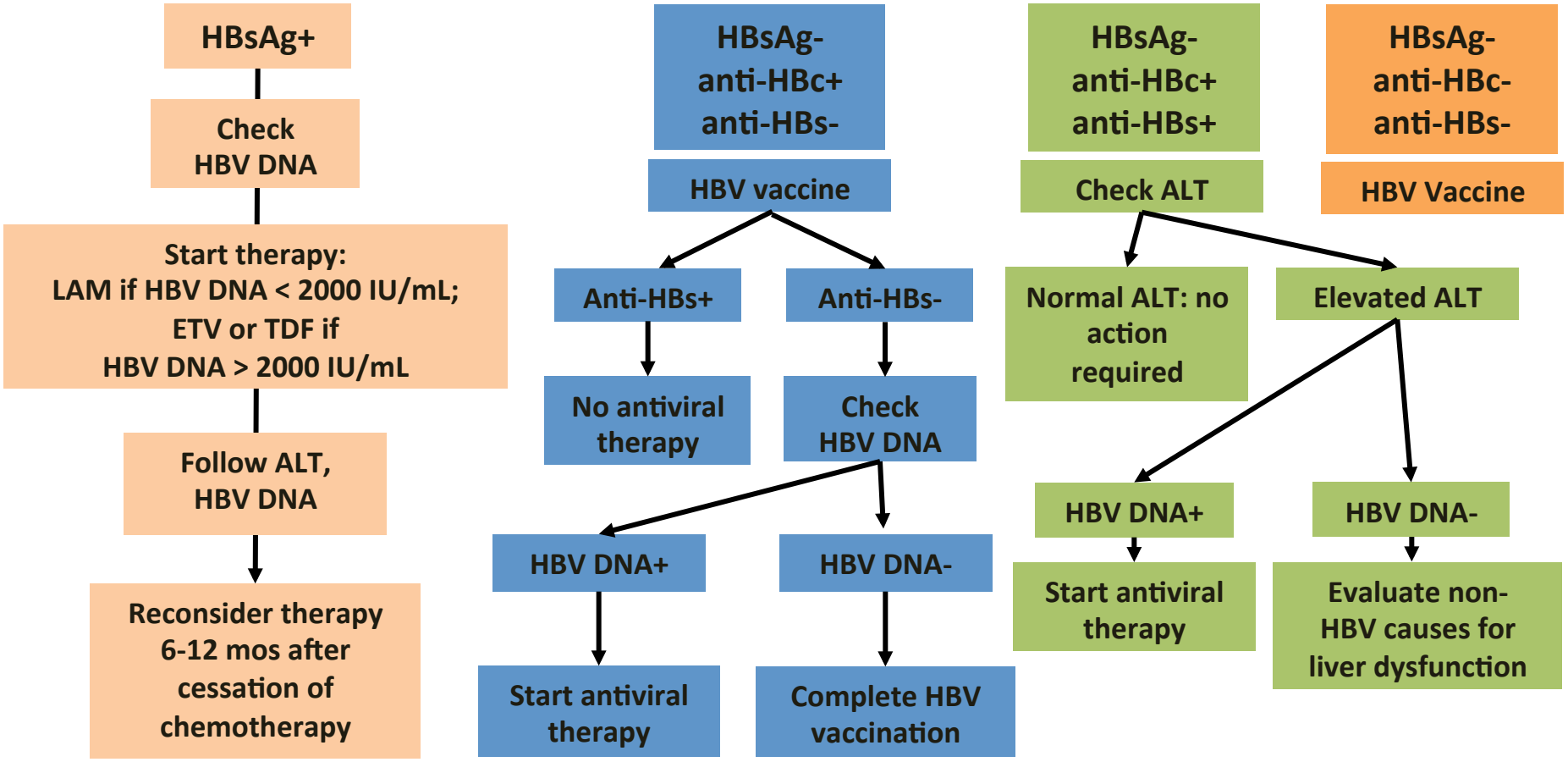
# Risk of Reactivation by Disease

- Bone marrow transplantation
- Organ transplantation
- Leukemia
- Lymphoma
- Myeloma
- Solid tumors
- HIV
- Autoimmune diseases
- Inflammatory bowel disease

Risk Increased with Rituximab Therapy


Alvarez-Suárez B, et al. Rev Esp Enferm Dig. 2010;102:542-552. Lau GK. Bone Marrow Transplant. 1997;8:795-799. Roche B, Samuel D. Liver Int. 2011;31(Suppl 1):104-110. Hwang JP, et al. AASLD 2011. Abstract 172.

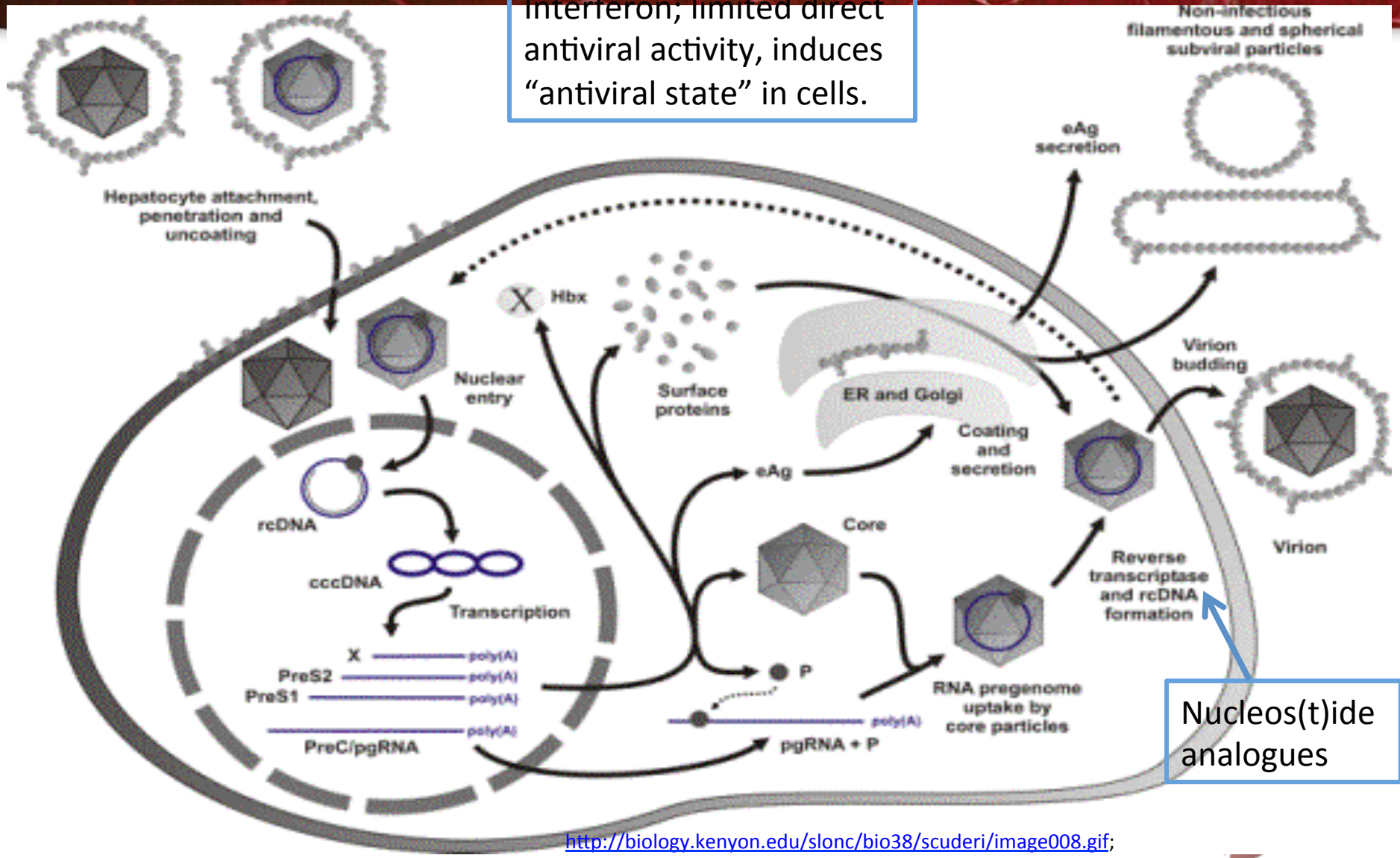
# HBV Management in Pts Receiving Chemotherapy, Immunosuppressive Rx




Roche B, Samuel D. Liver Int. 2011;31(Suppl 1):104-110.

# HBV life cycle

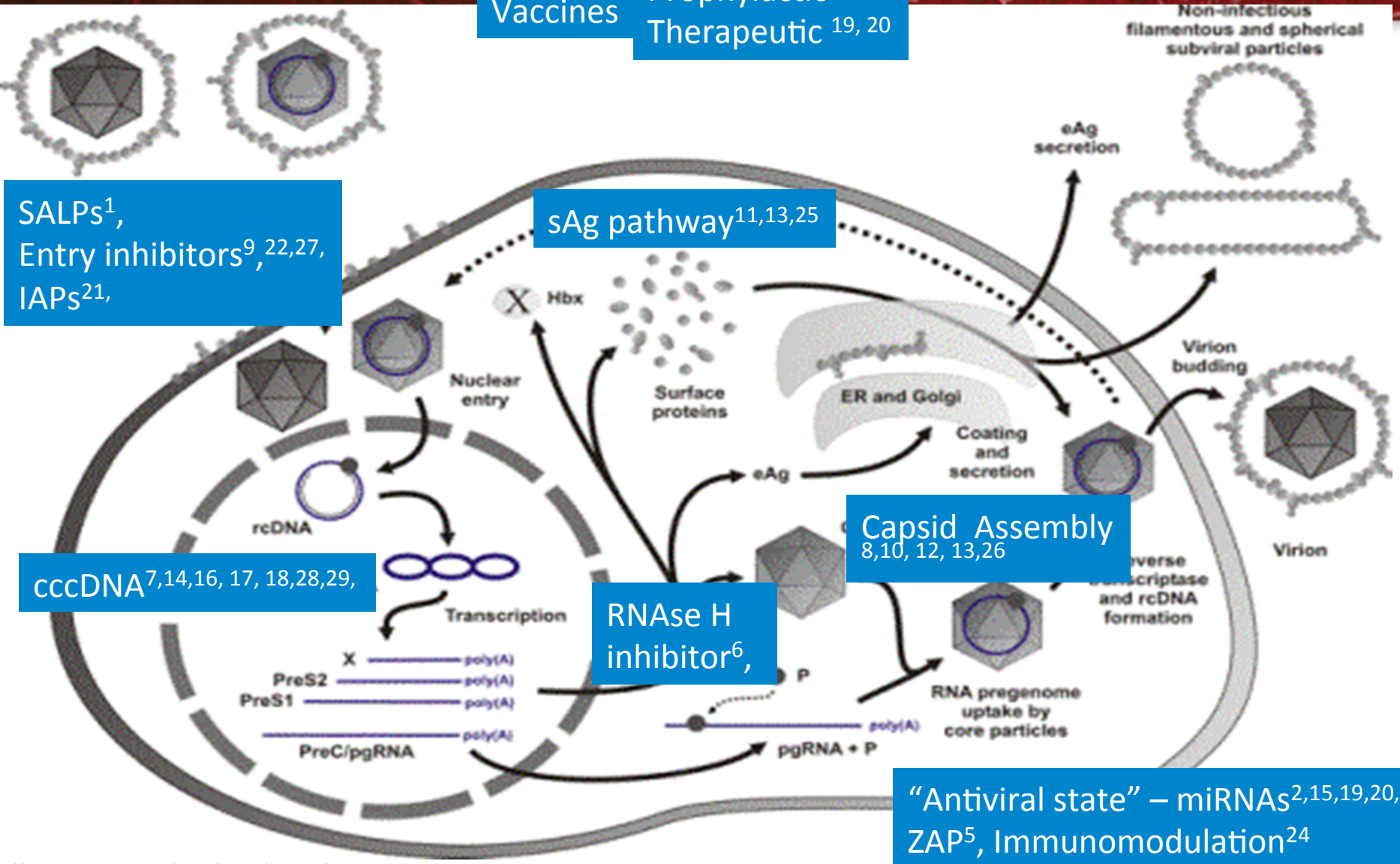
Interferon; limited direct antiviral activity, induces "antiviral state" in cells.




http://biology.kenyon.edu/slonc/bio38/scuderi/image008.gif;
Trepo et al, Lancet 2014, Wieland et al, PNAS, 2005; Sadler & Williams, Nat Rev Immunol 2008

# For the (near) future

Vaccines
Prophylactic [19]
Therapeutic [19, 20]




SALPs[1],
Entry inhibitors[9],[22,27],
IAPs[21],

sAg pathway[11,13,25]

Capsid Assembly
[8,10, 12, 13,26]

cccDNA[7,14,16, 17, 18,28,29],

RNAse H inhibitor[6],

"Antiviral state" – miRNAs[2,15,19,20,23]
ZAP[5], Immunomodulation[24]

://biology.kenyon.edu/slonc/bio38/scuderi/image008.gif

# The End….

Questions?

GreenShoots
FOUNDATION