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INSTITUT D'HÉPATOLOGIE DE LYON

ÉCOLE DOCTORALE 340

BMIC
BIOLOGIE MOLÉCULAIRE INTÉGRATIVE ET CELLULAIRE
UNIVERSITÉ DE LYON

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HBV Vaccination

Success and Barriers to Achieve HBV Eradication

VIRCAN 2024

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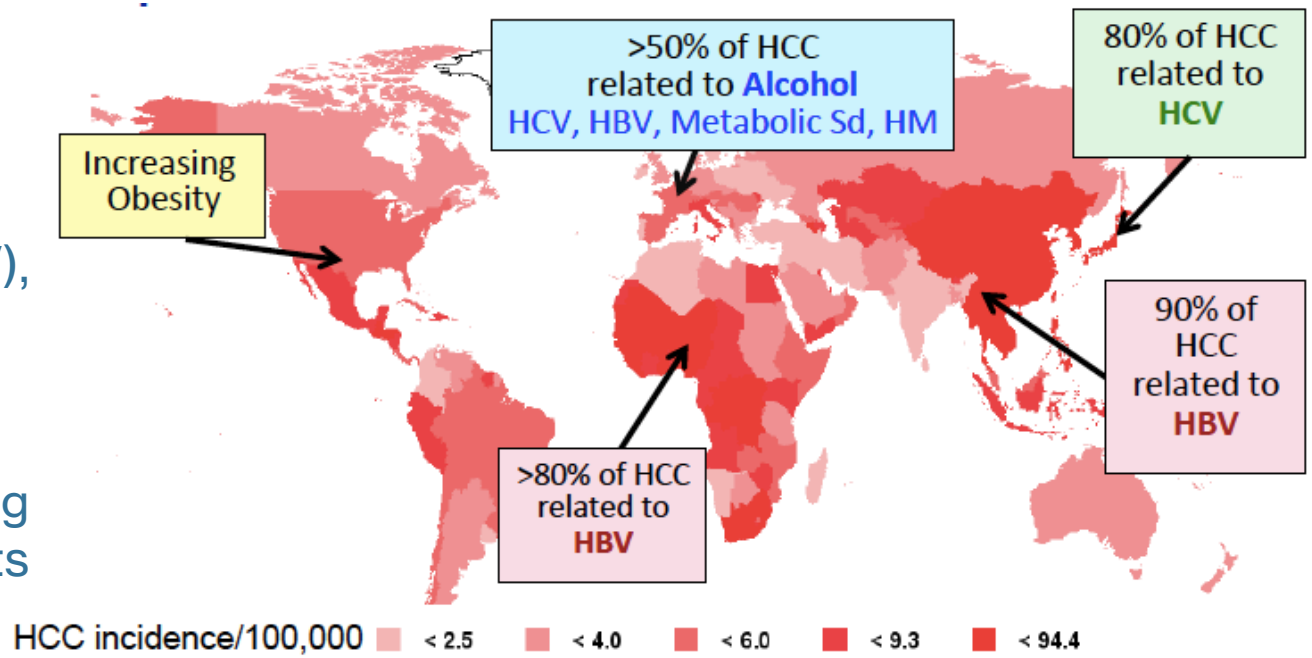
Hospices Civils de Lyon, France

Hospices Civils de Lyon

State of the Art and Issues

- Chronic infection by hepatitis B virus (HBV), as a major global health issue

- Hepatocellular carcinoma, second leading cause of death among cancer patients worldwide



Worldwide mapping of hepatocellular carcinoma incidence

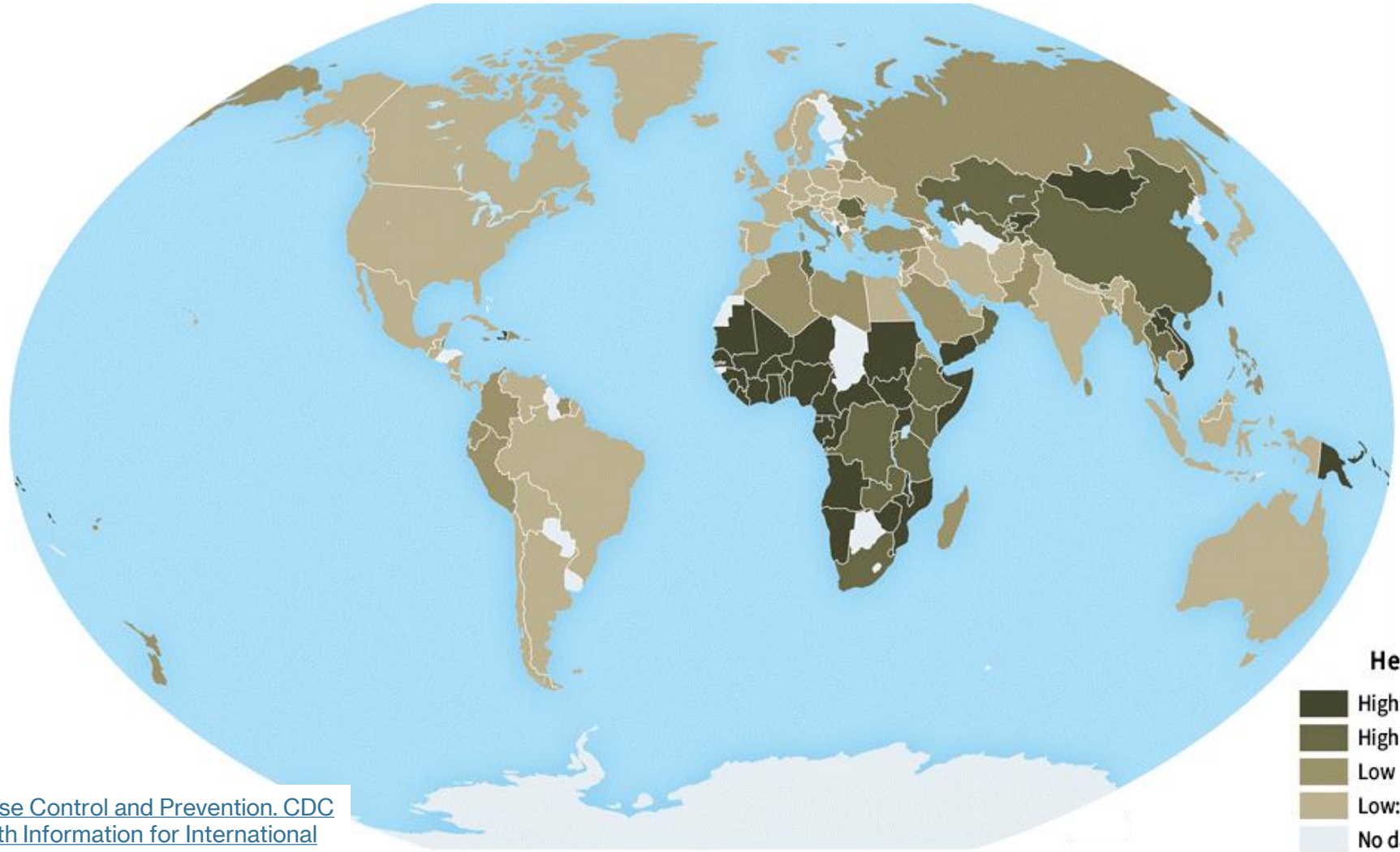
- Infection is usually asymptomatic, leading to late diagnosis. Without early diagnosis and access to treatment, up to 25% of patients with chronic hepatitis are at risk of developing hepatocellular carcinoma during their lifetime.

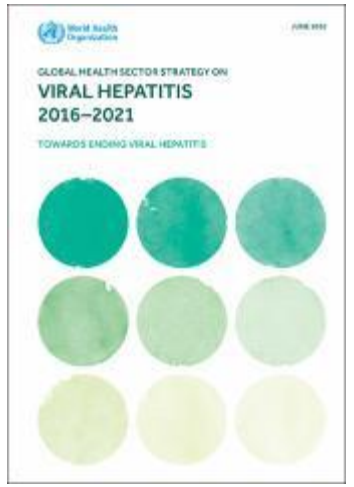
- In high income countries, HBV is more prevalent in key populations that are particularly remote from the healthcare system, such as migrants, the very poor and the homeless.

- In highly endemic areas, hepatitis B is most spread from mother to child at birth or through horizontal transmission before the age of 5 years, in the absence of resources and organisation to deliver prompt universal HBV vaccination.

Harriet Rumgay et al. J Hepatol 2022
WHO Global hepatitis report 2024: action for access in LMICs
Wen-Juei Jeng et al. Lancet 2023; 401: 1039–52

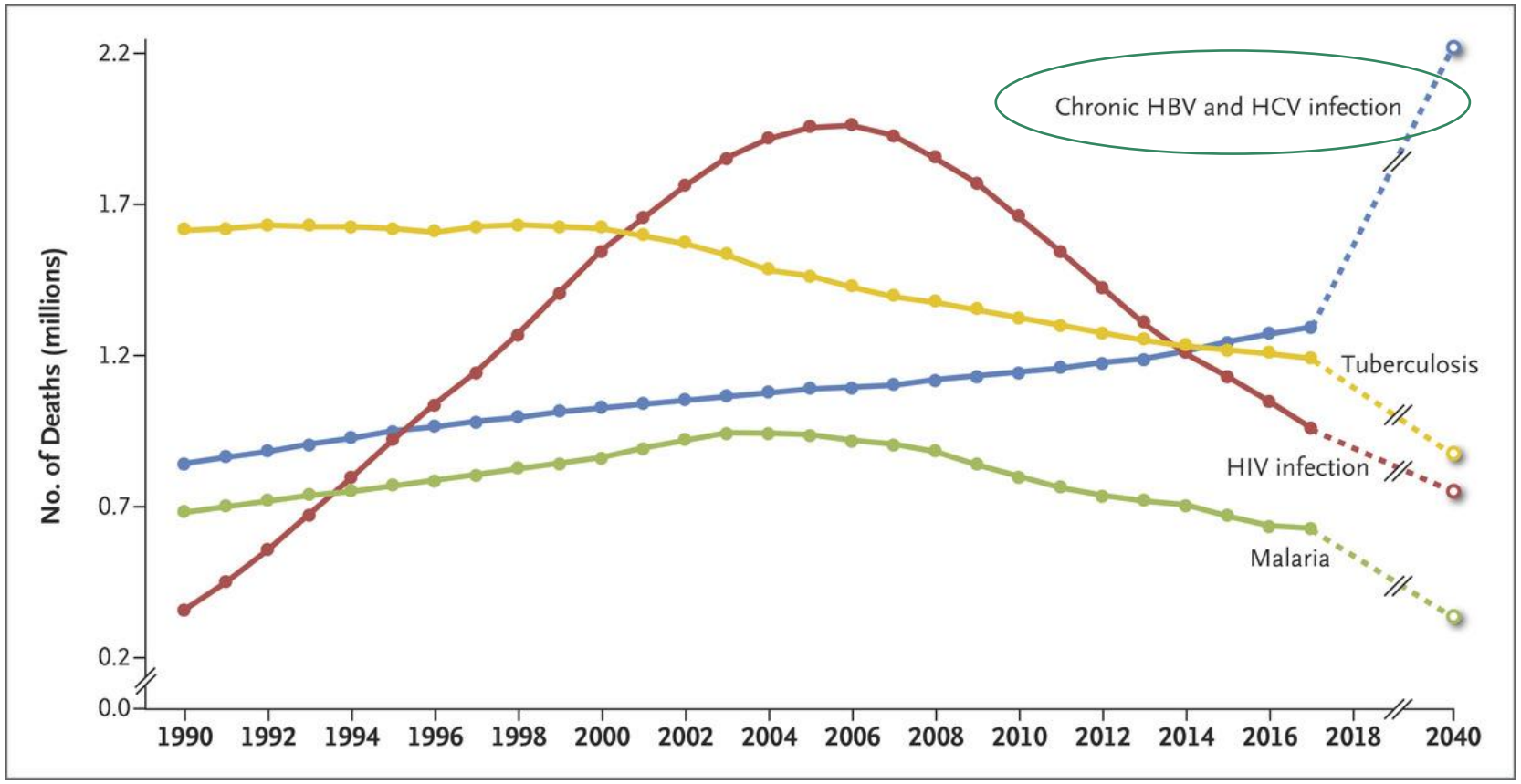
Countries most affected by chronic hepatitis B worldwide





Source: Centers for Disease Control and Prevention. CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press; 2019.

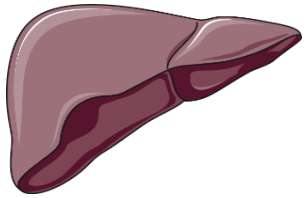
Worldwide Deaths from Chronic Viral Hepatitis as Compared with Deaths from Tuberculosis, HIV and Malaria

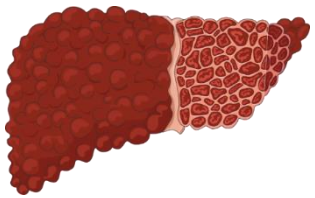


DL Thomas. N Engl J Med 2019;380:2041-2050

GLOBALLY

Evolution over 30 years





Viral susceptibility

5 - 10% of adults

Acute infection

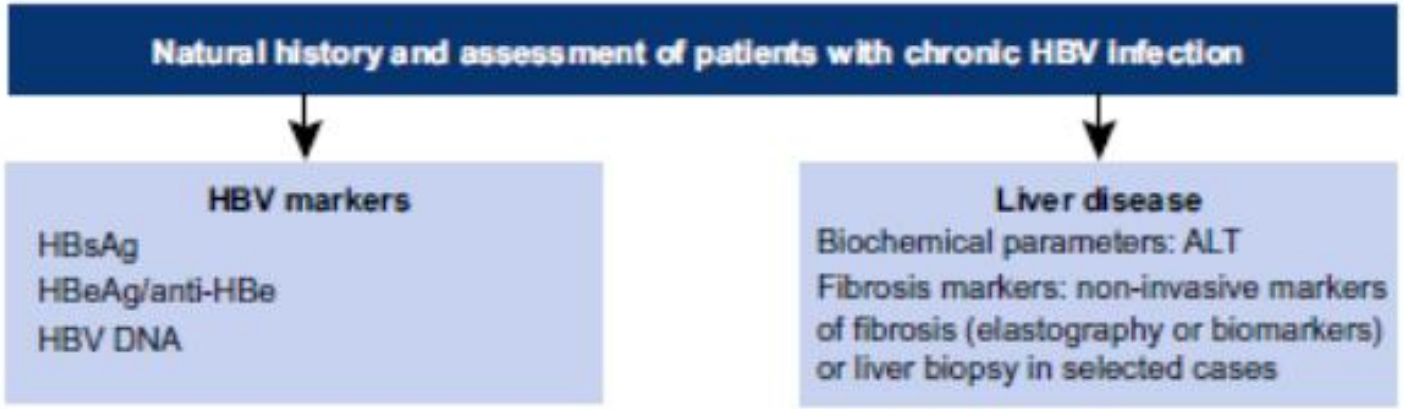
Chronic infection

15-40%

Cirrhosis and/or HCC

4th cause of death by cancer globally

Spearman et al. 2017
Zoulim et al. 2018



	HBeAg positive		HBeAg negative	
	Chronic infection	Chronic hepatitis	Chronic infection	Chronic hepatitis
HBsAg	High	High/intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/ml	10^4-10^7 IU/ml	<2,000 IU/ml**	>2,000 IU/ml
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis

Fig. 1. Natural history and assessment of patients with chronic HBV infection based upon HBV and liver disease markers. *Persistently or intermittently. **HBV DNA

EASL 2017 Guidelines for Chronic Hepatitis B Care

Pietro Lampertico et al. J Hepatol 2017

WHO targets for the elimination of chronic viral hepatitis

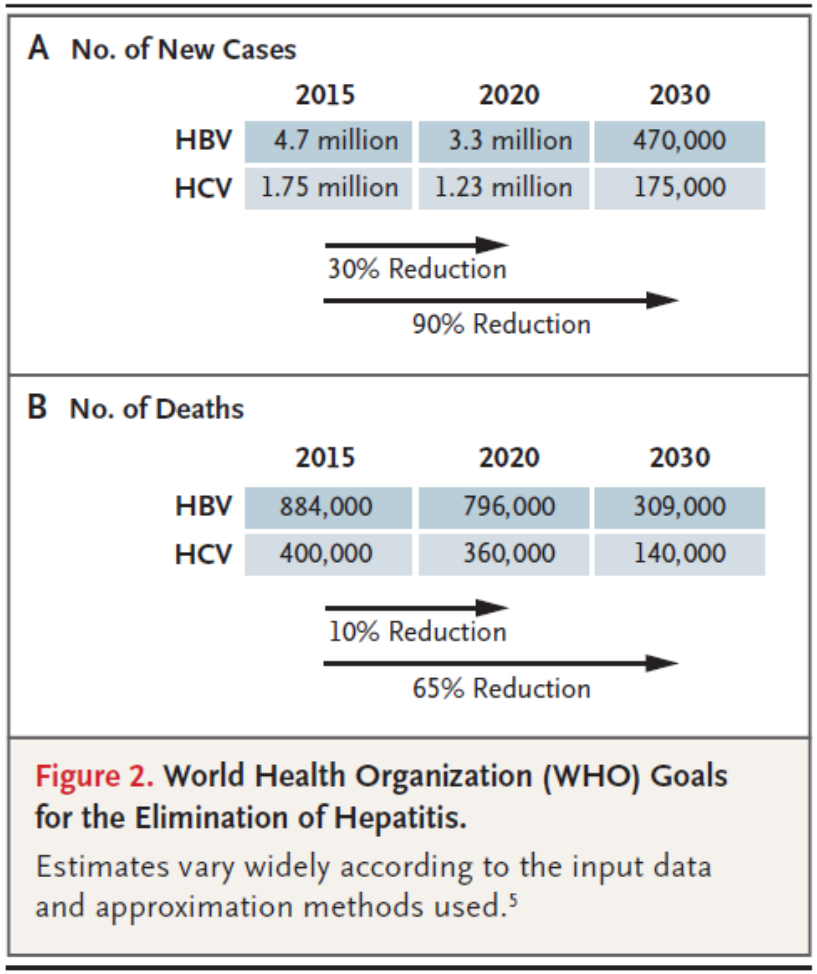


Figure 2. World Health Organization (WHO) Goals for the Elimination of Hepatitis.

Estimates vary widely according to the input data and approximation methods used.[5]

Table 1. Targets for the Primary Interventions Projected by the World Health Organization (WHO) to Eliminate Chronic Hepatitis by 2030.*

Intervention	Indicator	2015 Baseline	2020 Target	2030 Target
HBV vaccination	% of infants with HEPB3 vaccination	84	90	90
Prevention of maternal HBV transmission	% of infants with HBV vaccination ≤12 hr after birth	39	50	90
Blood safety	% of donations screened with quality assurance	97	98†	100
Injection safety‡	% of unsafe injections	5	0	0
Harm reduction§	No. of syringes or needles distributed/injection drug user/yr	27	200	300
HBV diagnosis	% of infected persons who receive a diagnosis	9	30	90
HCV diagnosis	% of infected persons who receive a diagnosis	20	30	90
HBV treatment¶	% of persons with diagnosed infection who are treated	8	—	80
HCV treatment¶	% of persons with diagnosed infection who are treated	7	—	80

* Data are from the WHO 2017 Global Hepatitis Report[5] and 2016–2021 Global Health Sector Strategy.[4] The 2015 baseline figures are approximated. For hepatitis B virus (HBV) vaccination, three doses of hepatitis B vaccine (HEPB3) are given with other routine childhood immunizations, often as a pentavalent vaccine. HCV denotes hepatitis C virus.
† The target is given as 95% in the 2017 Global Hepatitis Report[5] and the 2016–2021 Global Health Sector Strategy.[4]
‡ Injection safety is expressed in the 2016–2021 Global Health Sector Strategy[4] as the percentage of injections administered with safety-engineered devices in and out of health care facilities, a practice that began in 2015 at 5% of all injections and needs to rise to 50% and 90% in 2020 and 2030, respectively.[5]

DL Thomas. N Eng J Med 2019

Universal HBV Vaccination

- WHO estimates that 254 million people were living with chronic hepatitis B infection (CHB) in 2022, with 1.2 million new infections each year
- Hepatitis B infection acquired in adulthood leads to CHB in less than 5% of cases, whereas infection in infancy and early childhood leads to CHB in about 95% of cases, resulting in an estimated 1.1 million deaths a year
- Prompt universal HBV vaccination is the most cost-effective way to prevent new HBV infection and its complications
- All neonates should receive the hepatitis B vaccine as soon as possible within 24 hours after birth, followed by two or three doses of hepatitis B vaccine at least four weeks apart.
- This safe and highly effective recombinant vaccine offers nearly full protection against the HBV and is the basis for strengthening and prioritising infant and childhood vaccination

Xiang Li et al. Lancet 2021; 397: 398–408
GBD 2019 Hepatitis B Collaborators. Lancet Gastroenterol Hepatol 2022; 7: 796–829
The Polaris Observatory Collaborators. Lancet Gastroenterol Hepatol 2023; 8: 879–907
Shevanthi Nayagam et al. Lancet Gastroenterol Hepatol 2023; 8: 635–45

Barriers to Achieve HBV Eradication

- Despite the introduction of universal hepatitis B vaccination and effective antiviral therapy, the estimated overall seroprevalence of hepatitis B surface antigen remains high at 6·1% in sub-Saharan Africa.
- Hepatitis B is also spread by needlestick injury, tattooing, piercing and exposure to infected blood and body fluids, such as saliva and menstrual, vaginal and seminal fluids
- Transmission of the virus may also occur in healthcare settings, in the community or among persons who inject drugs
- Sexual transmission is more prevalent in unvaccinated persons with multiple sexual partners and adult vaccination is also required in high-risk populations to reduce HBV infection.
- As of 2020, 98% of countries worldwide have adopted universal infant HBV vaccination with 83% coverage of the three to four-dose series, but timely coverage of birth dose remains less than 50%.

Mingjuan Tan et al. Lancet Gastroenterol Hepatol 2021; 6: 106–19
WHO Global hepatitis report 2024: action for access in LMICs

HBV priority elimination strategies

PREVENT NEW INFECTIONS

- Cost-effective prevention of new infections via universal implementation of the HBV birth-dose vaccine
- Full vaccine coverage is safe, efficient, and available
- Catch-up vaccination campaigns for teenagers and young adults
- Prevention campaigns for migrants in high income countries

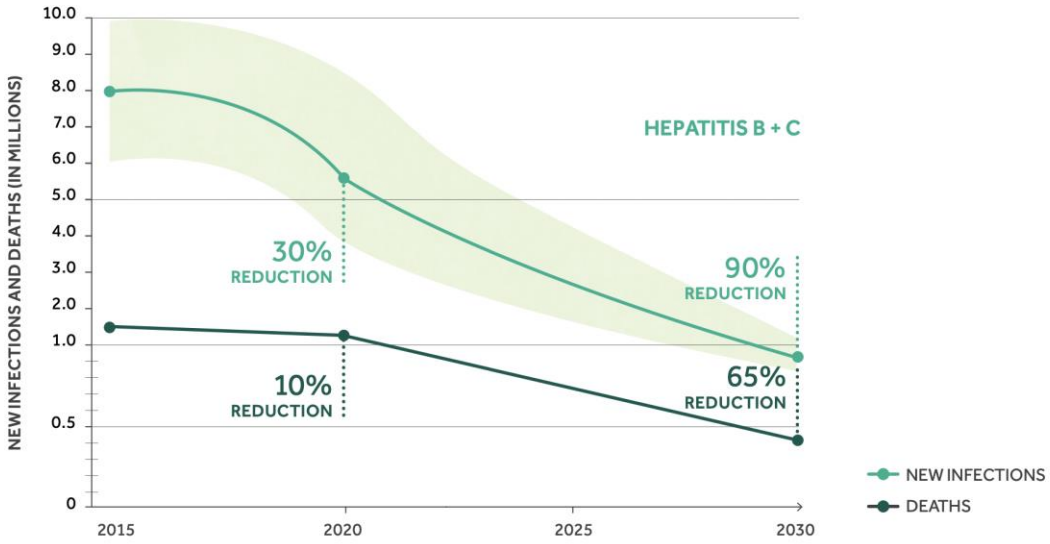
DIAGNOSE AND TREAT CHRONIC INFECTIONS

- Access to affordable diagnostics to identify HBV-infected individuals
- Enable linkage to care and antiviral therapy thanks to political stakeholders and civil society organizations
- Removing of stigma by tailored country-specific prevention
- Prevention campaigns for migrants in high income countries
- Cascade of care and linkage to care, for key populations
- Development of simple, relevant and effective prognostic scores to broaden eligibility for antiviral treatment
- Development of curative therapies

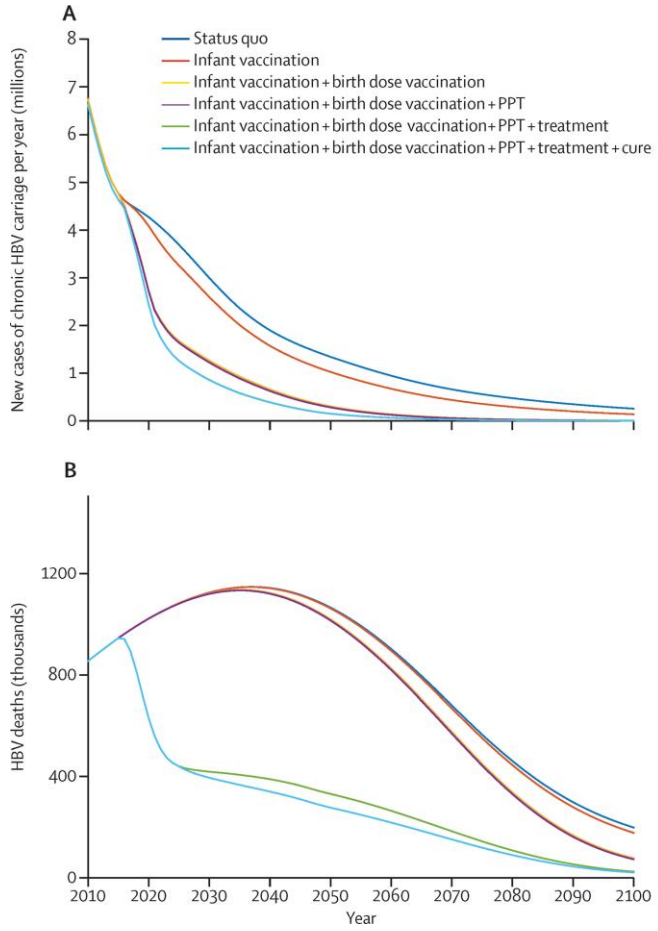
WHO Global hepatitis report 2024: action for access in LMICs
Wen-Juei Jeng et al. Lancet 2023; 401: 1039–52

Panorama for achieving the 2030 WHO hepatitis elimination target

Hepatitis B elimination goals



WHO Impact targets for viral hepatitis elimination



Global impact of interventions against HBV. WHO GHSS.
Nayagam et al. Lancet Infect Dis. 2016 Dec;16(12):1399-1408

Prognostic and access to care factors of chronic hepatitis B

Sociology and economics

Access to vaccination

Access to antiviral treatment

Human Sciences

Disease knowledges

Health litteracy

Believes

Health Geography

Access to screening, diagnosis, and follow-up

Biology

Microbiology

Immunology

Molecular Biology

Genetics et epigenetics

Clinical status

Steatosis

Fibrosis

Cirrhosis

Liver cancer (HCC)

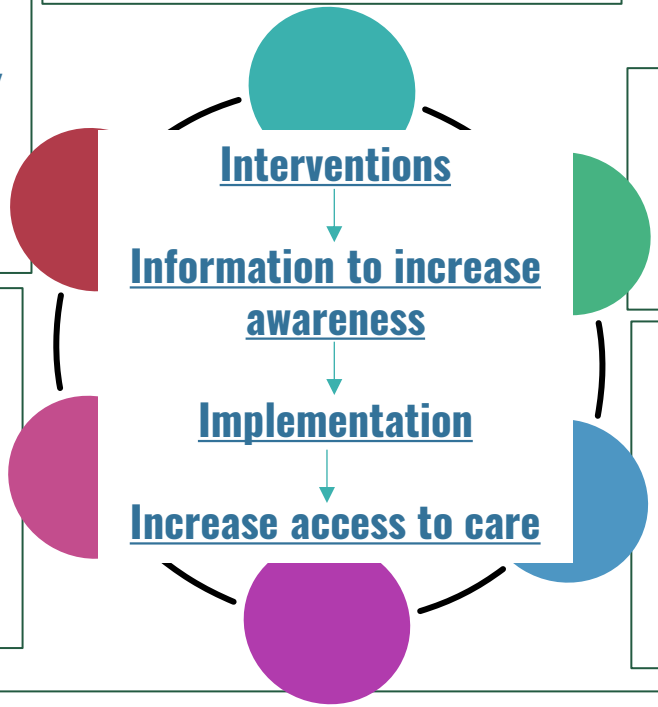
Epidemiology

Birth in high-endemic countries

Way of life and comorbidities

Food intoxication (alcohol, aflatoxin)

Interventions to improve prognostic of Chronic Hepatitis B



Prevent transmission by birth vaccination and antiviral treatment

Raise awareness (family disease), fighting discrimination with civil society organisations, promote partnerships and mobilize resources

Scale up screening, care and treatment services

Increase health equities within the hepatitis response

Simplify service delivery of viral hepatitis services

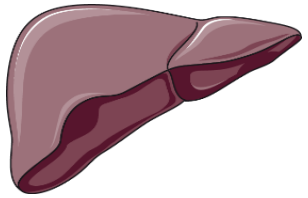
&

Bringing care closer to communities

Formulate evidence-based policy and data for action

AFRICA

Evolution over 30 years



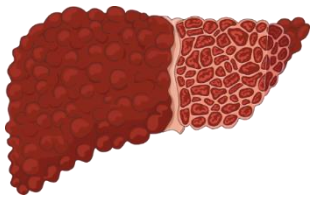
Viral susceptibility

Vaccination schedule?

Acute infection

Availability / eligibility of antiviral treatment?

Chronic infection

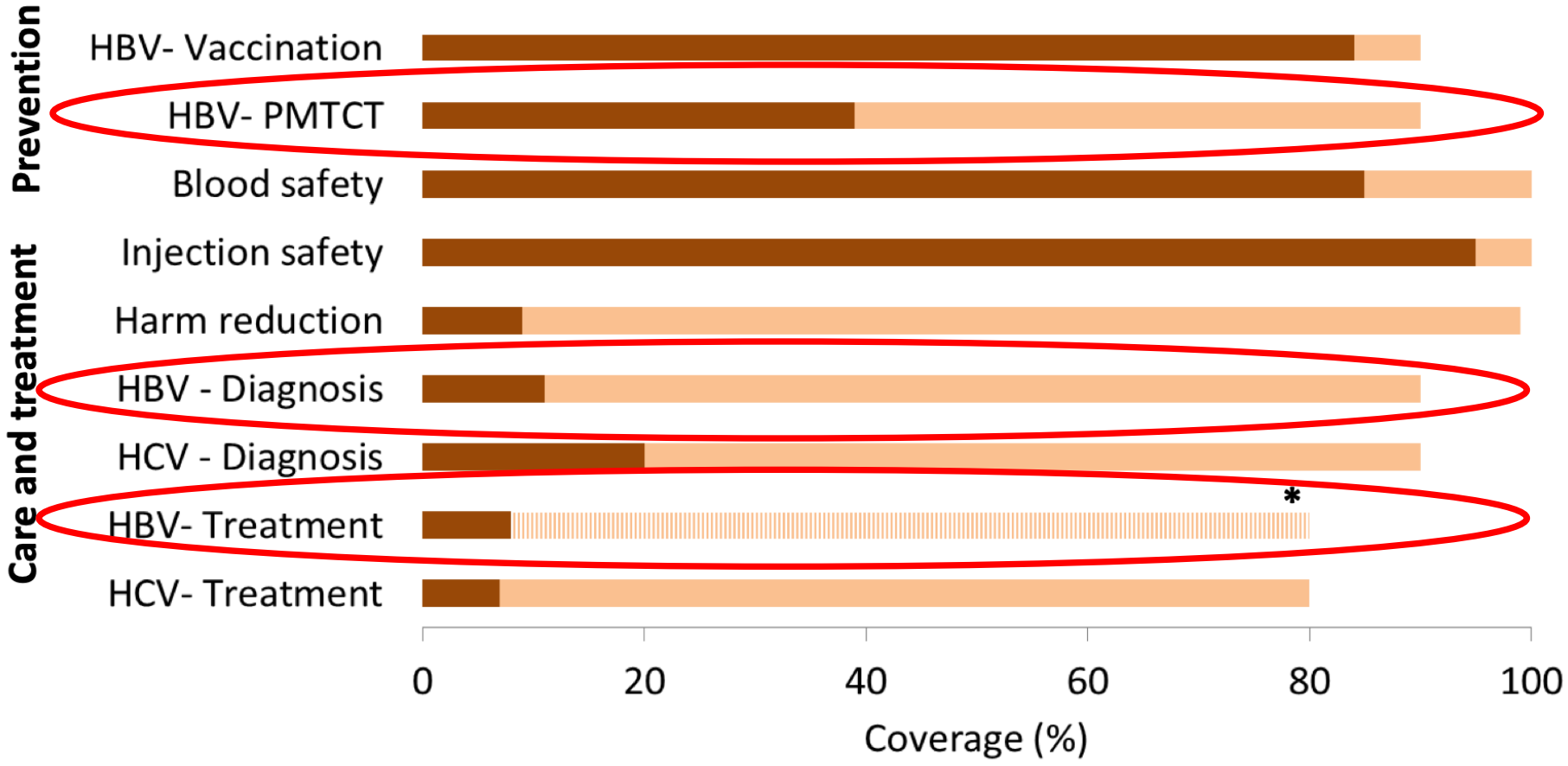


Cirrhosis and/or HCC

3rd cause of death by cancer in Africa

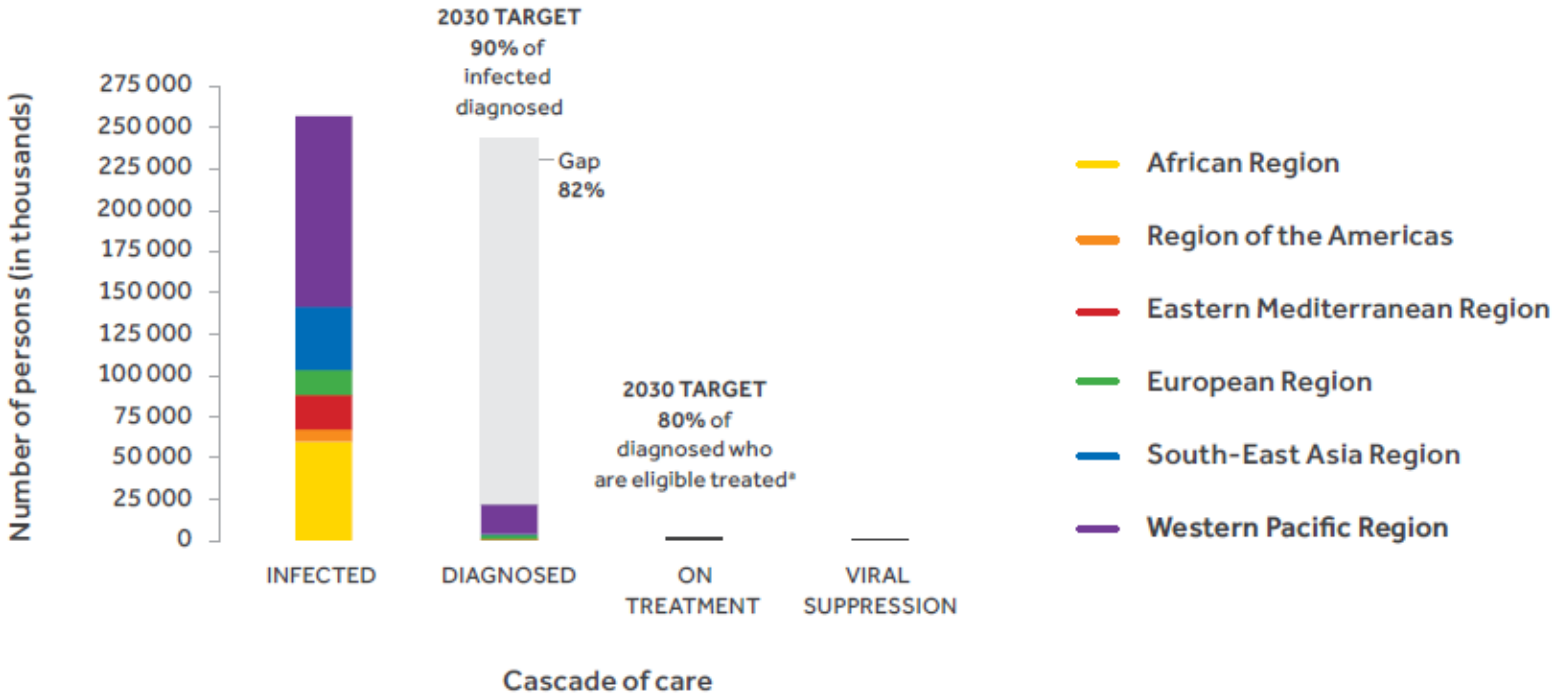
Spearman et al. 2017
Zoulim et al. 2018

Scale up of interventions



Maud Lemoine et al. Lancet Glob Health 2016
Wendy Spearman et al. Lancet Gastroenterol Hepatol 2017
Amina Sow et al. JHEP Reports 2022

Treatment eligibility and coverage, the challenging issue



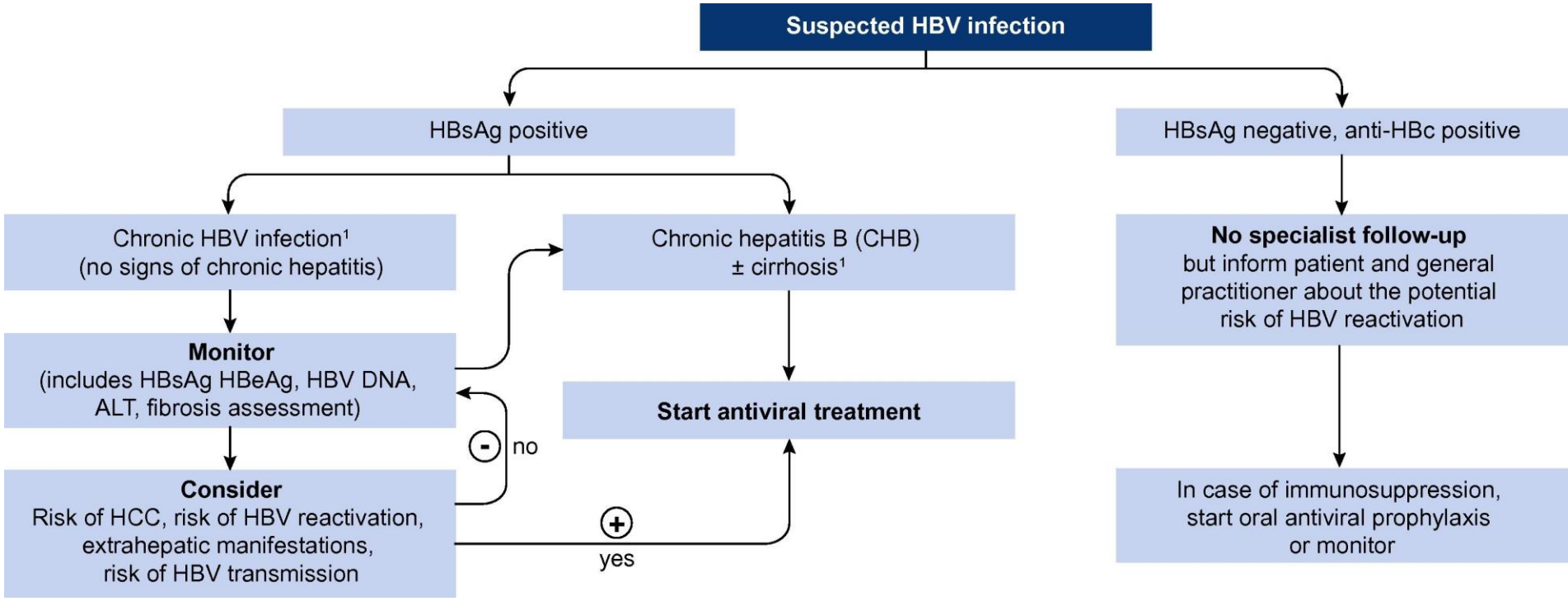
9% of HBV-infected patients are aware of their status[1]

4 – 9% of screened patients in Africa are in need of treatment[2]

8% of those in need of treatment have access to treatment[1]

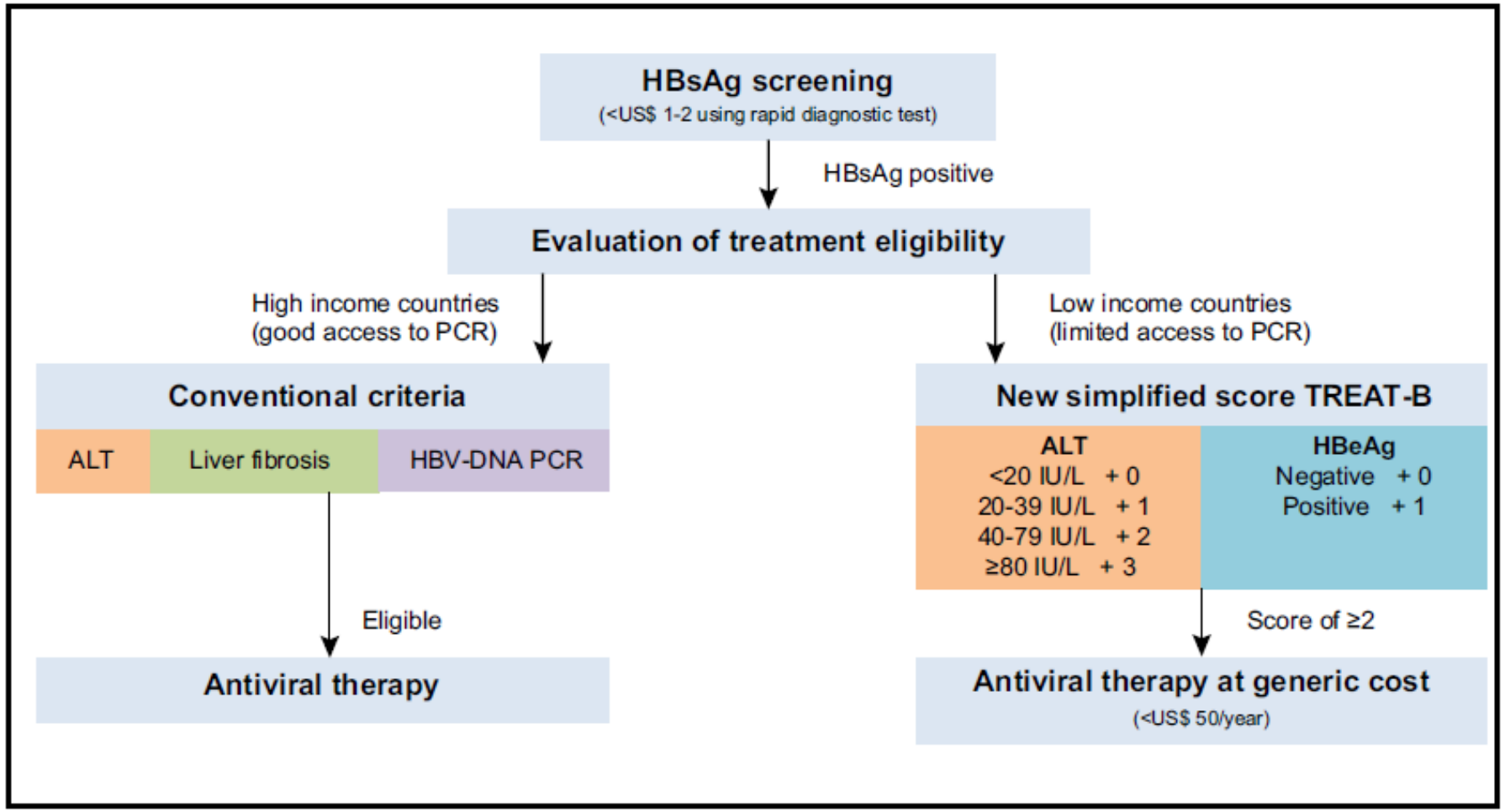
Global Hepatitis Report 2017
Lemoine et al. Lancet Glob Health 2016

EASL 2017 Guidelines for Chronic Hepatitis B Care



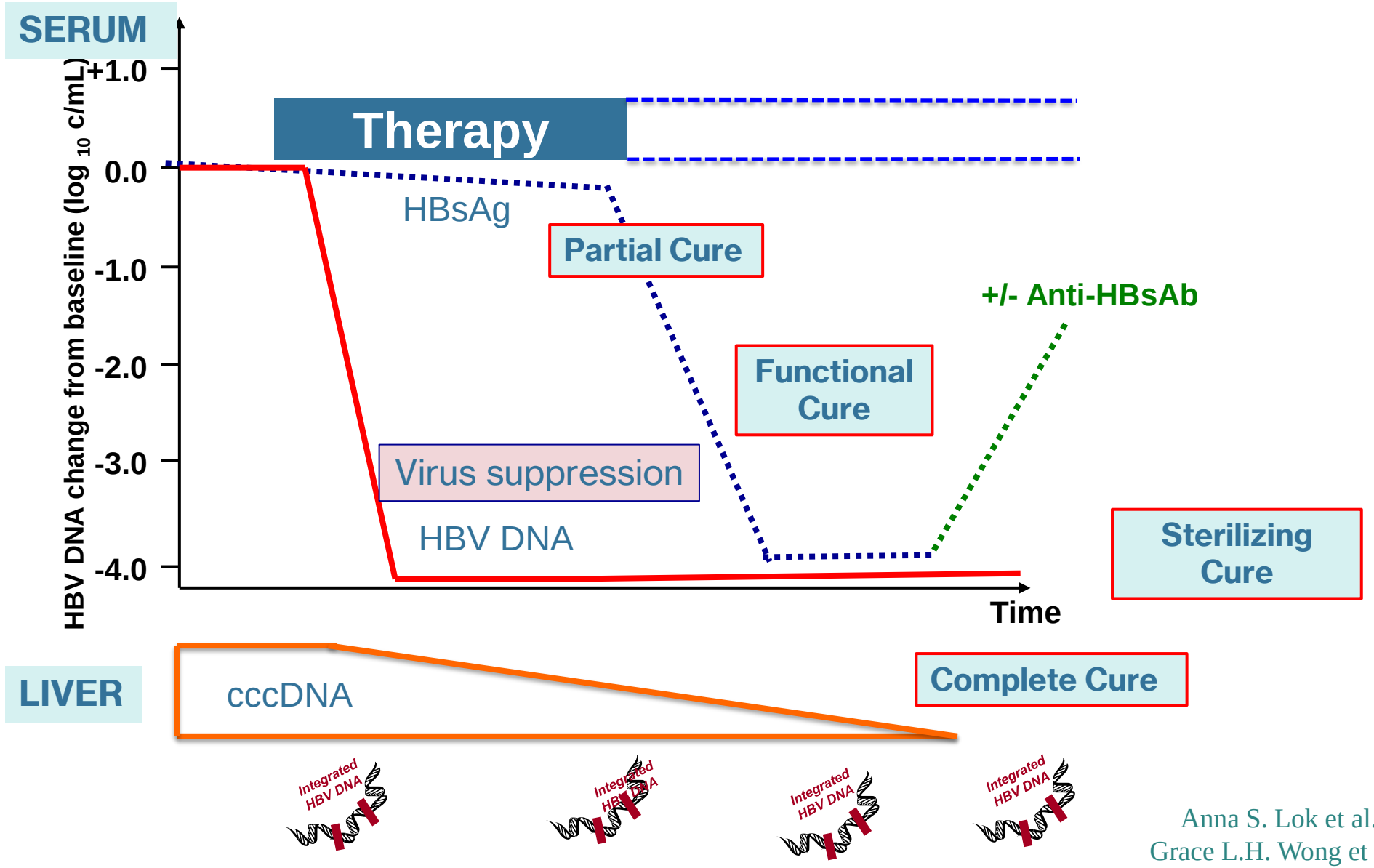
Pietro Lampertico et al. J Hepatol 2017

Development of a simple score based on HBeAg and ALT for selecting patients for HBV treatment in Africa



Y Shimakawa et al. J Hepatol. 2018, 69, 776–784

Definition of HBV cure: what do we want to achieve ?



Anna S. Lok et al. Hepatology 2017
Grace L.H. Wong et al. J Hepatol 2021
Barbara Testoni et al. Sem Liver Dis 2017

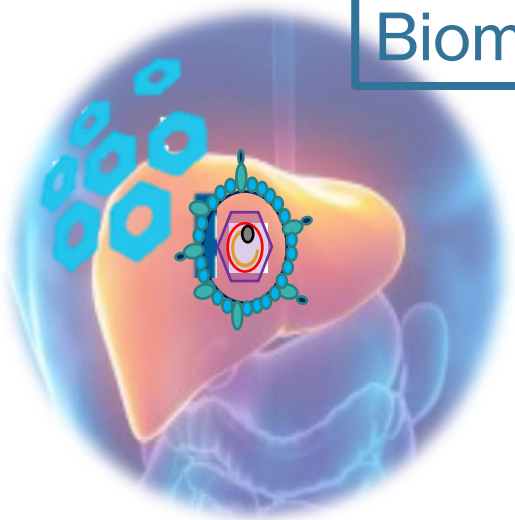
Cure

Access to care

Clinical development

Biomarkers

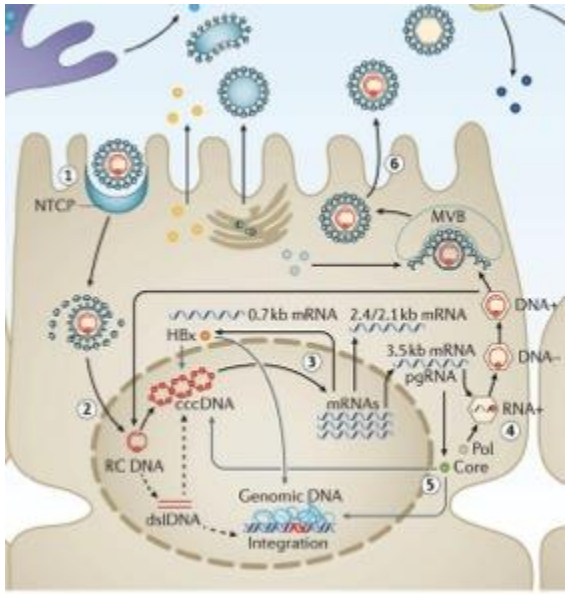
Antivirals

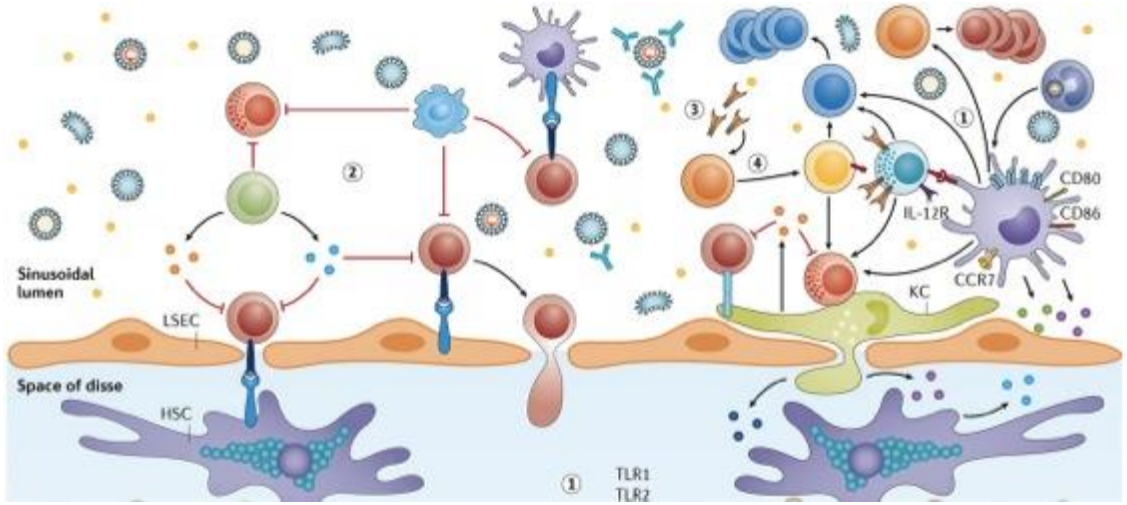


Immunotherapy

Drug Discovery

Mechanisms of viral persistence





cccDNA reservoir

Antigenic load

Liver tolerance

HBV persistence

Defective CD8+ response

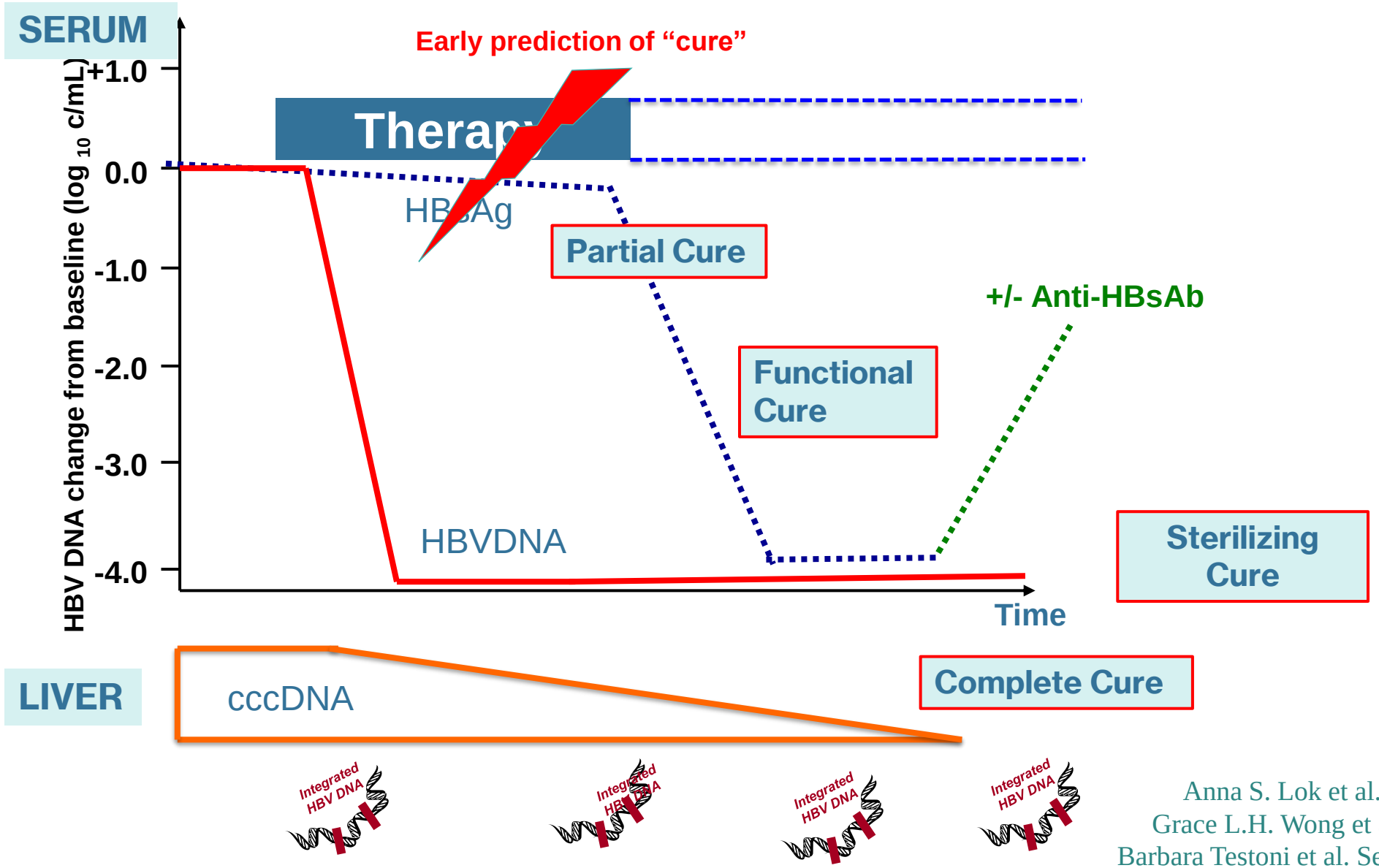
Defective B cell response

Inefficient innate response

Defective immune responses

Locarnini, S. & Zoulim, F. et al. Global strategies are required to cure and eliminate HBV infection. Nat. Rev. Gastroenterol. Hepatol. 2016

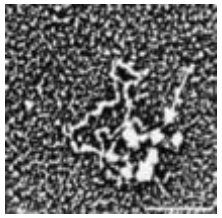
Need for biomarkers to predict the cure of infection



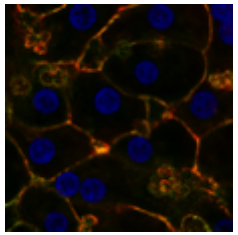
Anna S. Lok et al. Hepatology 2017
Grace L.H. Wong et al. J Hepatol 2021
Barbara Testoni et al. Sem Liver Dis 2017

Major virologic discoveries for HBV cure research programs

- **Better knowledge of the viral life cycle**
- Receptor – cccDNA - HBx

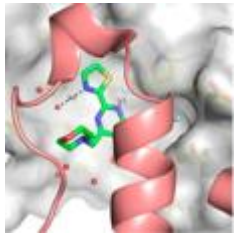


- **Improvement of cell culture for target identification and drug screening**
- Hepatoma cell lines – receptor and cccDNA formation
- Primary Human Hepatocytes and other culture systems



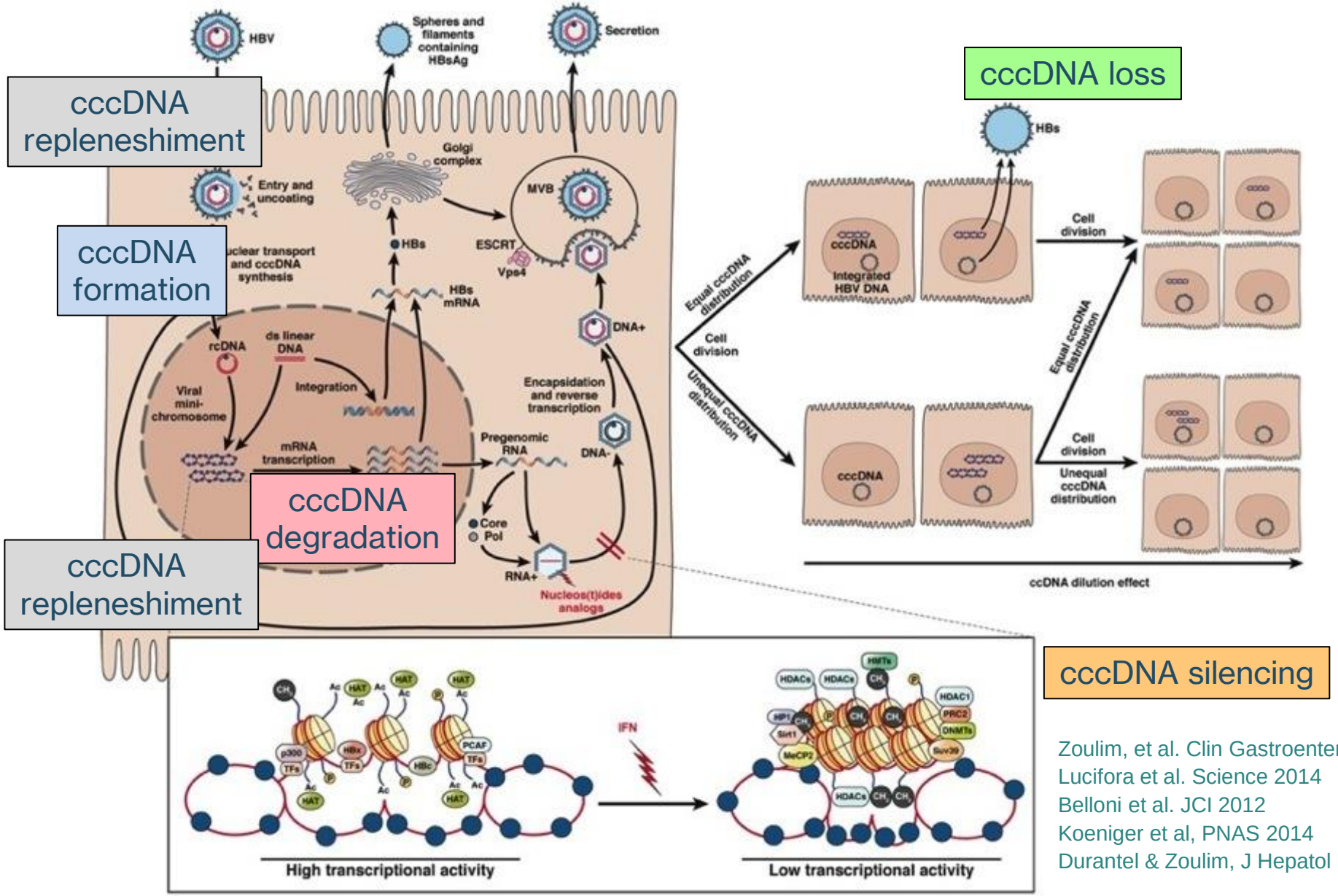
- **Improvement of animal models for target identification and drug screening**
- Liver humanized mouse models

- **Identification & characterization of novel targets**



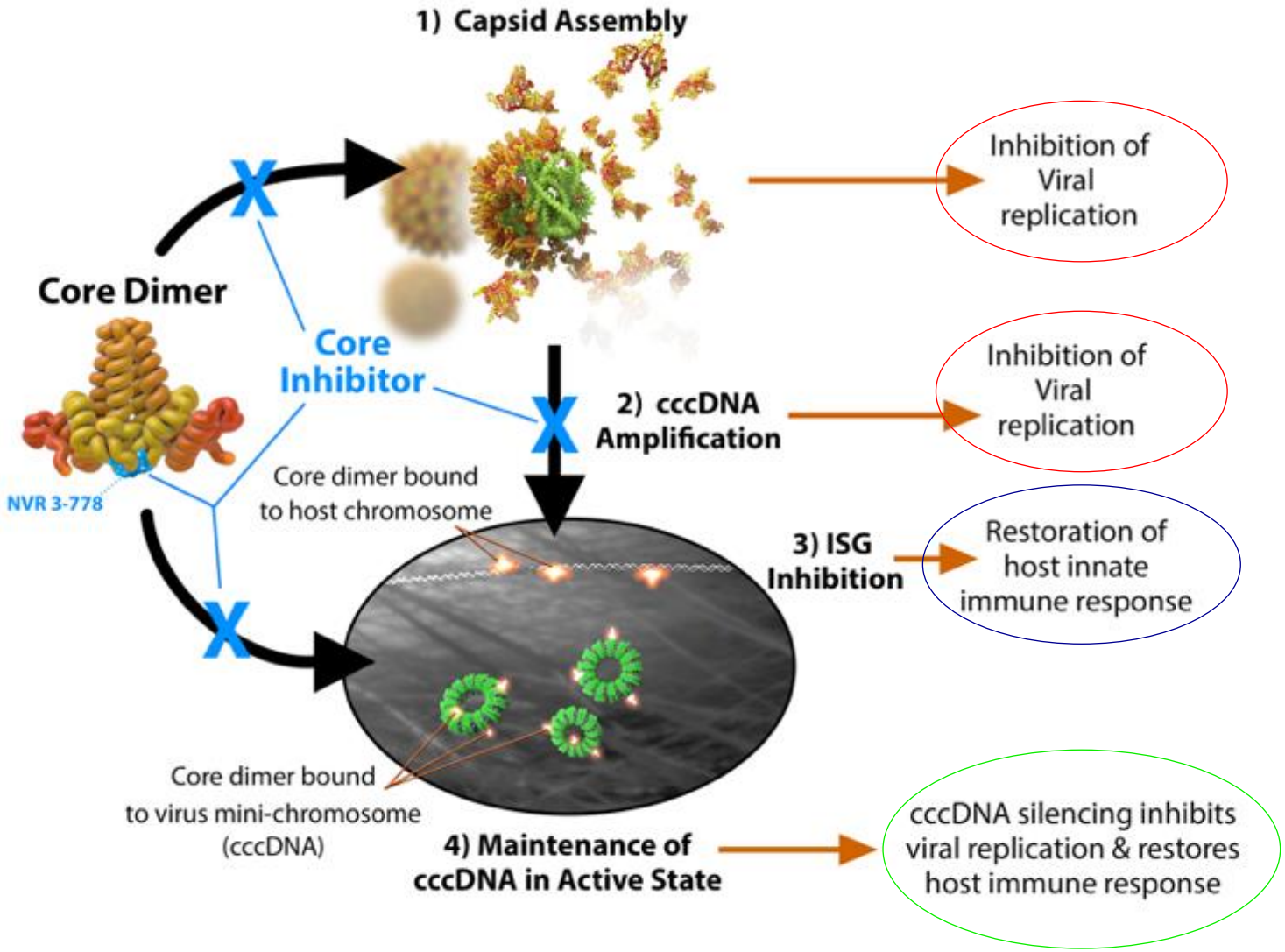
Zeisel et al. Gut 2015; Li et al. elife 2012; Königer et al. PNAS 2014; Shlomai et al. PNAS 2014; March et al. Nat Protoc 2015; Dandri et al. J Hepatol 2016; Decorsière et al. Nature 2016

Targeting cccDNA, the viral minichromosome



Zoulim, et al. Clin Gastroenterol Hepatol 2013
Lucifora et al. Science 2014
Belloni et al. JCI 2012
Koeniger et al, PNAS 2014
Durantel & Zoulim, J Hepatol 2016

Targeting the HBV capsid with capsid assembly modulators

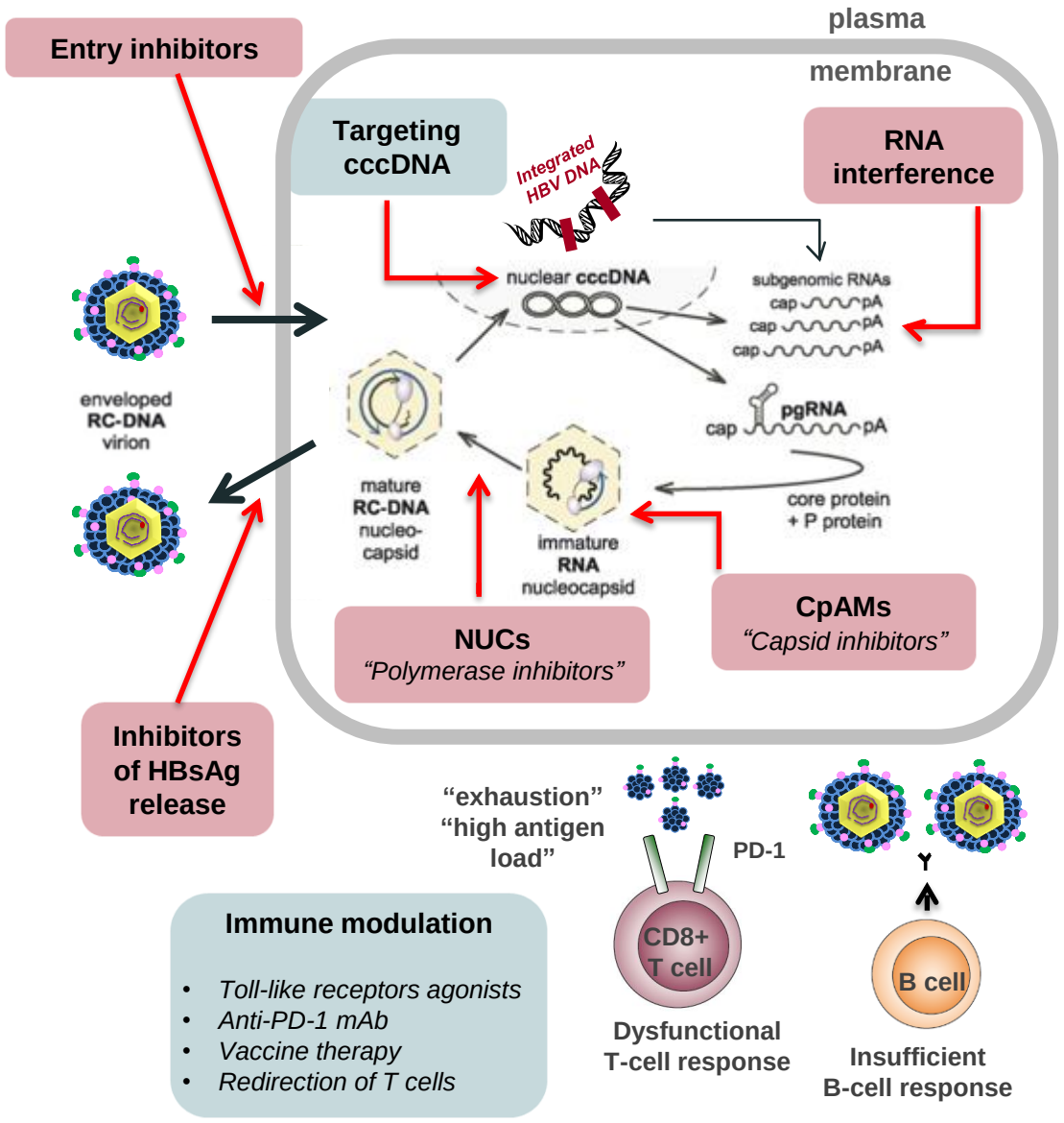


Billioud et al. Antiviral Res 2011; Klumpp K et al. PNAS 2015; Venkatakrishnan B et al. J Virol 2016

HBsAg targeting strategies

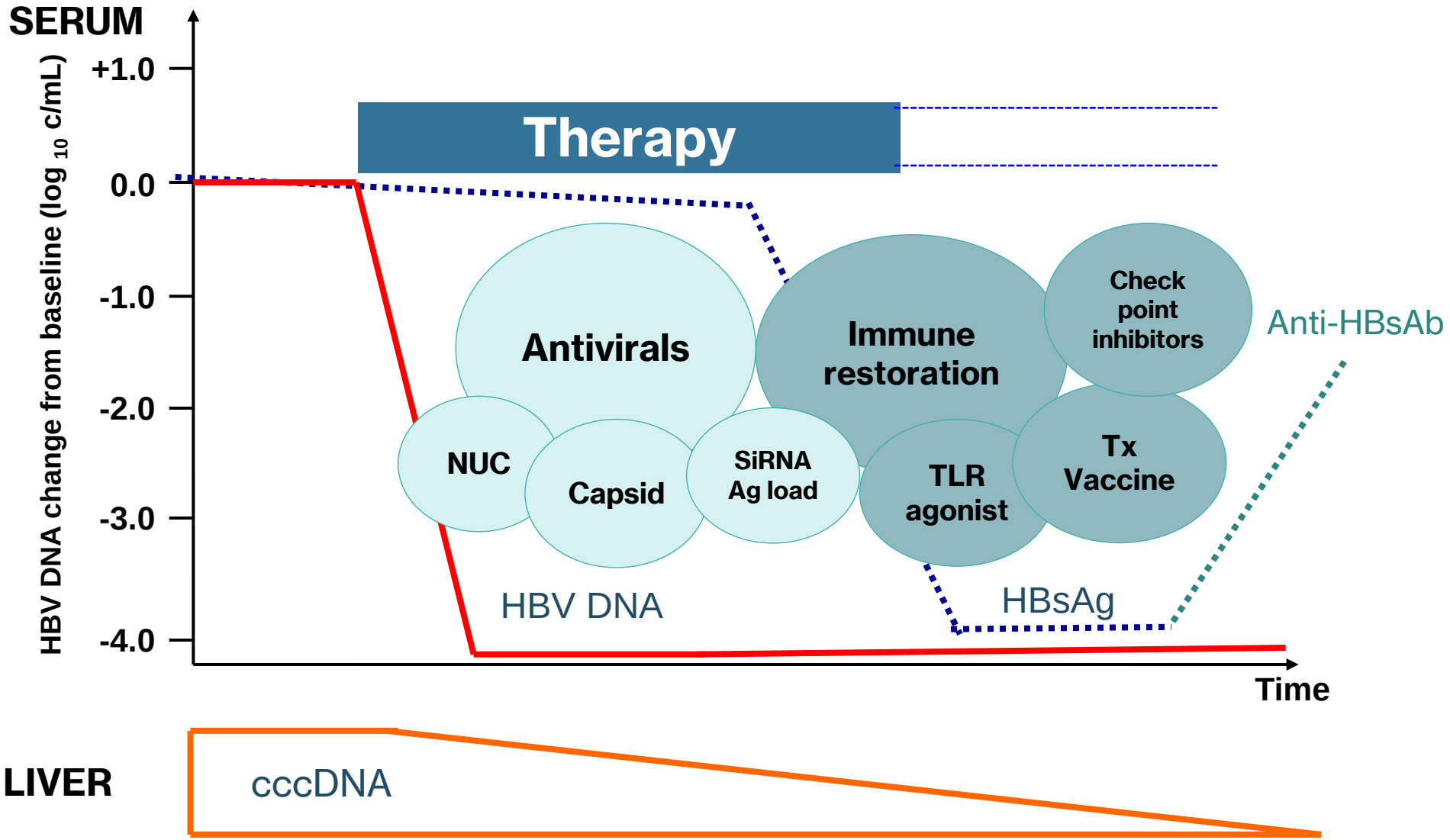
- HBsAg clearance an **endpoint of therapy**
- Decline in HBsAg levels may **restore the antiviral activity of exhausted T cells**
- **Several strategies** in evaluation
- RNA interference (SiRNA): « gene silencing »
- Nucleic acid polymers (NAPs): HBsAg release
- HBs antibodies

The main targets & drug discovery efforts



Revill, Zoulim et al. Nature Reviews Gastro & Hepatol 2016; Levrero et al. Current Opinion Virology, 2016

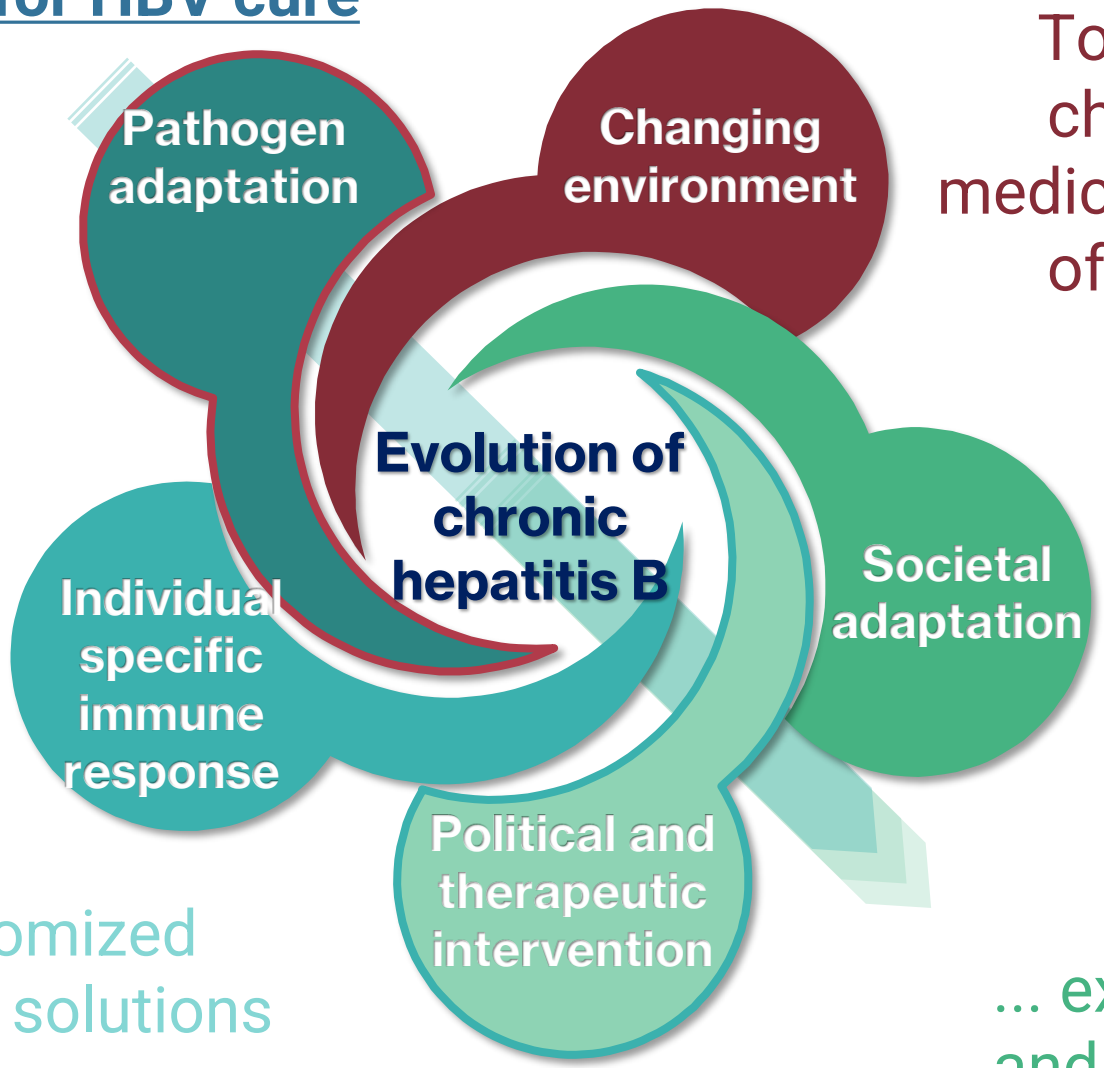
HBV cure - New treatment concepts – Will we need combination of DAA and immune therapy ?



Testoni et al. Liver International 2017

Chronic Hepatitis B and its Persistence in Civil Society

Concept One Health for HBV cure



To control the spread of chronic hepatitis B, the medical/societal management of the disease must be sustainable

To propose customized preventive/curative solutions

... extended to a psychosocial and economic approach

Multidisciplinary Collaborations and Targets

Key partnerships

Dr Isabelle Chemin, Inserm Lyon

Pr Marie Préau, Inserm Lyon

Dr Fayet & Fuentes, Inserm Lyon

Dr Pierre Pradat, CHU Lyon

Dr Hassan Ferrier, CHU Lyon

Dr Moana Gelu-Simeon, CHU Guadeloupe

Dr Antoine Jaquet, CHU Bordeaux

Pr Didier Ekouevi, Lomé

Dr Waliyou Salifou, Dapaong

Pr Jeffrey Lazarus, Barcelona

Pr Maud Lemoine, London

Pr Massimo Iavarone, Milan

Dr Sivhour Chiek, Battambang

Key activities

Epidemiology

Health Geography

Psychology

Molecular biology

Medicine

Public Health

Key resources

Clinical, biological and imaging database of CirB-RNA cohort

POC tests HBV, HDV, HCV, HIV

Artificial Intelligence

Molecular biology

Imagerie : Fibroscan, Echostéthoscope

Topics & Skills

Human Sciences

Health Geography

Health Economic

Epidemiology

Public Health

Medicine

Clinical Microbiology

Molecular

Imaging

Data Science

Communication

Organizations

Health Associations

Social and Civil Organizations

Hospitals

Health stakeholders

Universities

Industries Partnerships

Innovations

Social sciences Innovations

Health tech innovations

Biomedical Innovation

Assessment criteria

Acceptability

Feasibility

Accessibility

Cost utility

Prognosis

Ongoing Funding

France : IHU EVEREST, HCL, Inserm, CRCL, Université de Lyon , CHU de Guadeloupe

Europe : Ospedale universitario di Milano, Imperial College London, Global Health Barcelona

Togo : CHU de Lomé, Université de Lomé, NGO VIE, CHR Dapaong

Cambodia: Battambang Provincial Hospital, NGO LAFETT-MH, Battambang District hospitals

Targets

Facilitating access to care for people living with chronic hepatitis B

Study the multidisciplinary prognostic factors of chronic viral hepatitis B

Study of the medico-economic impact of implementing the Triple Ti access to care strategy for people living with chronic hepatitis B in disadvantaged areas