



# Hepatitis B y Delta

Maria Buti

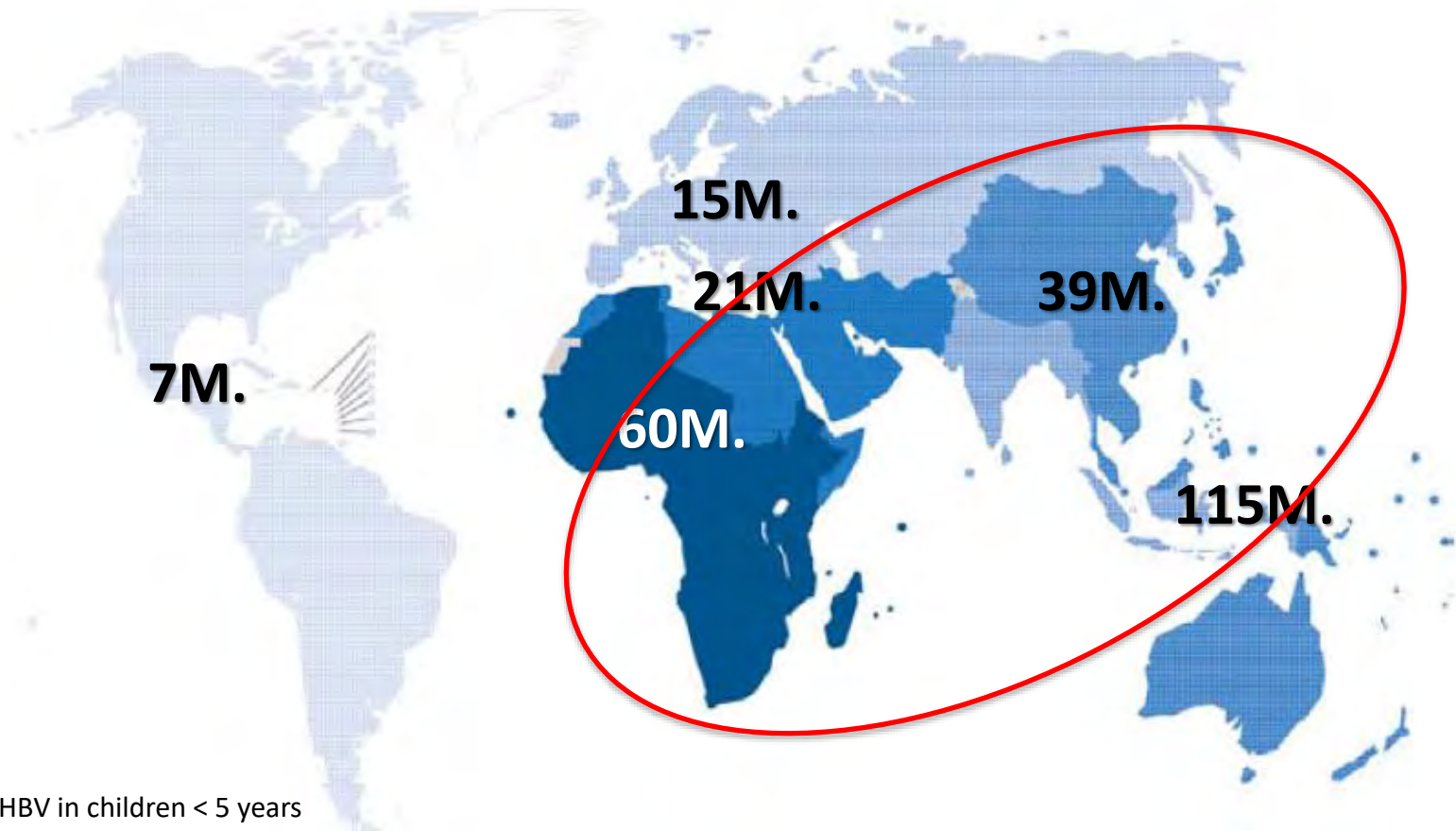
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Barcelona

# Avances tecnológicos y ataques terroristas dominaron los primeros años del nuevo milenio



# Chronic Hep B, a silent and neglected killer for years<sup>1</sup>



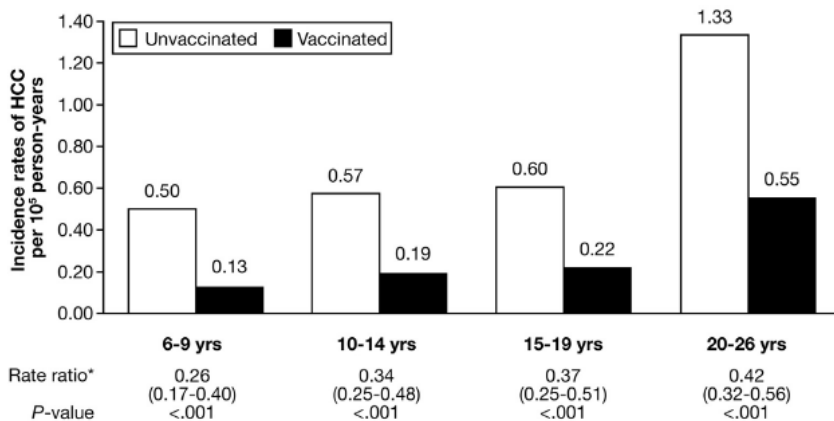
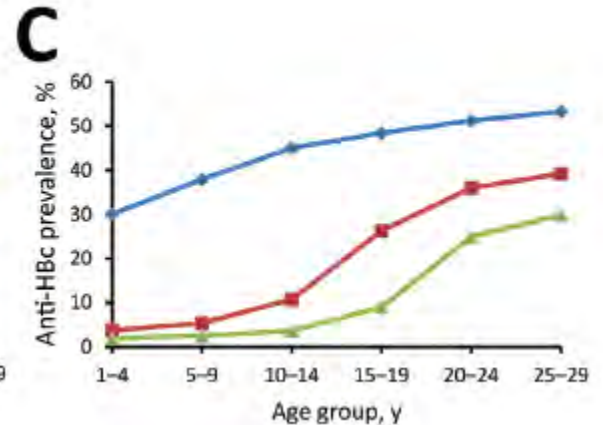
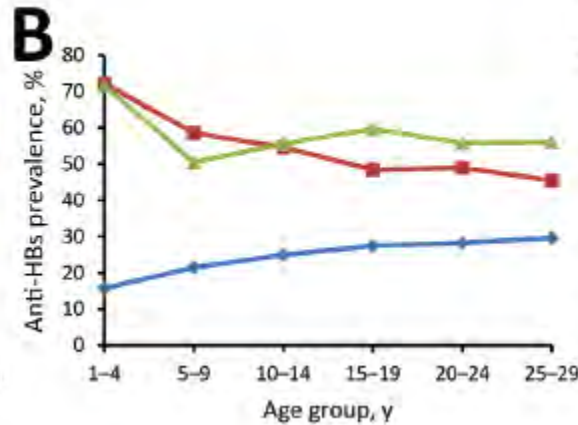
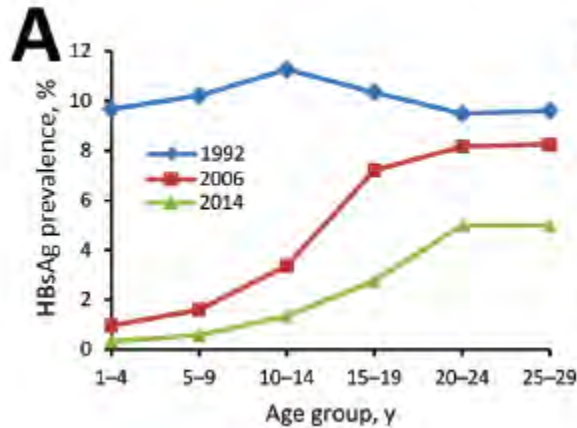
**TOTAL: 257 M.**

Incidence of HBV in children < 5 years

<sup>1</sup>Lemoine, J Hepatol 2016. <sup>2</sup>Global Hepatitis Report 2017

# Impact of birth dose vaccine in Asia

## HBsAg and Anti-HBs Ab dynamics in China after global implementation of immunization<sup>1</sup>



**Impact of immunization in HCC occurrence in the long term (Taiwan)<sup>2</sup>**

\*Rate ratio of vaccinated/unvaccinated birth cohort

<sup>1</sup>Cui, Emerg Inf Dis 2017

<sup>2</sup>Chang, Gastroenterol 2016

# HBV birth dose, a challenge in Africa

**HBV birth dose vaccine:** administration of the vaccine within the 24 hours of life

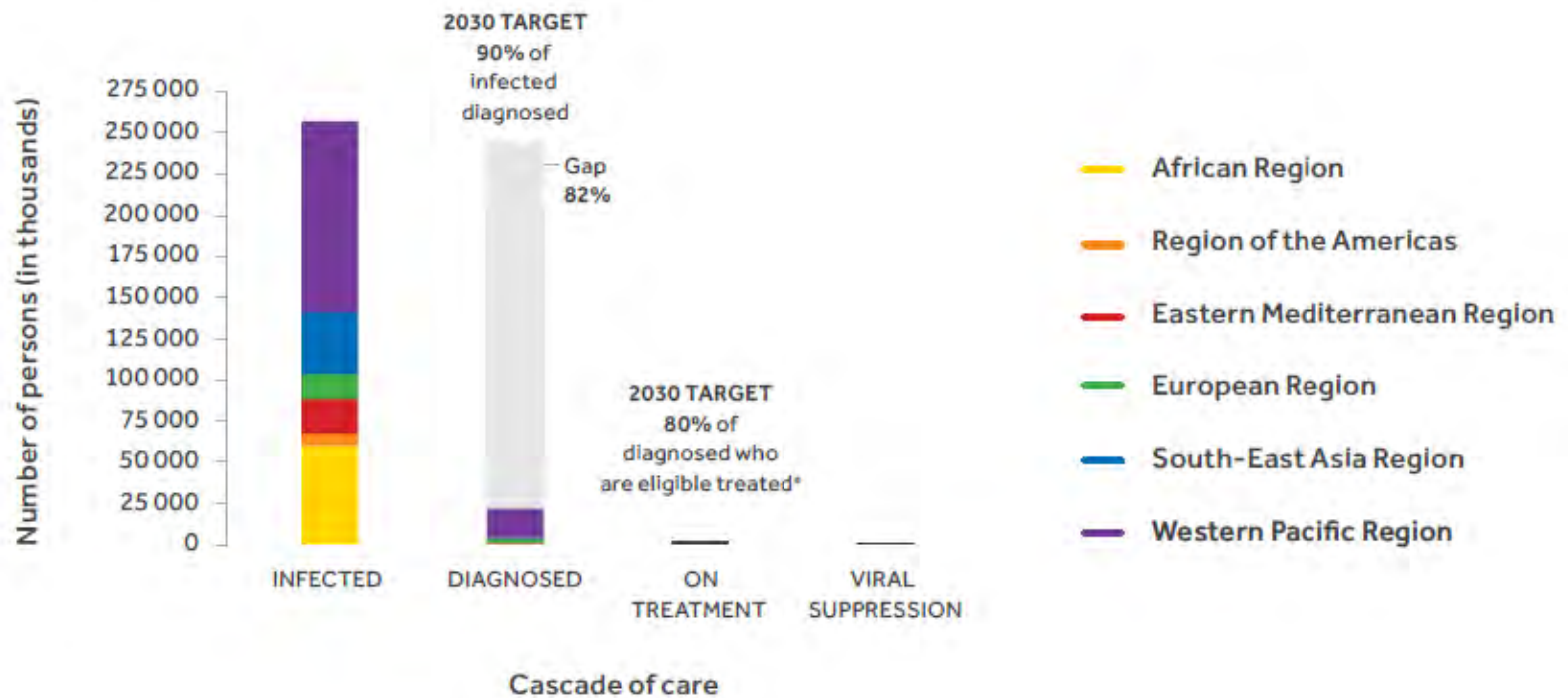
= **current WHO recommendation** to prevent perinatal HBV transmission

⇒ **Poor coverage:** 39% globally and only 11% in Africa

- 50% of women give birth at home/non-medical centers
- Birth dose vaccine is not provided by the Vaccine Alliance (GAVI) or the local governments
- Cold chain



# Treatment eligibility and coverage, the challenging issue



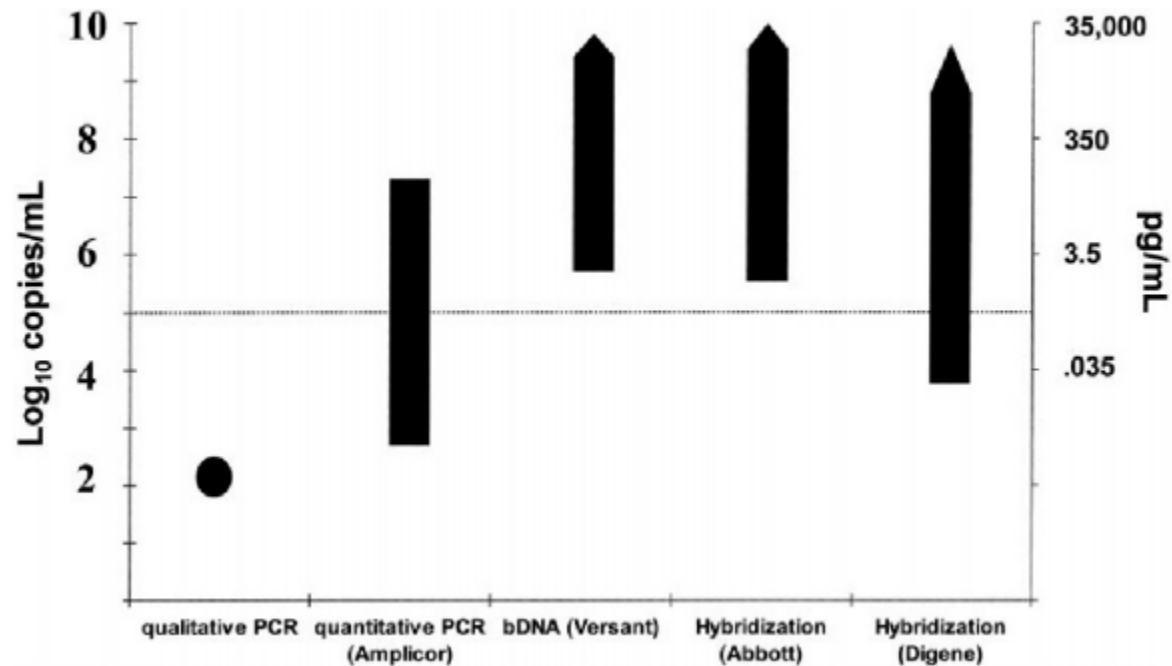
**9% of HBV-infected patients are aware of their status<sup>1</sup>**

**4 – 9% of screened patients in Africa are in need of treatment<sup>2</sup>**

**8% of those in need of treatment have access to treatment<sup>1</sup>**

<sup>1</sup>Global Hepatitis Report 2017. <sup>2</sup>Lemoine, Lancet Glob Health 2016

# Linear range of detection of HBV DNA in serum



expressed as either log<sub>10</sub> copies per milliliter (left axis) or picograms of DNA per milliliter (right axis). PCR, polymerase chain reaction; bDNA, branched DNA



# Advances in Diagnostics and Point-of-Care Testing

## Saliva tests



- Results within minutes
- No expertise or laboratory required
- Can be self administered
- Antibody result only

## Dried blood spot



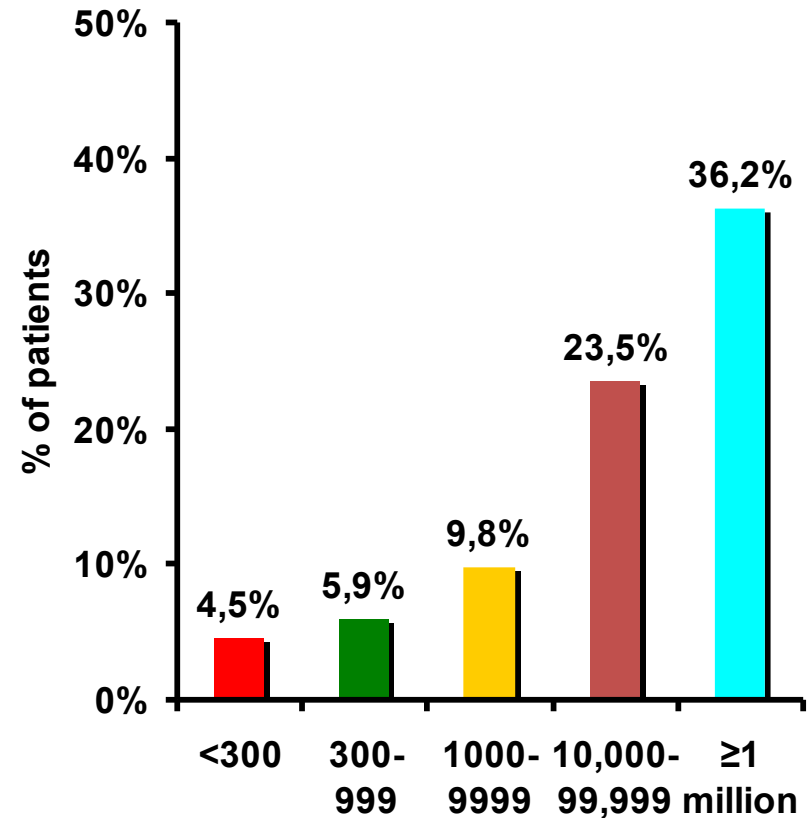
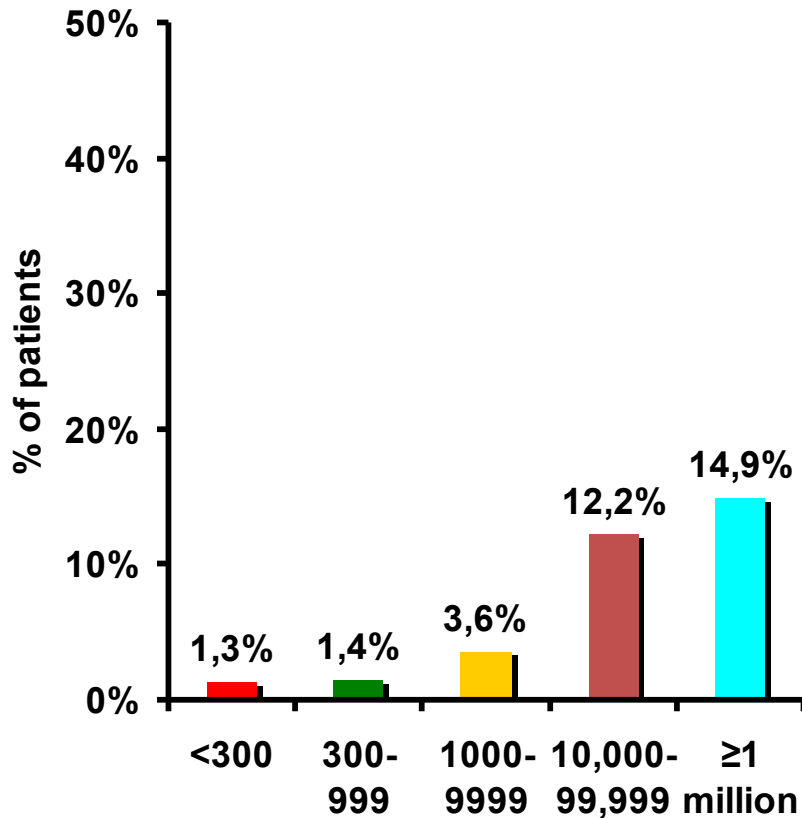
- Minimal expertise required
- Suitable for mass screening
- Results take 2-3 days
- Can give viral load

## Point-of-care HBV DNA testing

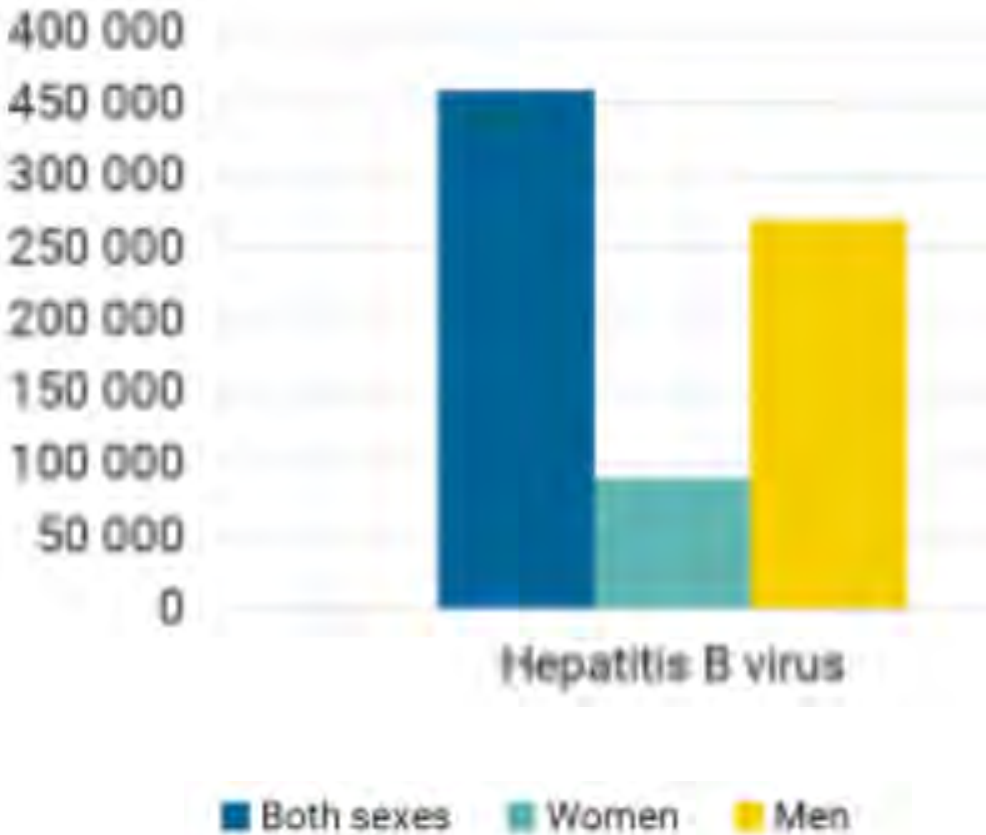


- Minimal expertise required
- HBV DNA result in one hour
- Limited capacity
- Ideal for instant linkage to care

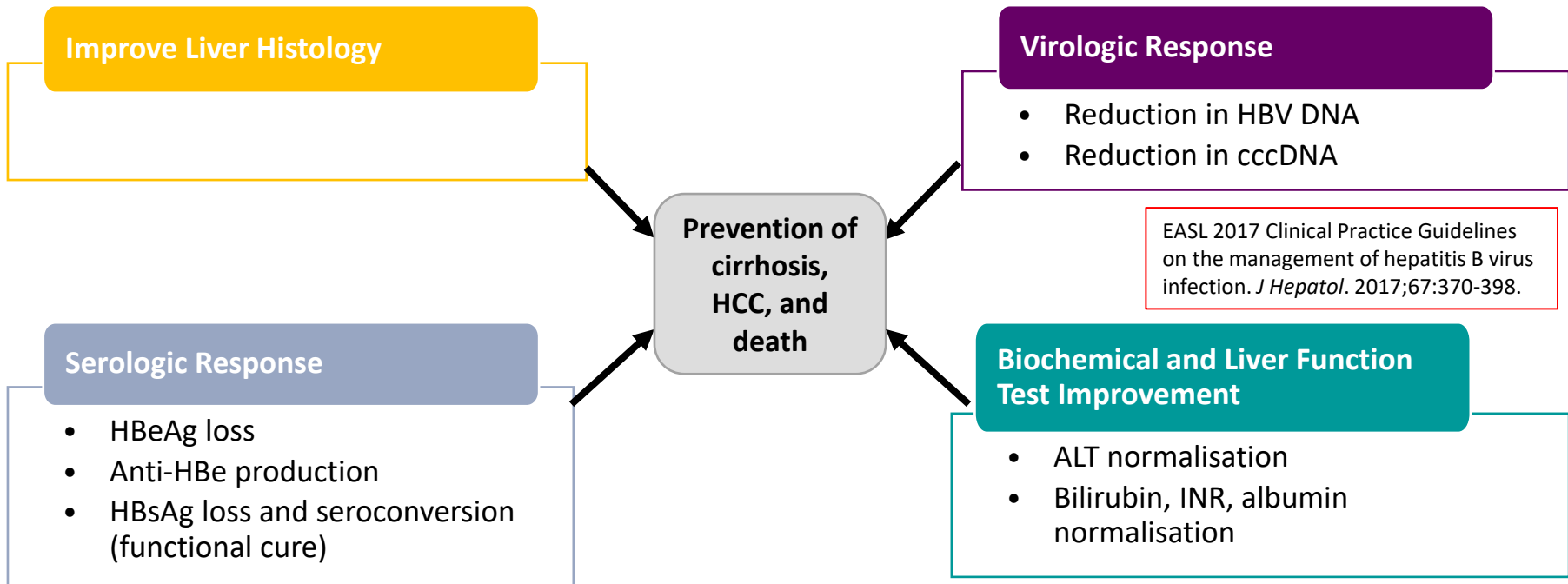
# High Baseline HBV DNA Associated with Increased Risk of Cirrhosis and HCC



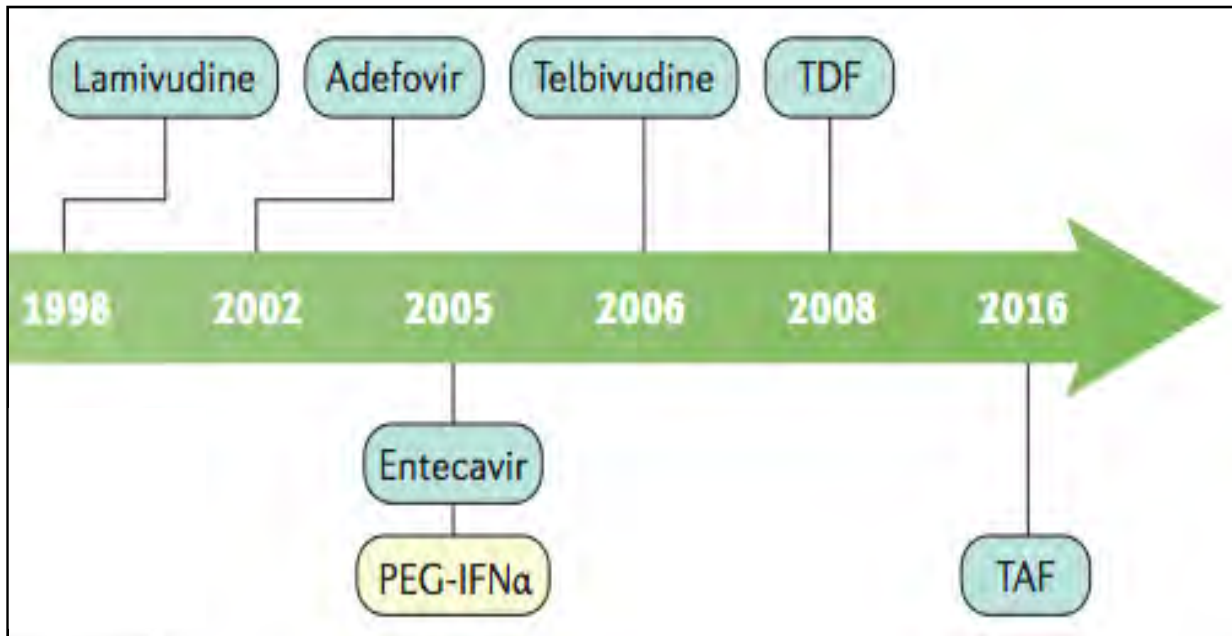
# Estimated Cancer Deaths attributed to Hepatitis B in 2019



# Goals of Therapy for HBV



# Evolution of Treatment for HBV



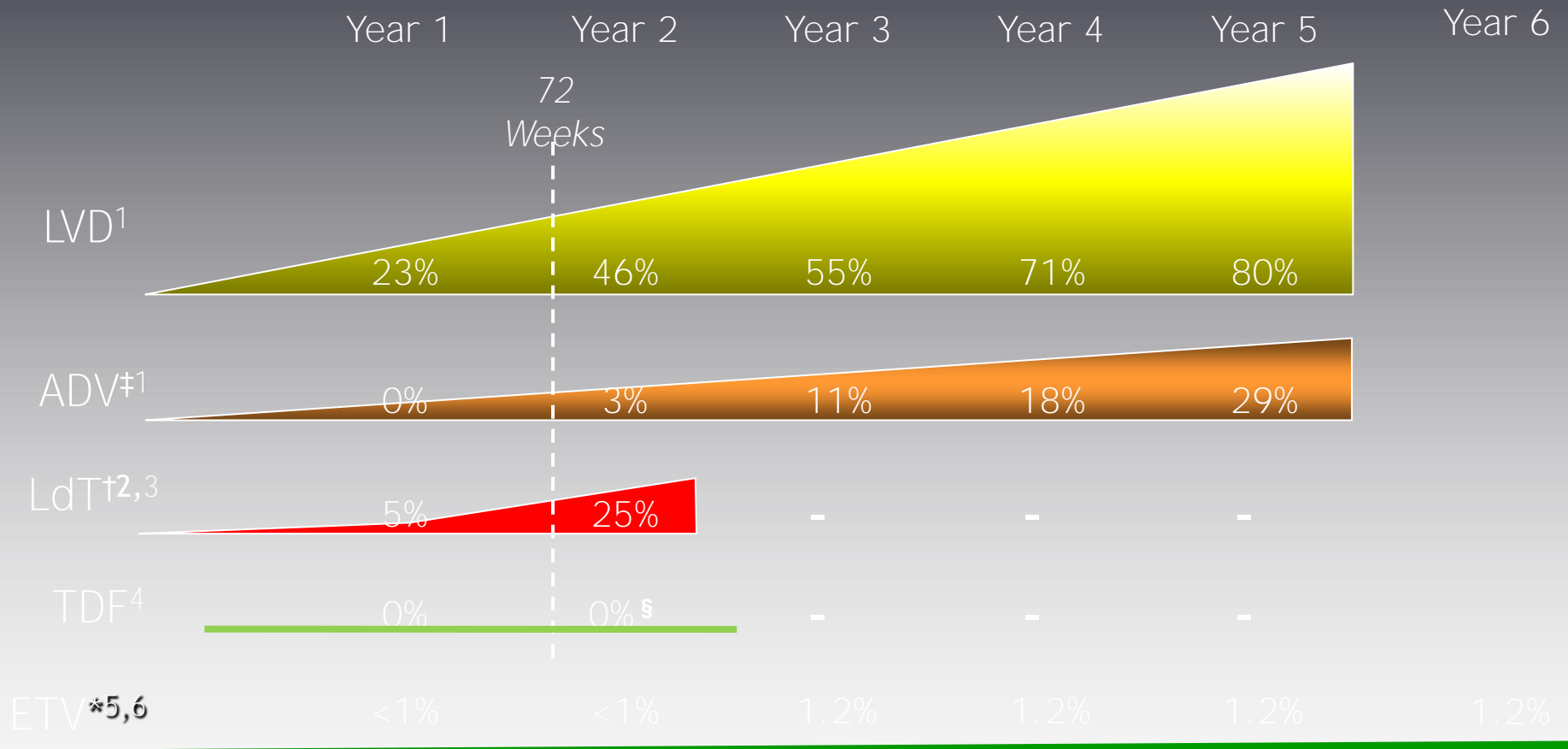
2020

Pipeline **>50** drugs  
in preclinical,  
phase 1-3 clinical  
study

10 years of rapid growth

Improved safety profile over TDF

# Resistance Rates through 6 Years among Nucleos(t)ide-naïve Patients



These trials used different populations, exclusion criteria, follow-up end points, and they were not head-to-head comparisons for all the drugs. \* Cumulative probabilities of resistance; taken: <sup>1</sup> Naïve HBeAg (+); <sup>‡</sup> Naïve HBeAg (-); N/A not available.

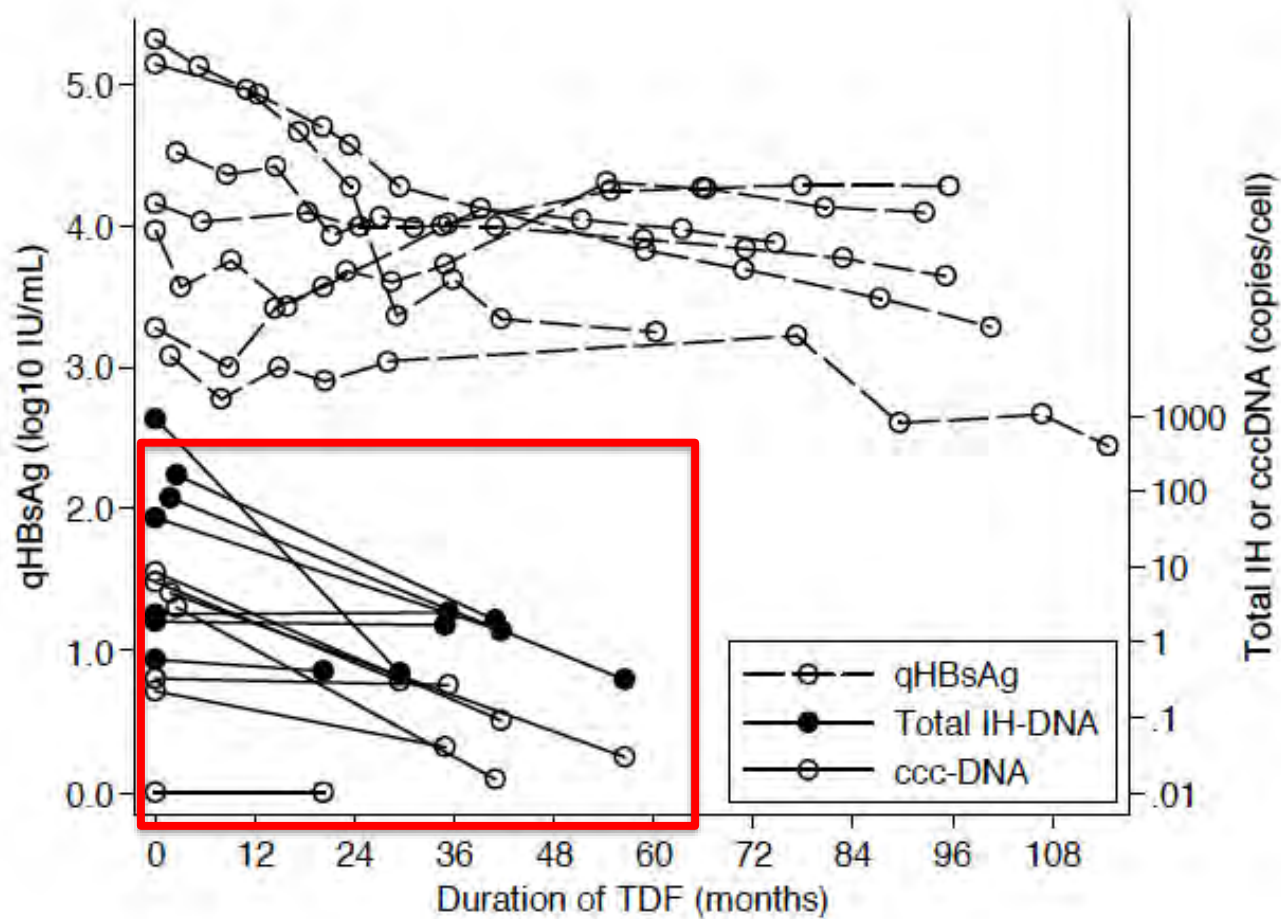
## Efficacy and Safety of the recommended NUCs

	<b>TDF</b>	<b>TAF</b>	<b>Entecavir</b>
<b>Antiviral Efficacy</b>	<b>+++</b>	<b>+++</b>	<b>+++</b>
<b>HBsAg loss</b>	<b>Rare</b>	<b>Rare</b>	<b>Rare</b>
<b>Drug resistance</b>	<b>No</b>	<b>No</b>	<b>Naive 1.2% at year 6 Previously treated +++</b>
<b>Dose adjusted to renal function</b>	<b>Yes</b>	<b>No</b>	<b>Yes</b>
<b>Bone alterations</b>	<b>+</b>	<b>No</b>	<b>No</b>
<b>Cost</b>	<b>Generics</b>	<b>++</b>	<b>Generics</b>

EASL Guidelines. J Hepatol 2019, Terrault N et al. Hepatology 2018; SK et al. Hepatol Int. 2016

# ... but no functional cure

Persistence of DNA synthesis despite « viral suppression »



New round of infection and/or replenishment of the cccDNA pool occur despite « viral suppression »



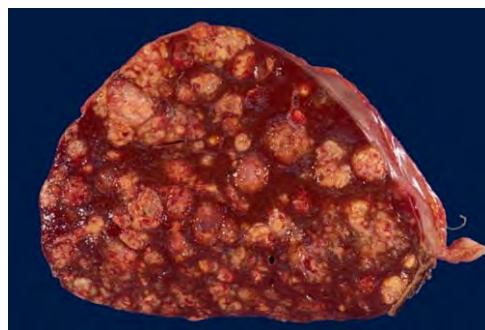
# Challenges in NUCs suppressed CHB patients

**Adverse Events**



**Increase HBsAg loss and  
Viral suppression**

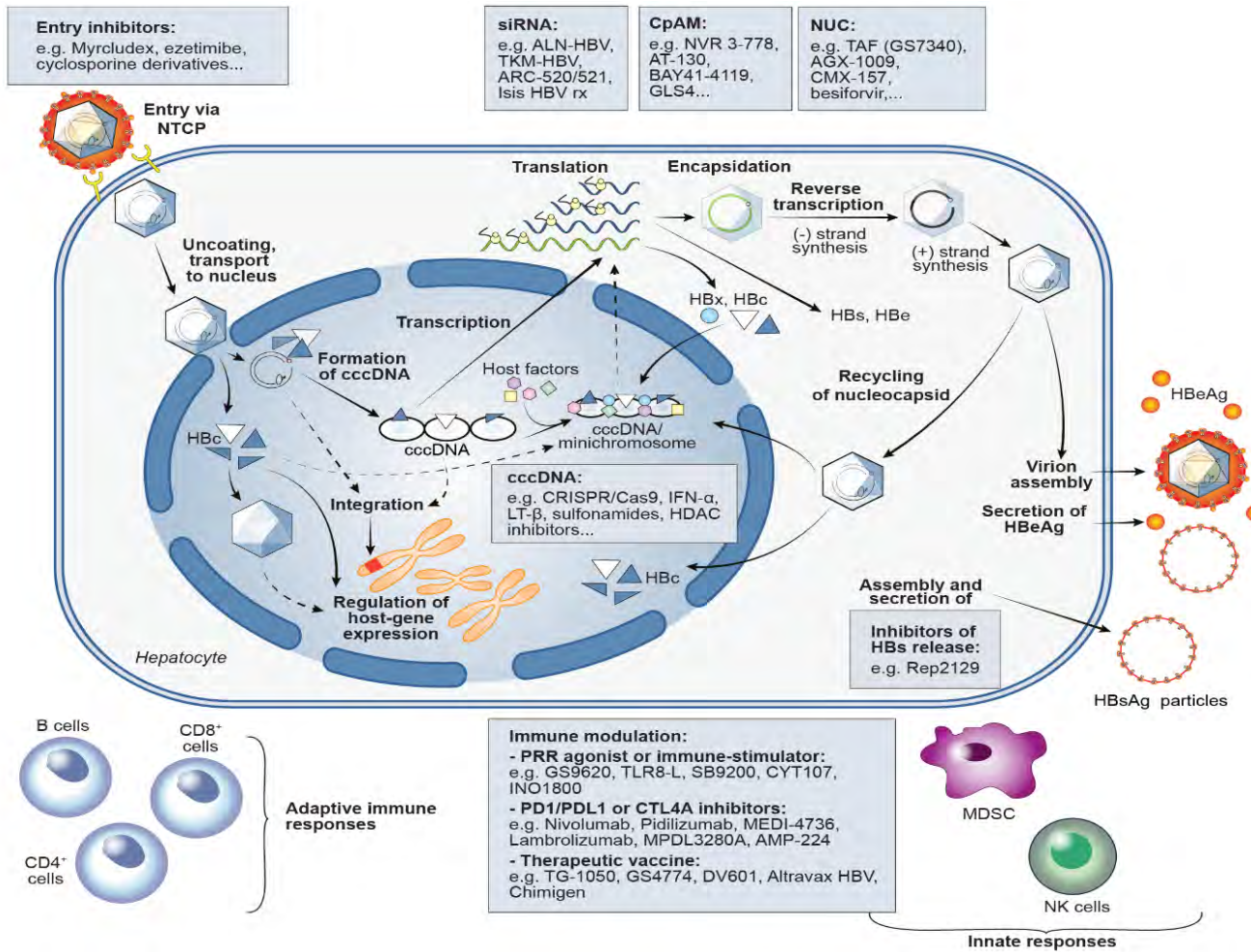
**Reduce HCC  
risk**



**Financial burden**



# Multiple targets in host and virus



# Upcoming strategies for HBV cure ?

Antivirals

Prevent viral production and  
Re-amplification of cccADN



Host immunity  
stimulation

Stimulating host immune response or  
prevent its inactivation



## HBV functional cure

Inhibition of HBV  
antigen production

Inhibits the steps of replication cycle (entry,  
diffusion, capsid formation, HBx functioning  
and HBsAg release)

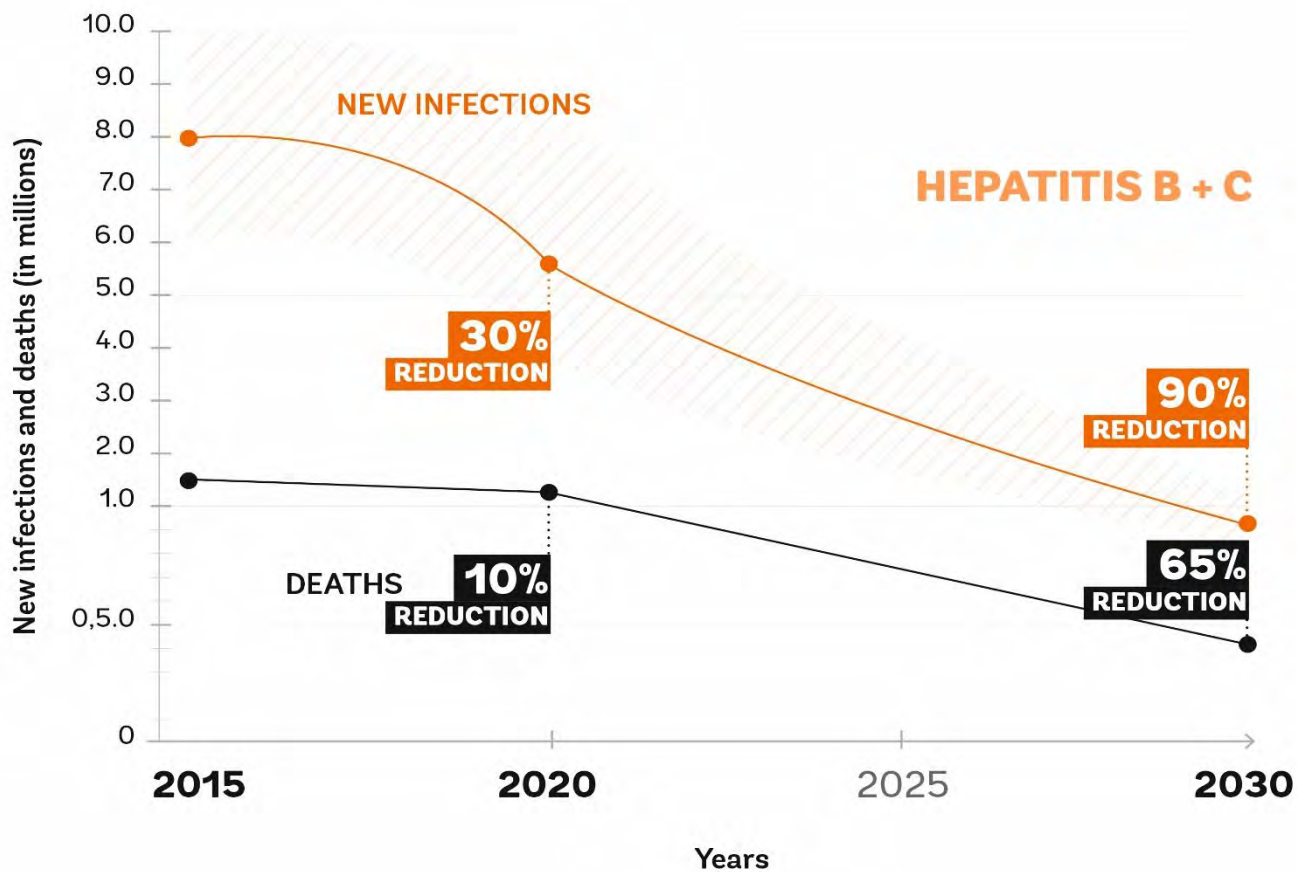


cccDNA inhibition

Decrease or inhibition of cccDNA



# SDG for 2030: viral hepatitis elimination



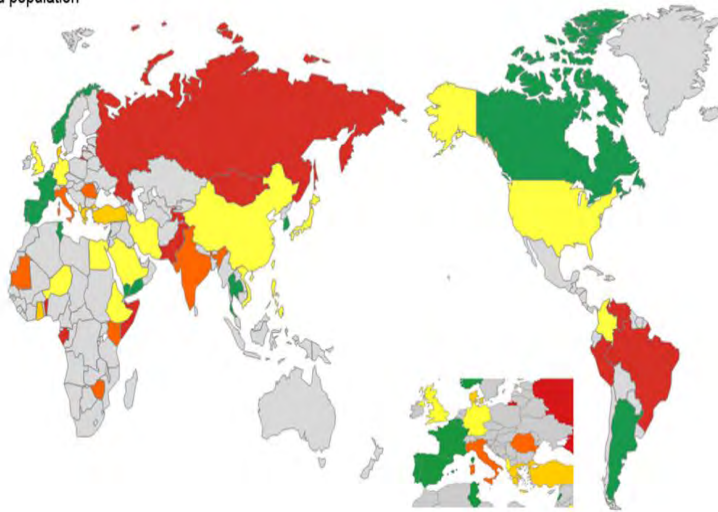
**6-10 million infections (in 2015) to  
900,000 infections (by 2030)**

**1.4 million deaths (in 2015) to under  
500,000 deaths (by 2030)**

# Prevalencia Hepatitis D

**72 millones**

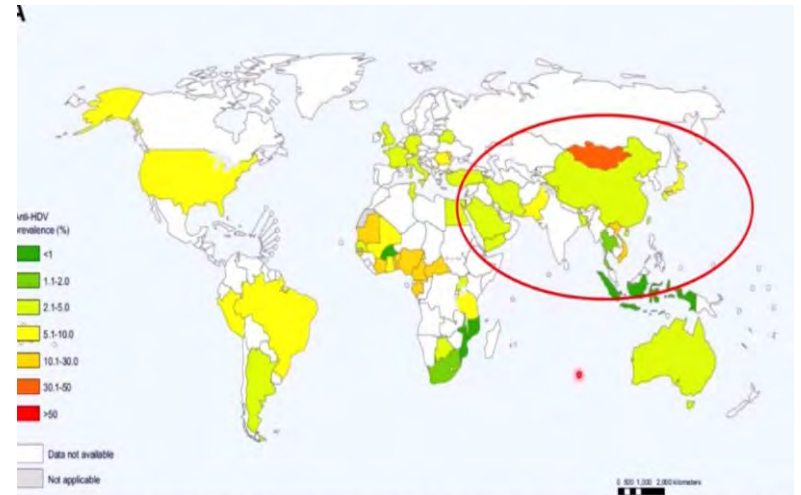
Mixed population



10.58% HBsAg carriers

Chen et al Gut 2019

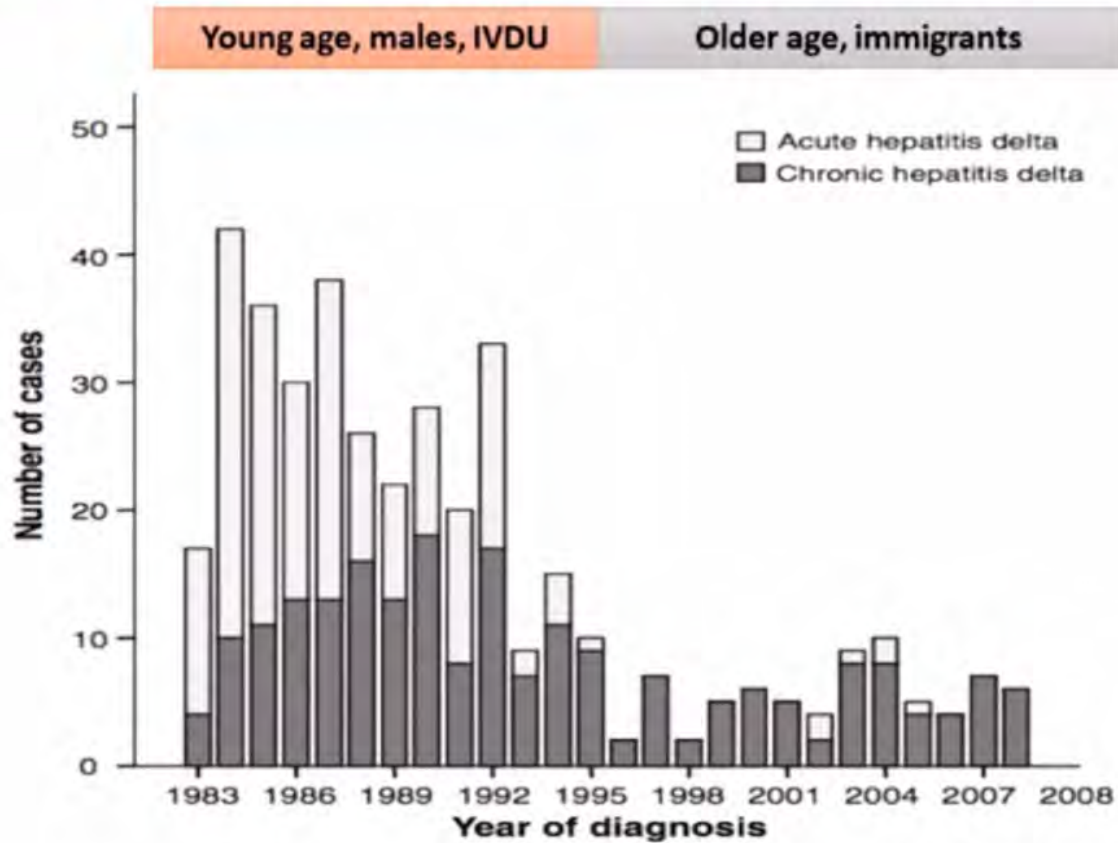
**12 millones**



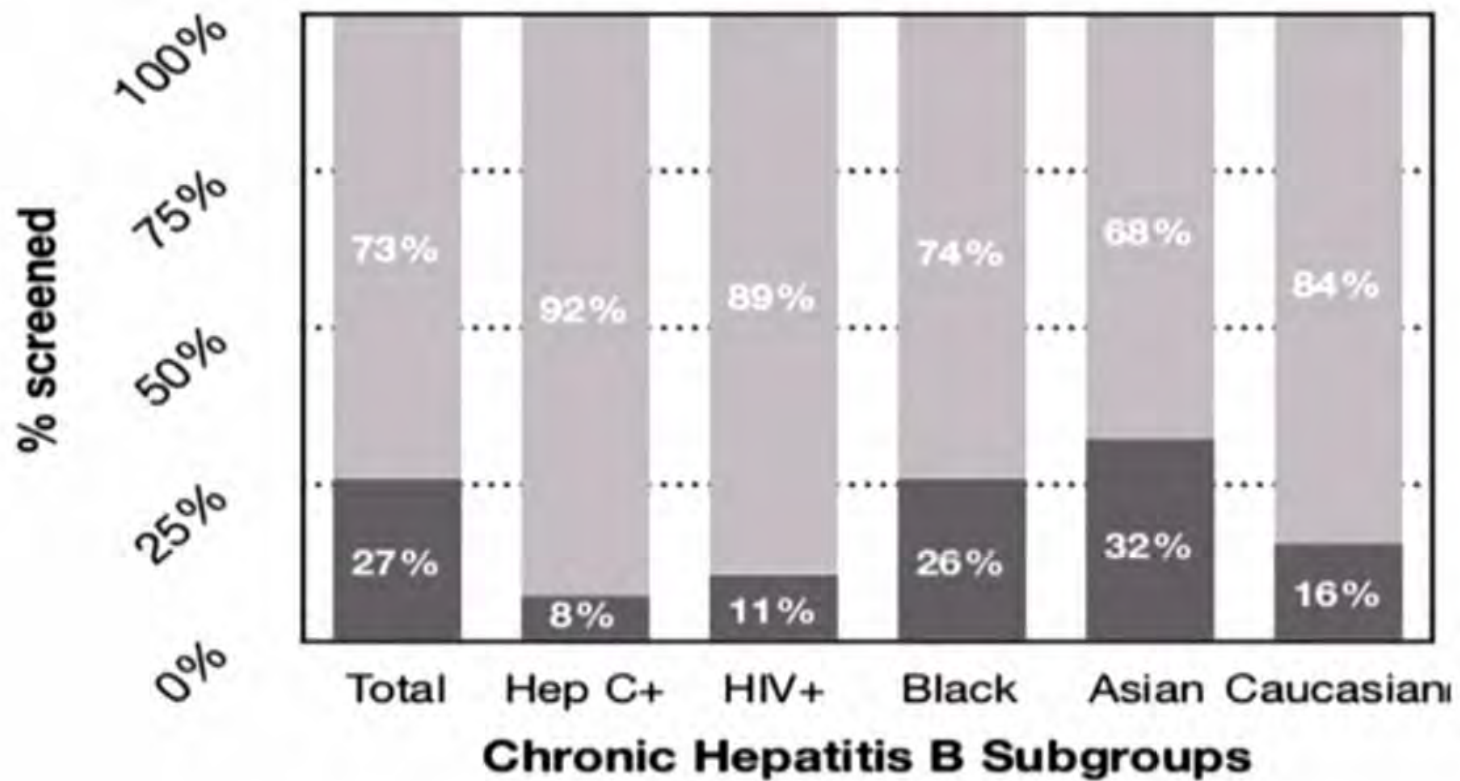
Among HBsAg-positive people, estimated HDV prevalence is **4.5%** (95% CI 3.6-5.7)

Stockdale J Hepatpl 2020

# Changing epidemiology of HDV infection in Spain



## Hepatitis D Screening Rates Among Patients with Chronic HBV

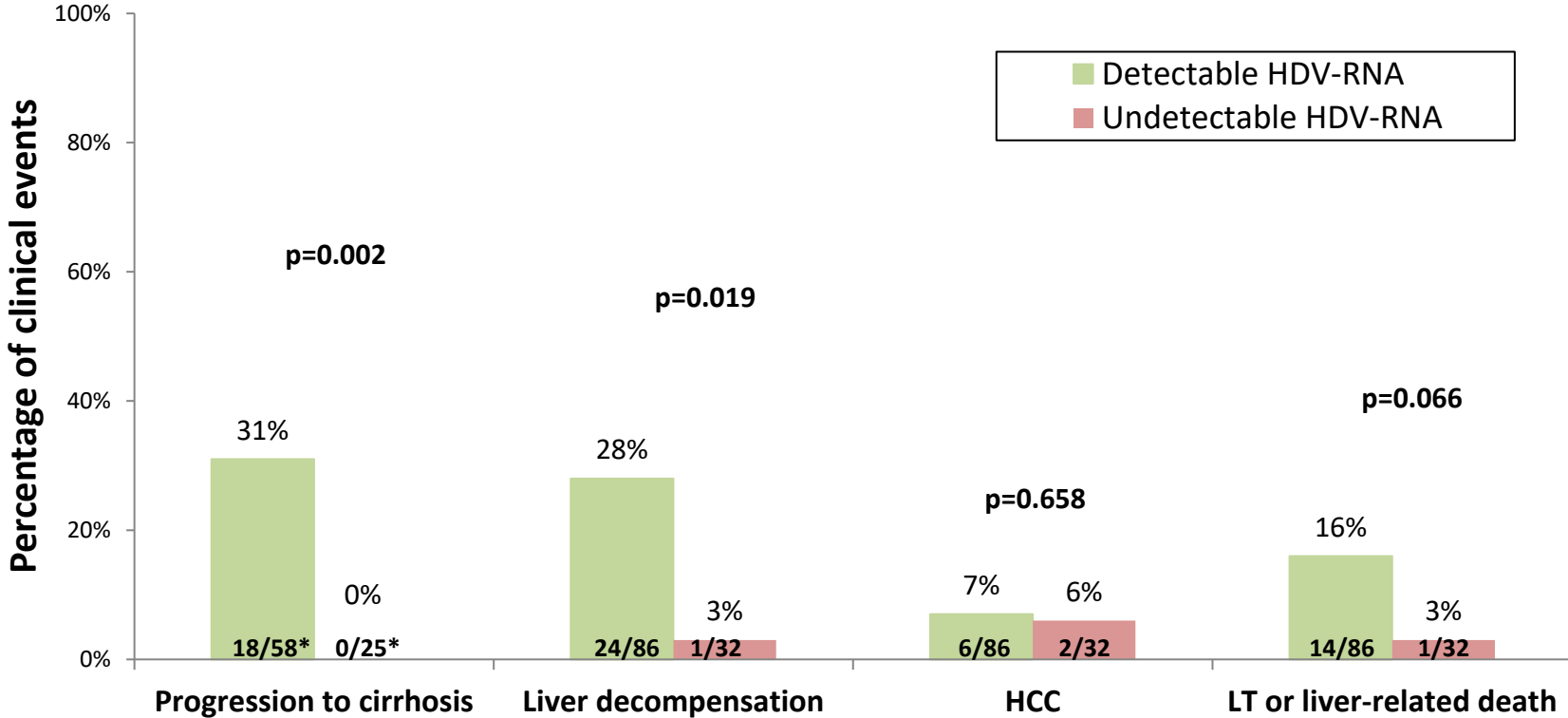


■ Screened      ■ Not-screened

Moore A et al. Hepatology 2019; 70(Suppl.): 585A-586A

# Probability of developing clinical events in chronic hepatitis delta

Multicentre study including 118 anti-HDV subjects followed for a median of 8 years



Palom A, et al. Aliment Pharmacol Ther 2019

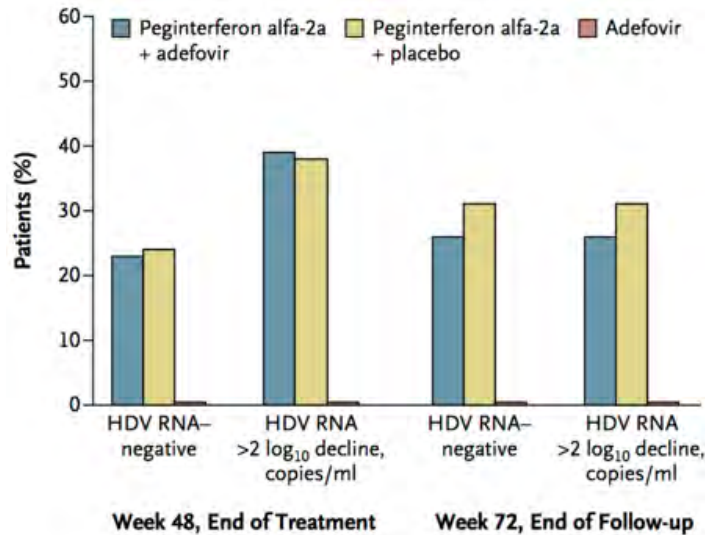


# 48 wks course of PegIFN+ADV vs PegIFN vs ADV in Chronic Hepatitis Delta

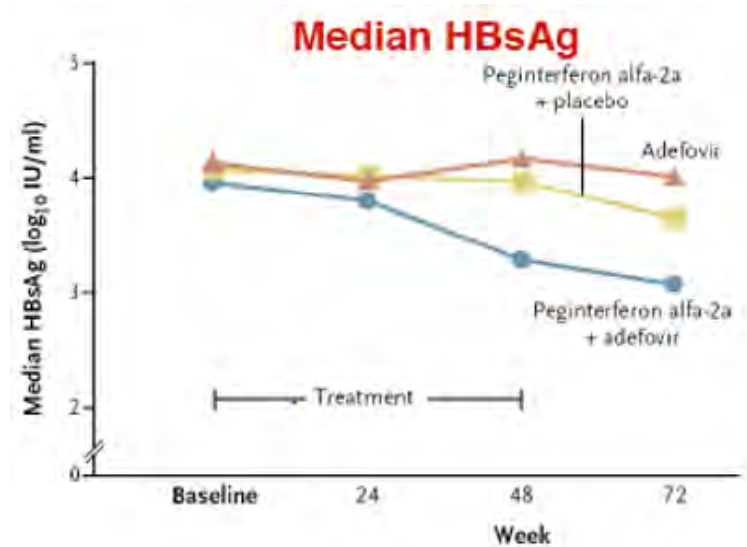
N=90  
Chronic  
Hepatitis Delta

<b>PEG-IFN<math>\alpha</math>-2a (180 <math>\mu</math>g/wks) + ADV 10 mg/day (n = 31)</b>
<b>PEG-IFN<math>\alpha</math>-2a (180 <math>\mu</math>g/wks) + placebo (n = 29)</b>
<b>ADV 10 mg/day (n = 30)</b>

Primary End-Point: HDV RNA undetectable and Normal ALT at week 48



All HDV GT 1  
14-24% cirrhosis

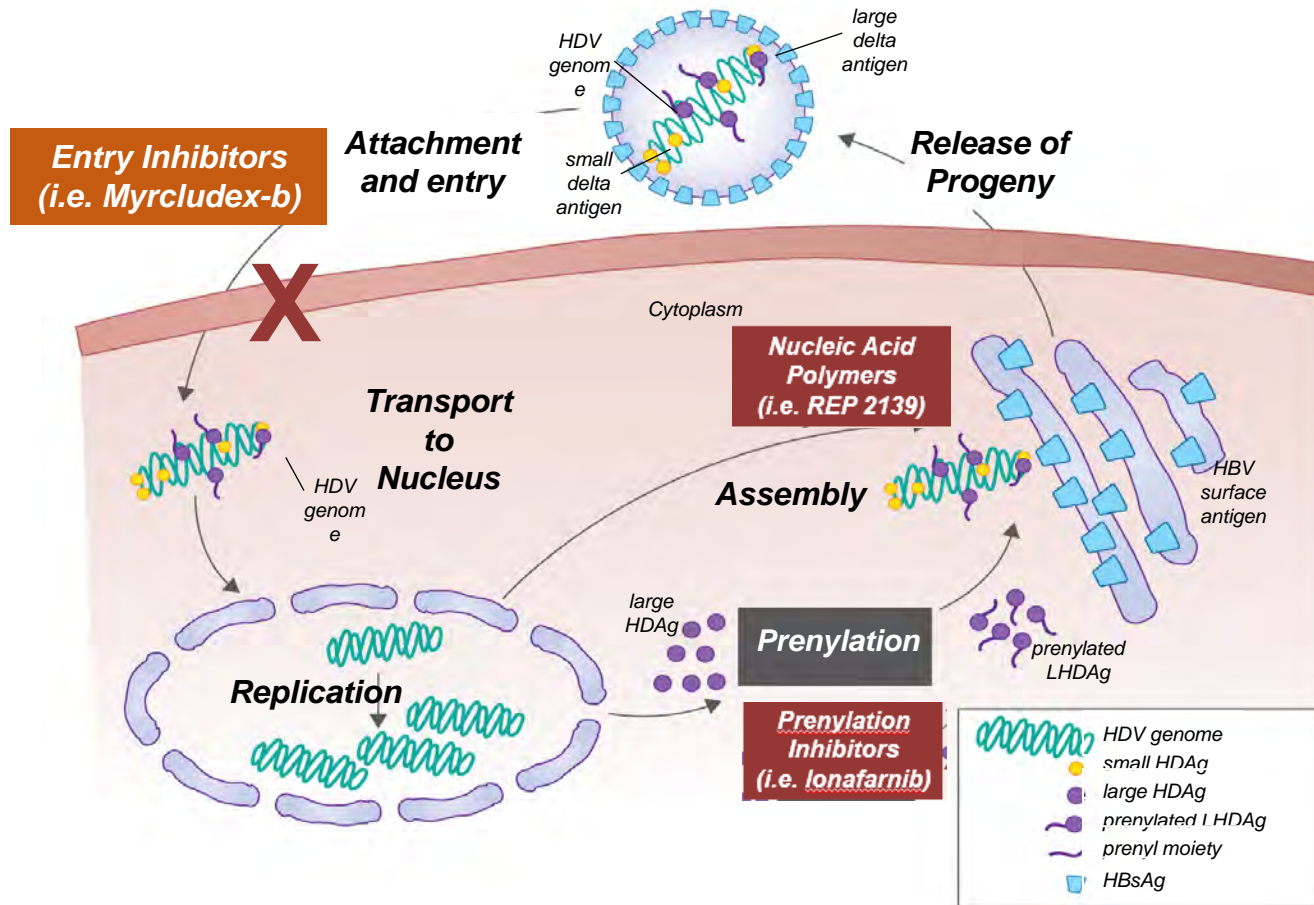


HBsAg loss: 2 patients treated with PegIFN/ADV

Wedemeyer H. et al, N Eng J Med 2011;364:322-331

High frequency of HDV recurrence after therapy discontinuation

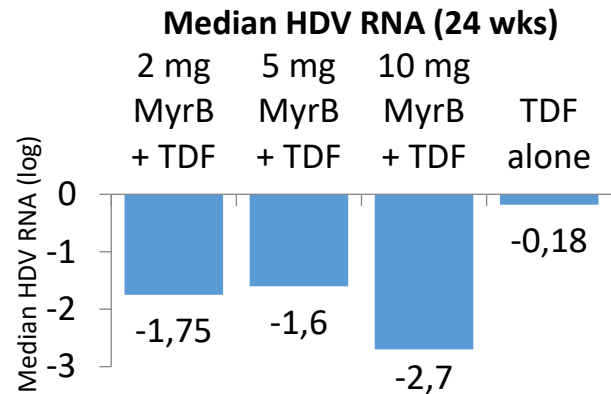
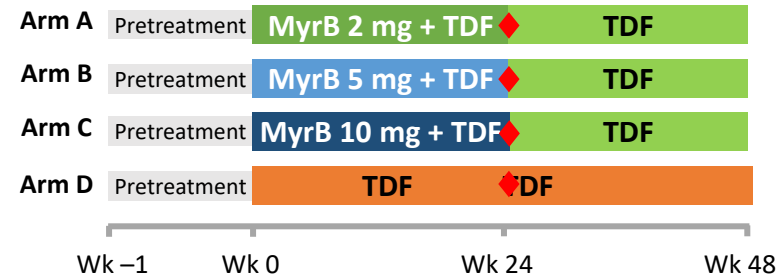
# The HDV Life Cycle



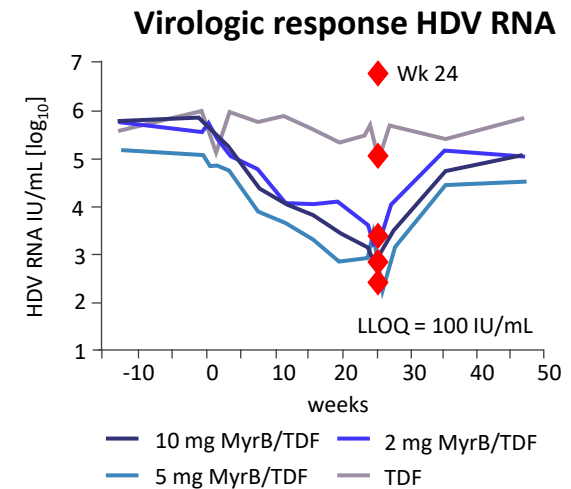
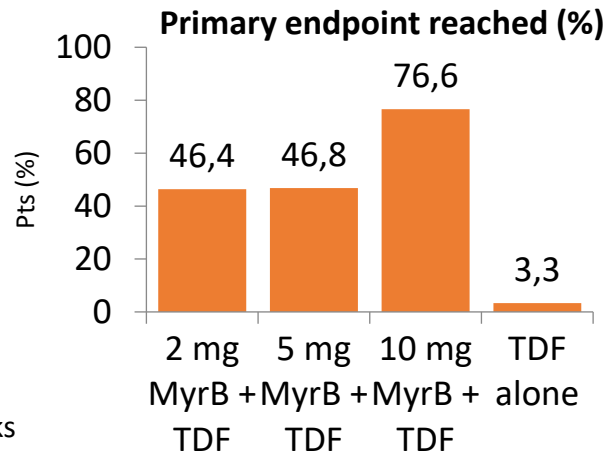
# Final results of a multicenter, open-label Phase 2b trial to assess safety and efficacy of Bulevirtide + TDF in patients CHD (MYR 202)

## Study design

- 120 patients randomized into 4 treatment arms in a ratio of 1:1:1:1
  - 30 patients per arm; 50% of patients were cirrhotic
- Myrcludex B was self administered by patients SC QD
- All patients received TDF (oral QD) during entire study period
- Primary endpoint: HDV RNA decline by  $\geq 2 \log_{10}$  from BL to Wk 24



- HDV RNA levels were still declining at 24 weeks



# Bulevirtide (Myrcludex B)



EUROPEAN MEDICINES AGENCY  
SCIENCE. MEDICINES. HEALTH.

## **4.1 Therapeutic indications**

Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.

## **4.2 Posology and method of administration**

Treatment should be initiated only by a physician experienced in the treatment of patients with HDV infection.

Bulevirtide should be administered at 2 mg once daily (every 24 h  $\pm$  4 h) by subcutaneous injection as monotherapy or in co-administration with a nucleoside/nucleotide analogue for treatment of underlying HBV infection.

EL año 2020 ha esta dominado por



Las vacunas contra la covid-19 fueron elegidas por la revista Science como el descubrimiento científico más importante del año



NOBELPRISET I KEMI 2020  
THE NOBEL PRIZE IN CHEMISTRY 2020

KUNGL. VETENSKAPS-  
AKADEMIEN  
THE ROYAL SWEDISH ACADEMY OF SCIENCES



**Emmanuelle Charpentier**  
Born in France, 1968  
Max Planck Unit for the Science of  
Pathogens, Germany



**Jennifer A. Doudna**  
Born in the USA, 1964  
University of California, Berkeley, USA  
Howard Hughes Medical Institute

Solo juntos podremos conseguir la salud para todos

