ICE-HBV

International Coalition to Eliminate HBV

PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

HBV Cure Science 101

Anna Kramvis, BScHons, PhD

ICE-HBV Governing Board Member

WITS UNIVERSITY

Research Professor/Director

Hepatitis Virus Diversity Research Unit

University of the Witwatersrand

South Africa

HVDRU

Disclosure

Relations that could be relevant for the meeting	Company names
Sponsorship or refund funds	• ICE-HBV (non-profit) • Wits (non-profit)
Payment or other financial remuneration	• None
Shareholder rights	• None
Other relations	• None

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Overview

- **Why** do we need a HBV cure now?
- **What** does HBV cure entail and **what** are the challenges?
- **How** do we achieve it?
- **ICE-HBV** and the way forward…….

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

http://www.nature.com/nrgastro/journal/v12/n4/images/nrgastro.2015.28-i1.jpg

Is HBV Cure a pipedream?

- HCV can be cured in 12 weeks using direct antiviral agents.
- Basic HBV science has advanced to make drug discovery for cure more feasible:
  - Discovery of the NTCP receptor
  - New in vitro systems
  - New animal models

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

https://hbr.org/2018/01/the-art-of-strategy-is-about-knowing-when-to-say-no

2030 WHO Global Hepatitis Strategy

In May 2016, the World Health Organization (WHO) adopted a global hepatitis strategy with the goal of **eliminating** viral hepatitis as a public health threat by 2030.

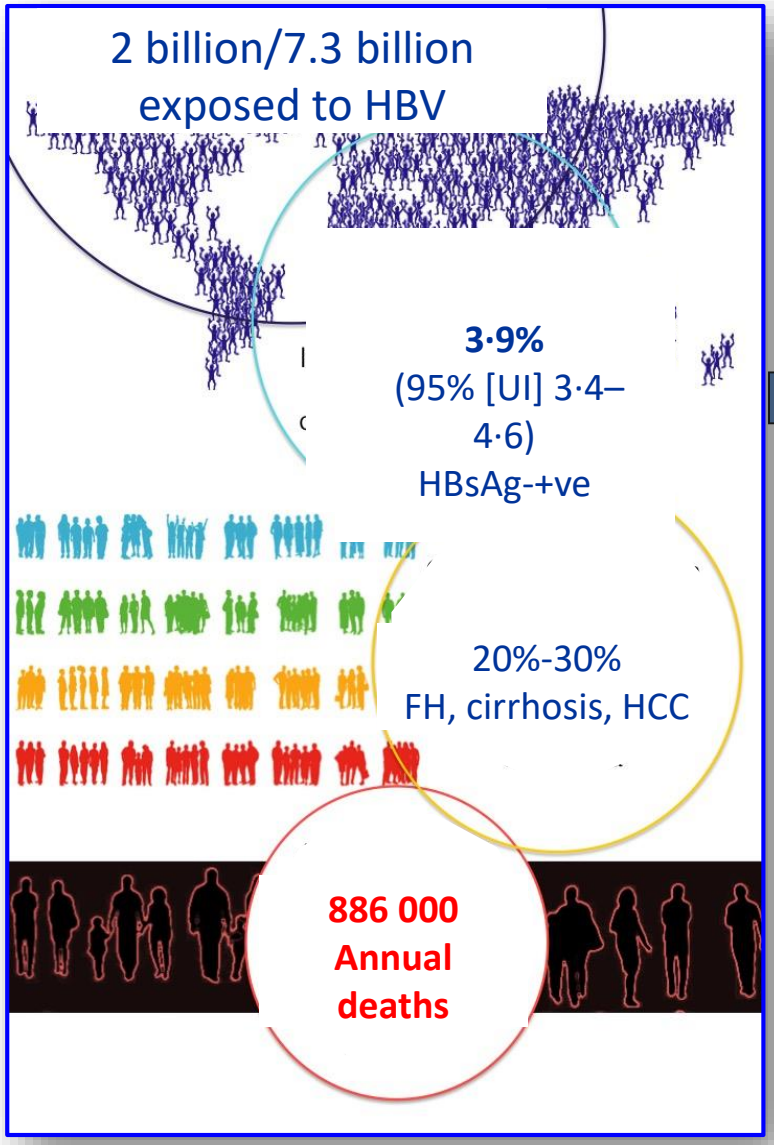
The targets to be achieved by 2030 are:

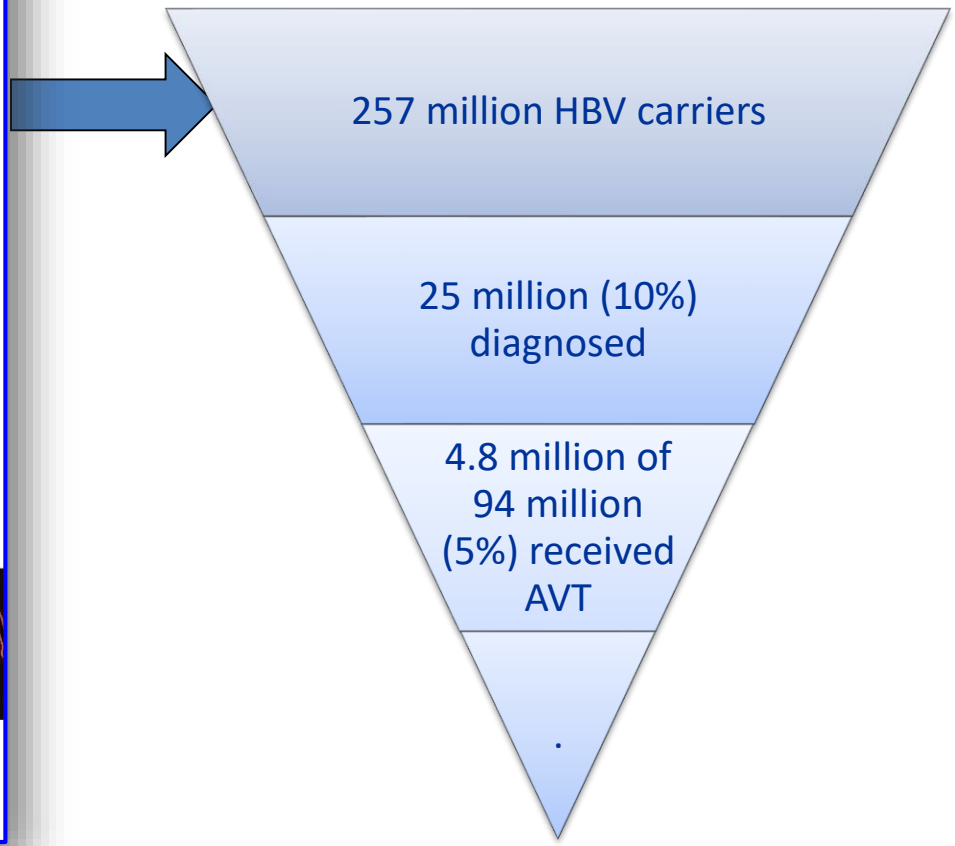
- **90%** reduction in new cases of chronic hepatitis B and C;
- **65%** reduction in mortality due to hepatitis B and C;
- **80%** of treatment-eligible persons with chronic hepatitis B and C infections being treated.

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

www.who.int/hepatitis/publications/hep-**elimination**-by-2030-brief/en/

HBV Diagnosis/ Treatment Cascade



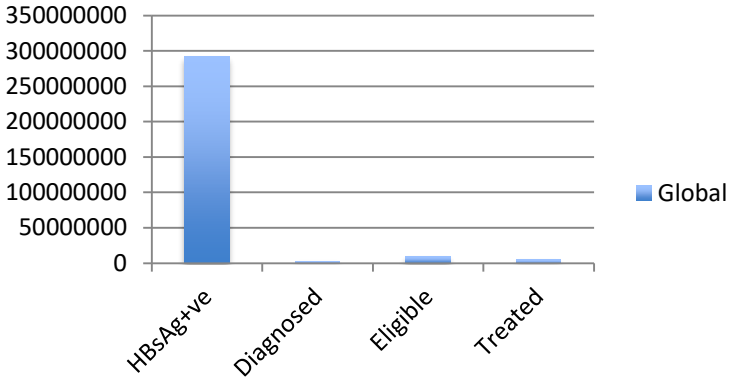


ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Razavi-Shearer et al (2018)Lancet Gastroenterol Hepatol 2018; 3: 383-403

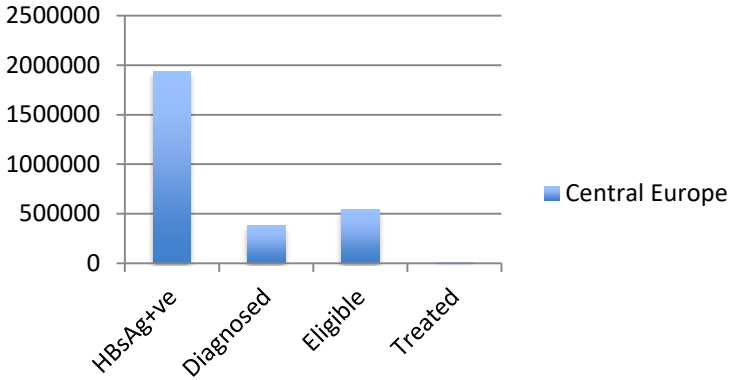
HBV Diagnosis/Treatment Cascade

Global



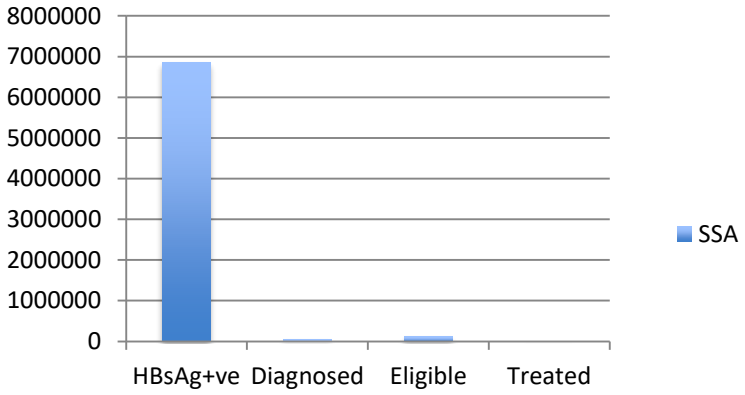
10% **5%**

Central Europe



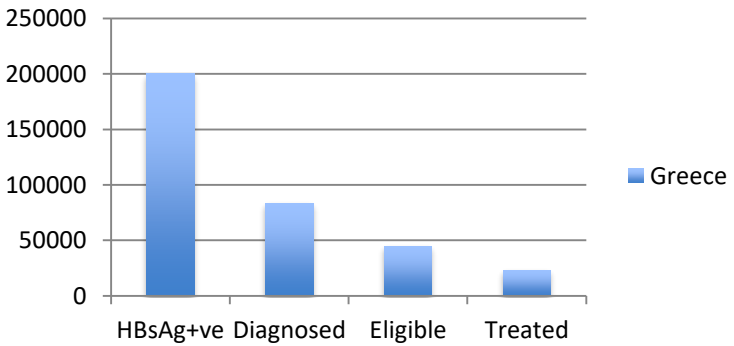
25% **3%**

SSA



<1% **<1%**

Greece



42% **51%**

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Razavi-Shearer et al (2018)Lancet Gastroenterol Hepatol 2018; 3: 383-403

Why we need a HBV cure?

Cure will help improve the diagnosis/treatment cascade and allow us to reach the WHO targets by:

1. Overcoming the limitations of the current treatments
2. Accelerating the reduction of HBV incidence
3. Decreasing the risk of hepatocellular carcinoma
4. Decreasing the morbidity and mortality of end stage liver disease and hepatocellular carcinoma
5. Reducing the costs of reaching WHO targets more rapidly

ICE-HBV
International Coalition to Eliminate HBV

PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Current Anti-HBV Therapy

Nucleos(t)ide Analogues [NUCs]

Lamivudine, telbidvudine, adefovir, entecavir and tenofovir decrease viral loads and have all been shown to decrease mortality as a result of cirrhosis and HCC.

Tenofovir, which has a high barrier against resistance, is the WHO preferred antiviral

Interferon-α Derivatives

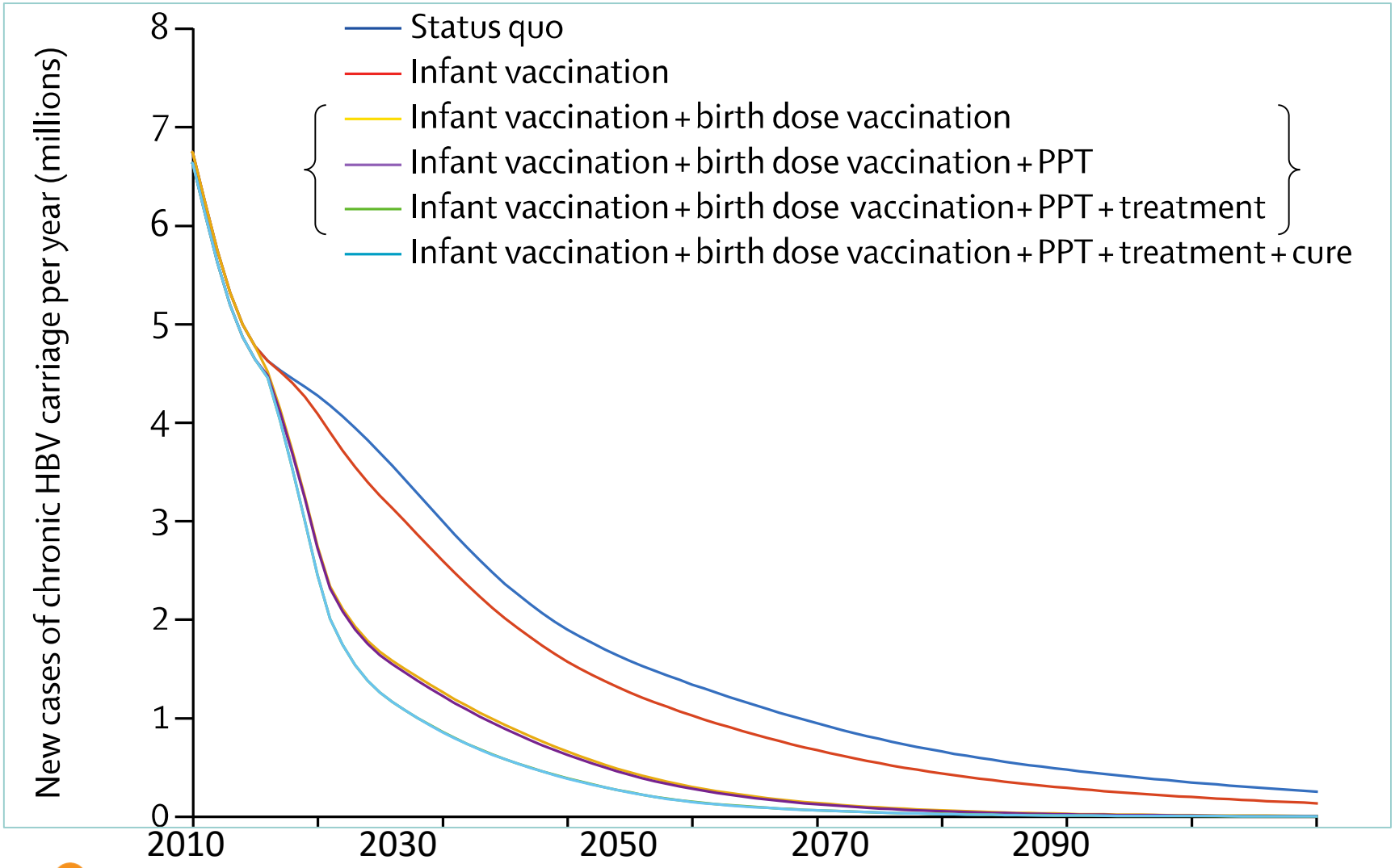
Finite treatment that boost the immune response to suppress viral loads.

Limitations

- HBsAg seroconversion is rare
- Need to be taken for life – a hindrance for adherence
- Injectable drugs weekly for 48 weeks are not popular
- Side effects/poor tolerability
- Do not eliminate cccDNA

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Accelerate Reduction of HBV Incidence



ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Nagayam et al Lancet Infect Dis 2016; 16: 1399-1408

Decrease Risk of Hepatocellular Carcinoma

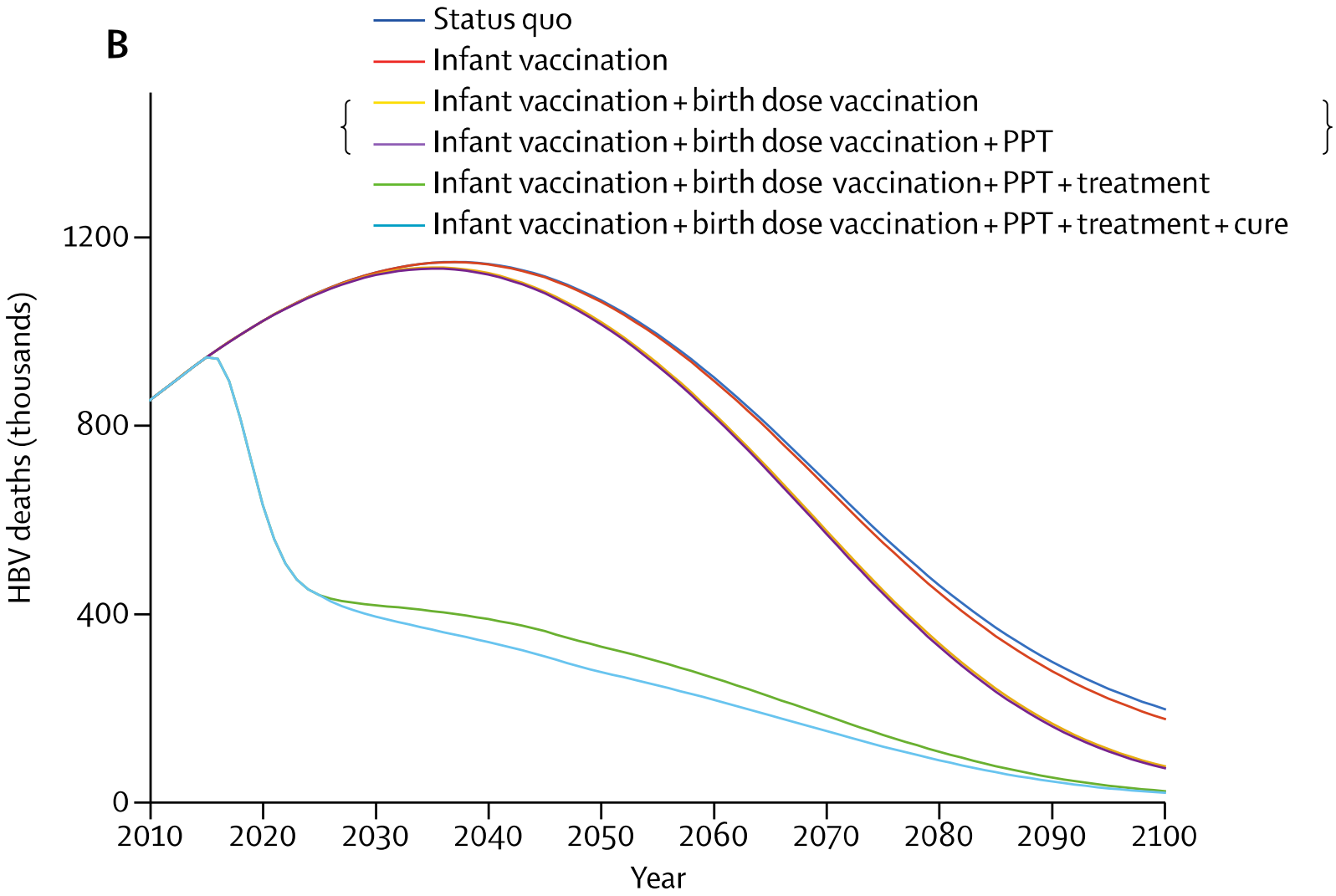
Serological Markers			Unadjusted OR (95%CI)	Adjusted* (95%CI)
HBV DNA	**Anti-HBc**	**HBsAg**		
-	-	-	1.00	1.00
+	-	-	2.56 (0.93-7.00)	1.59 (0.90-2.81)
-	+	-	**1.88 (1.12-3.17)**	2.60 (0.90-7.53)
+	+	-	**3.83 (1.22-12.06)**	3.76 (1.79-7.92)
+	+/-	-	**4.06(2.02-8.16)**	**5.10 (2.06-12.62)**
+	-	+	**7.67(2.50-23.54)**	**10.19 (2.99-34.75)**
+	+/-	+	**22.63(11.97-42.8)**	**34.48(16.26-73.13)**
+	+	+	**30.12(14.80-61.30)**	**46.71 (21.00-103.90)**

* adjusted for age group, sex, anti-HCV, country and province of birth and HIV

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Mak ….Kramvis PLoS One 2018; 13(5): e0196057

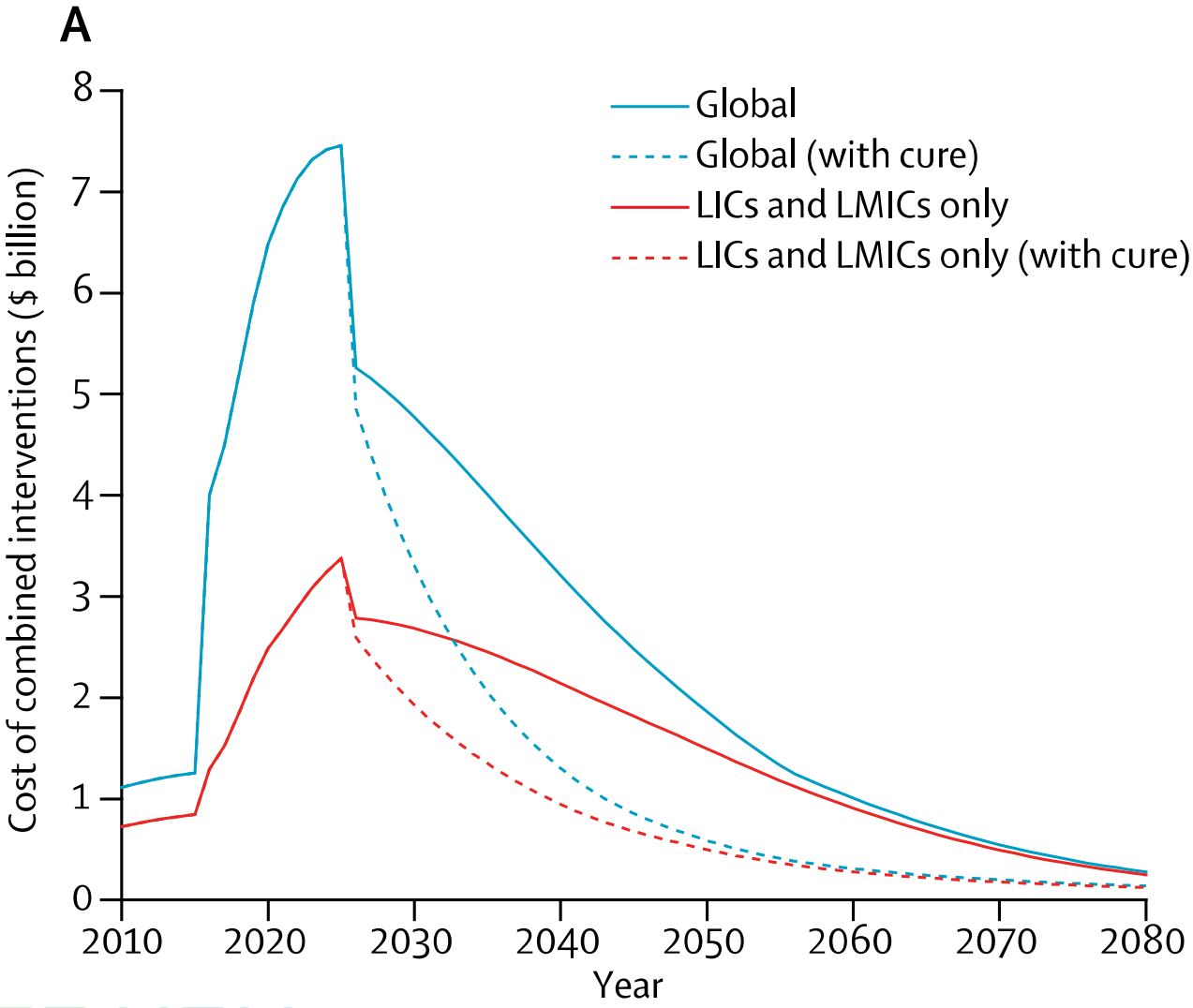
Decrease the morbidity of ESLD and HCC



ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Nagayam et al Lancet Infect Dis 2016; 16: 1399-1408

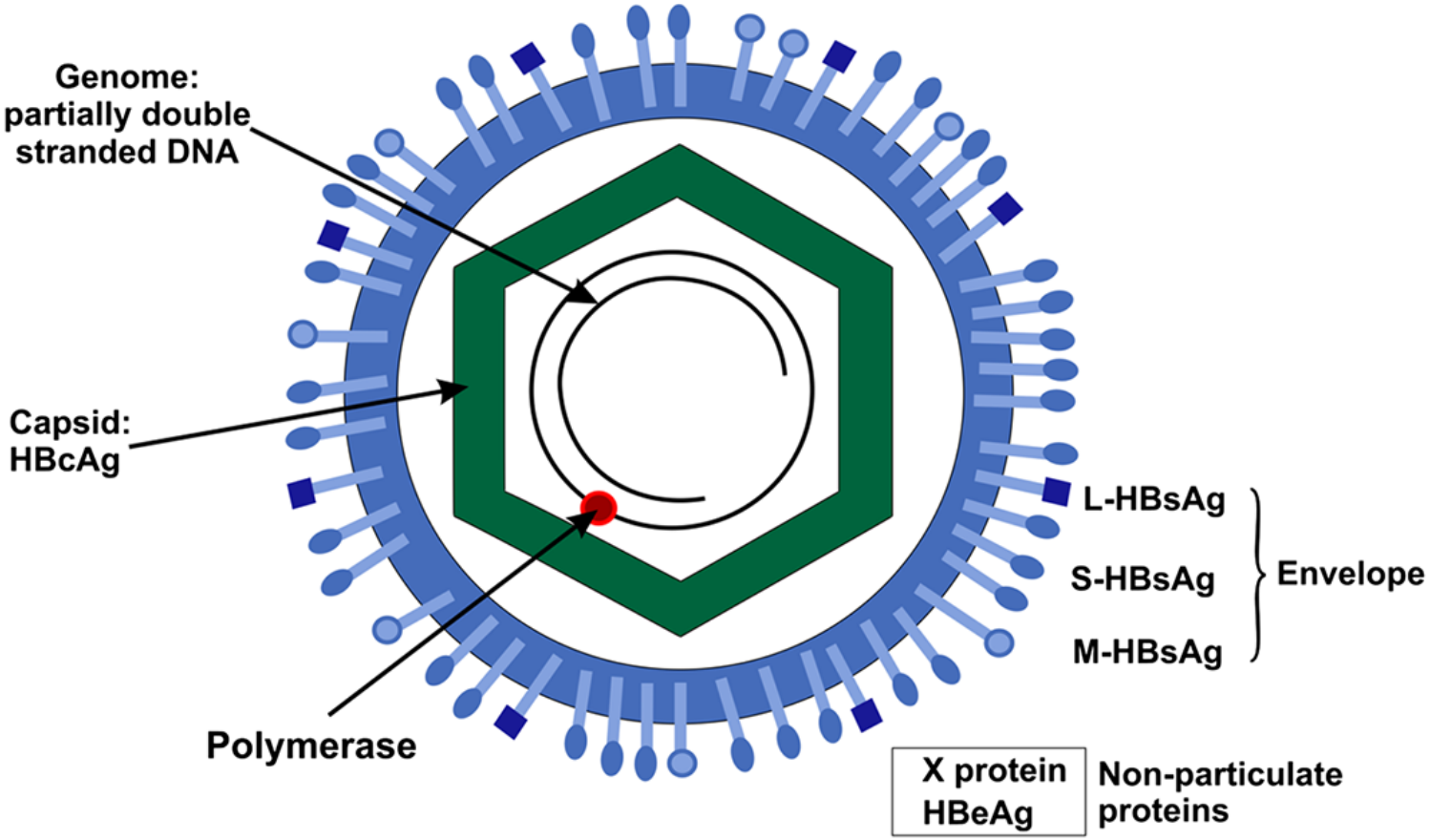
Decrease the cost of reaching WHO targets



ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Nagayam et al Lancet Infect Dis 2016; 16: 1399-1408

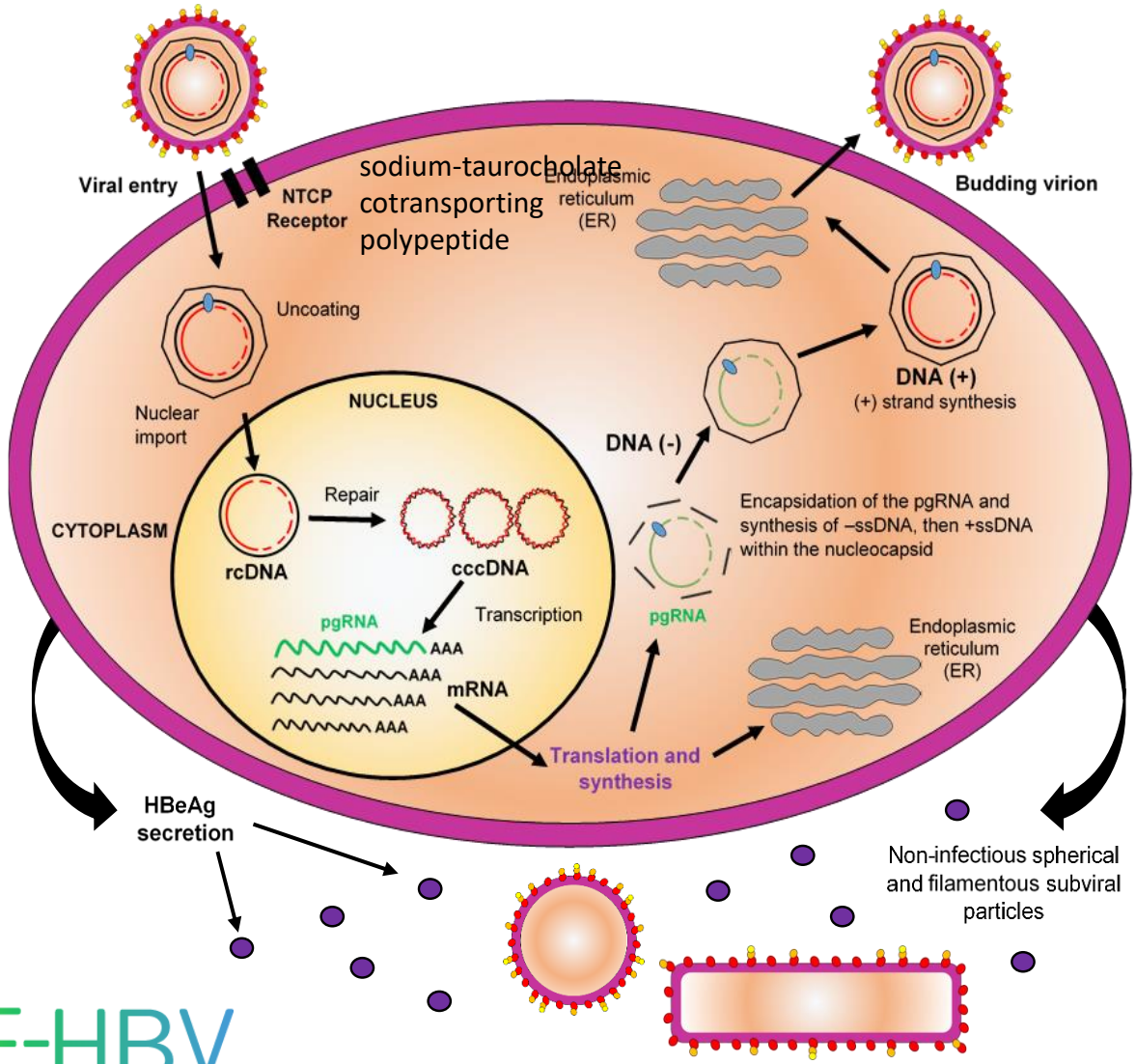
Molecular Virology of HBV



ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Kramvis Rev Med Virol 2016;26:285-303

The HBV Replication Cycle



ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Hillary Vos 2019; Masters Dissertation, University of the Witwatersrand

HBV Infection Treatment Outcomes: Definitions of Cure

- Sterilizing cure: the eradication of HBsAg and all HBV DNA including cccDNA and integrated HBV DNA
- Functional cure: the sustained loss of HBsAg, with or without anti-HBs seroconversion, with persistence of intrahepatic cccDNA.
- Remission of liver disease: resolution of residual liver disease including reversal of fibrosis, prevention of fibrosis progression and reducing the risk of liver cancer

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Revill et al www.thelancet.com/gastrohep. Pubished April 10 2019
Lok et al Hepatoogy 2017; 66: 1296 -1313

Challenge #1 to curing HBV infections

- The central molecule in HBV replication is the viral "cccDNA"
  - The cccDNA is the template for all of the viral RNAs
  - It is the master copy of the viral genome in cells
- cccDNA is long-lived in liver cells
- cccDNA is not replicated in cells
  - Cellular DNA maintenance molecules largely ignore it

Courtesy John Tavis

Challenge #2 to curing HBV infections

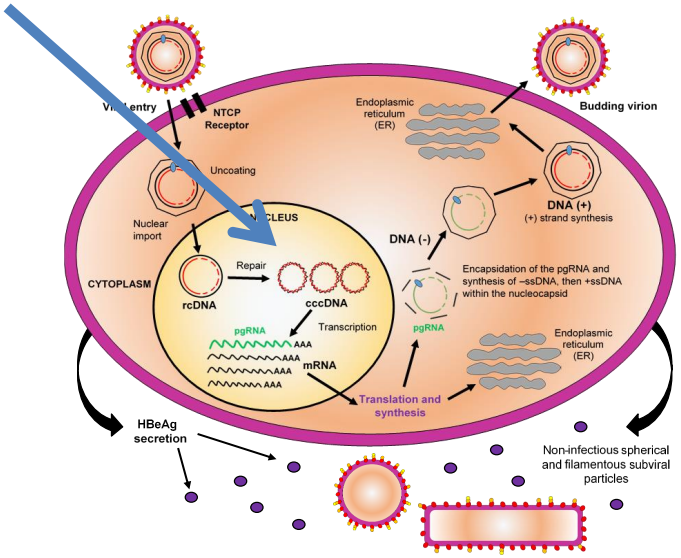
- HBV replicates in the liver
  - The liver is “immunosuppressive”, handicapping the ability of the body’s immune system to kill HBV
  - HBV “exhausts” immune responses, promoting chronic infection
- Training the immune system to clear HBV with vaccines or cytokine drugs will be very hard

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Courtesy John Tavis

cccDNA : Public Enemy #1

cccDNA



- cccDNA is a minichromosome with a $t_{1/2}$ of 10 to 20 weeks
- Not affected by NUCs and only partially impacted by IFN.
- Maintained by intracellular cycle
- Even a single copy of functional cccDNA in one cell could restart HBV replication if immunity is suppressed

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Hillary Vos 2019; Masters Dissertation, University of the Witwatersrand
,
Adapted from John Tavis
,

So how do we get rid of the cccDNA?

- **Nobody knows!** None of the current treatments achieve cccDNA loss.
- But….
  - *Natural clearance of an acute infection gets rid of the vast majority of the cccDNA safely, so the immune system can do it!*
  - The cccDNA is not always completely eliminated during resolution of an acute infection
  - The immune system can keep any residual cccDNA under control in almost all patients

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Adapted from John Tavis

So what must we be aiming for?

Paradigm shifts that lead to:

- Long-term off-treatment suppression in most treated individuals
- Sterilizing cure – elimination of cccDNA

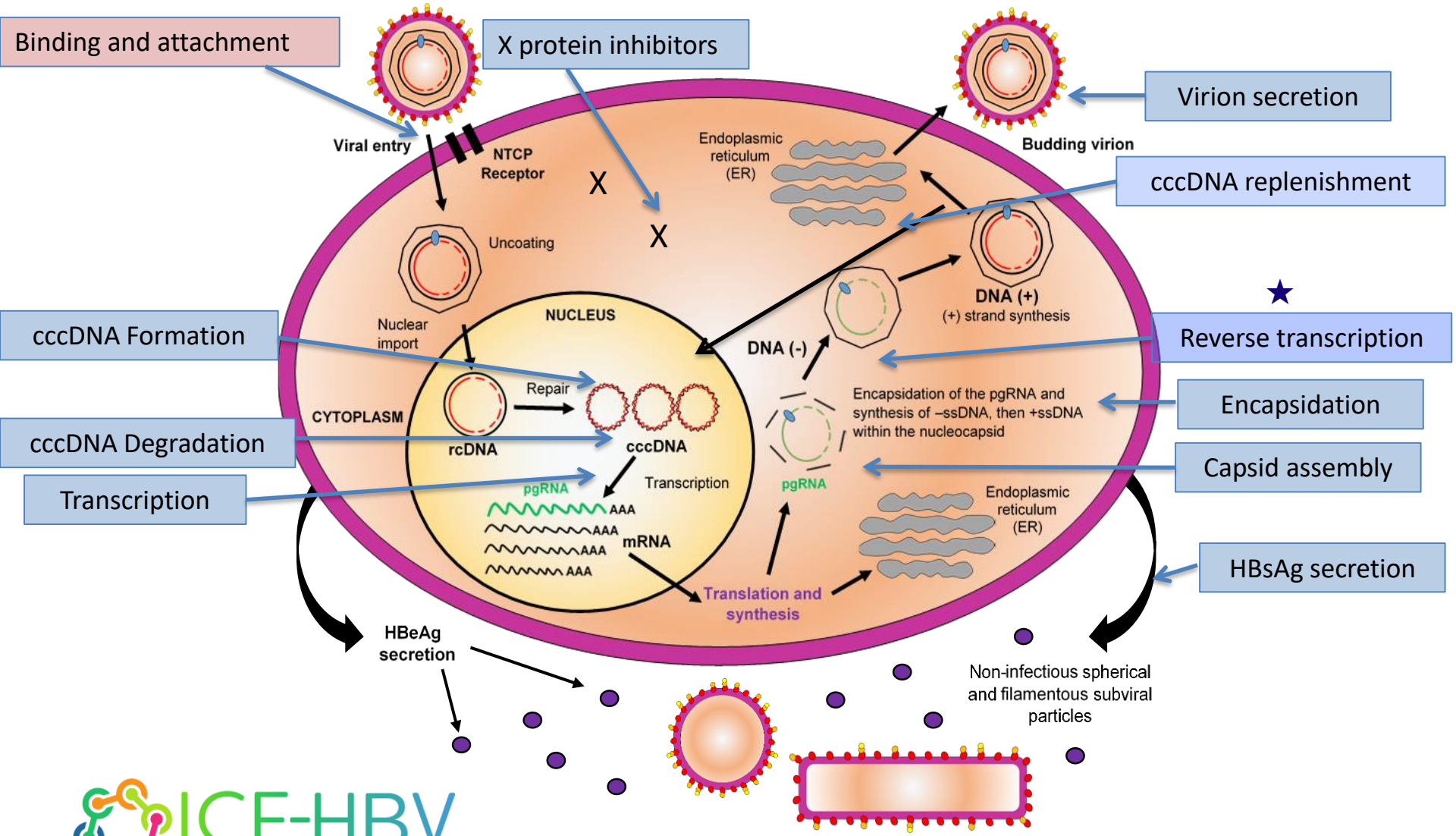
So what must we be aiming for?

Paradigm shifts that lead to:

- Long-term off-treatment suppression in most treated individuals
- Sterilizing cure – elimination of cccDNA

Functional cure seen following natural resolution of acute infection, with minimal cccDNA kept under long-term immune control without the need for ongoing antiviral drugs

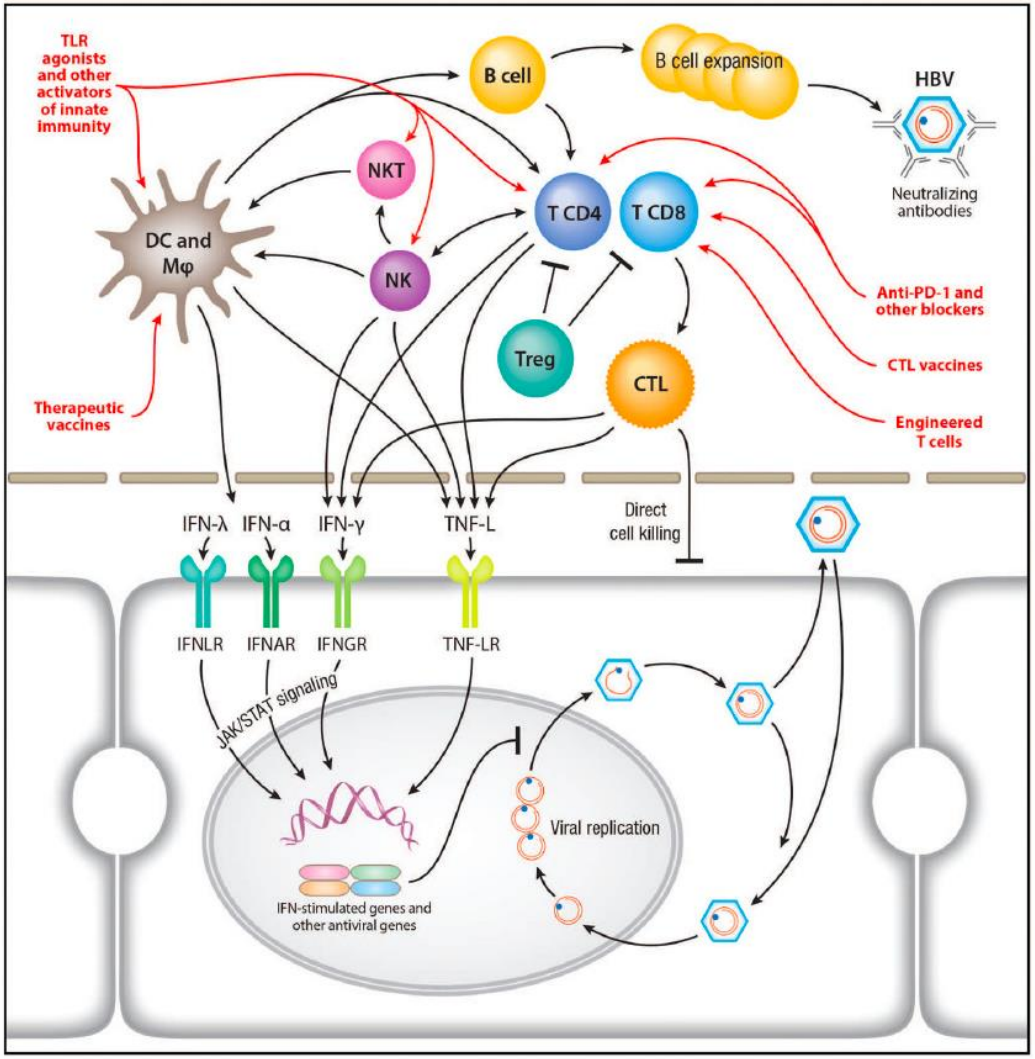
Novel Host-targetting and Direct-acting Antivirals



ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Hillary Vos 2019; Masters Dissertation, University of the Witwatersrand
Liang et al Hepatology 2015; 672:1893-1908
Arends et al Infect Dis Therap 2017; 6:461-476

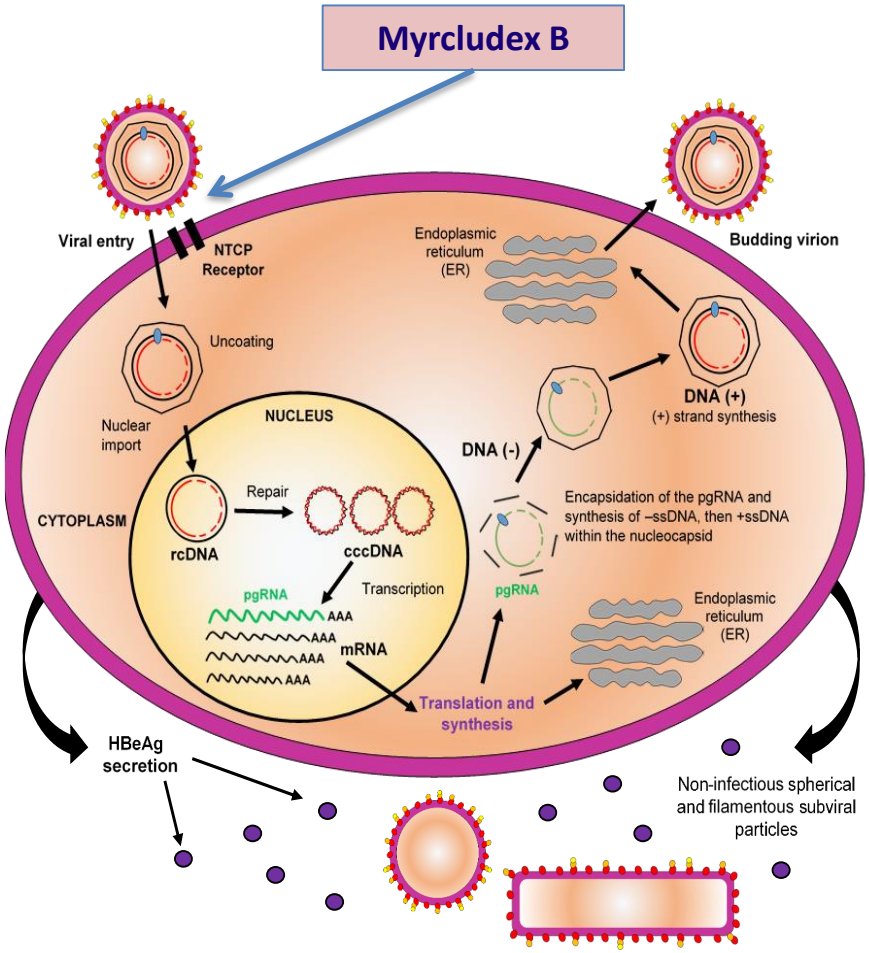
Novel Immune Modulatory Agents



ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Liang et al Hepatology 2015; 672:1893-1908

Example of Host-targetting Agent



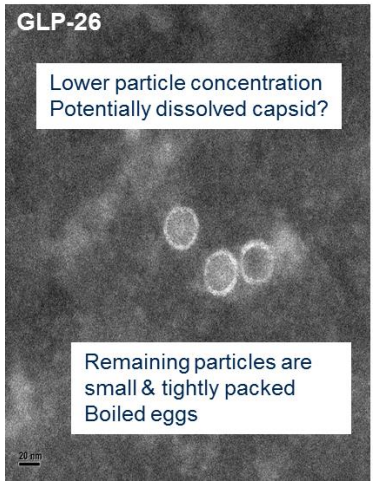
- Entry inhibitors stop HBV from getting into liver cells
- The drug furthest along is Myrcludex B
- Myrcludex B is likely to be approved in Europe for HBV and HDV in 2019

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

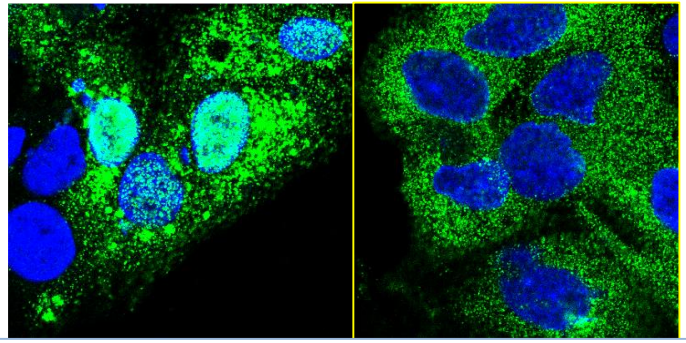
Hillary Vos 2019; Masters Dissertation, University of the Witwatersrand
Adapted from John Tavis

Example of Direct-acting Antiviral

Capsid Assembly Effector-GLP-26



Mock **+GLP-26**



HBV capsid protein reduced in nuclei of GLP-26 treated hepatocytes

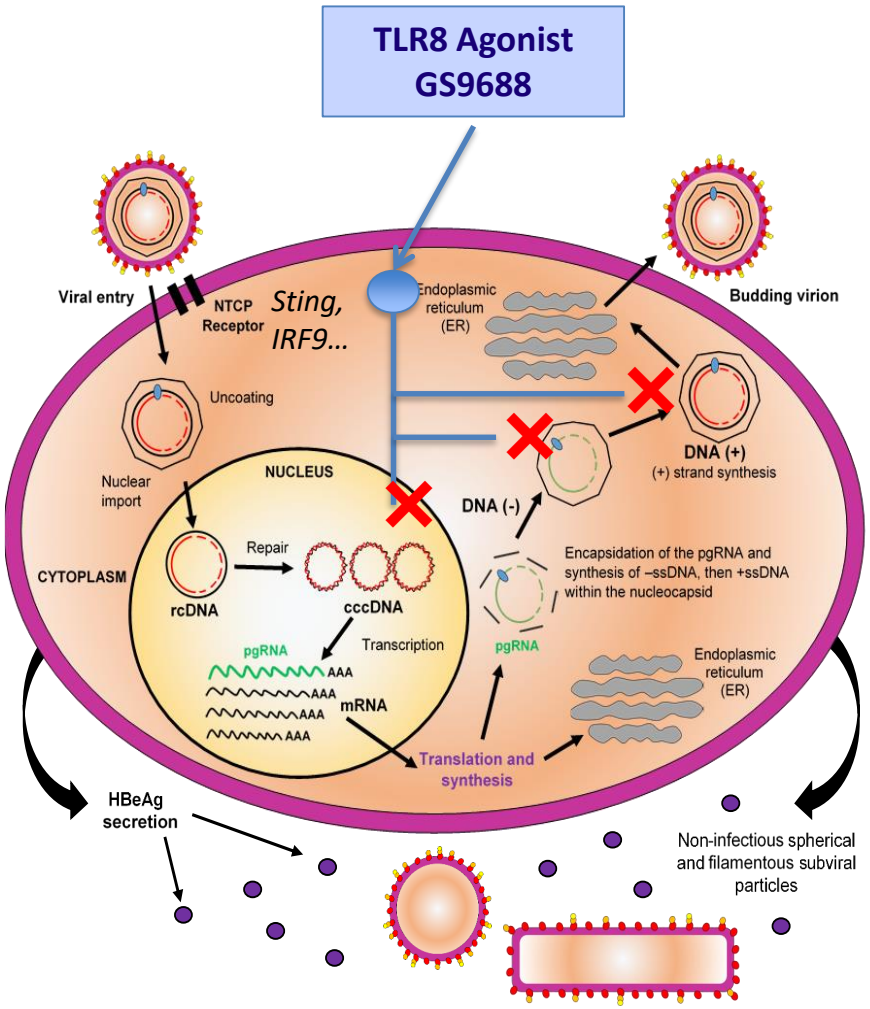
HBV capsid is essential for viral replication

- HBV capsid assembly effectors (CAEs) inhibit replication
- All genotypes as well as drug resistant strains
- Diminish or suppress cccDNA levels

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Schinazi Personal Communication

Example of Immune-stimulating Agent



- TLR8 detects viruses inside people's cells and turns on the cells' defenses such as NFκB and IRF5/7 that block HBV
- The leading compound working through TLR8, GS9688, is entering phase II trials

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Hillary Vos 2019; Masters Dissertation, University of the Witwatersrand
Adapted from John Tavis

Future Cure Therapies?

- Combination because:
  - HBV's many genotypes and variable disease course mean no one drug will cure everyone
  - cccDNA's durability means we will have to hit it from multiple angles at the same time
- Cure therapy is likely to be long (a year?) and need exceptionally safe drugs

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Adapted from John Tavis
https://www.future-science.come/futuredrugdiscovery

ICE-HBV's View of Cure Therapy

Step 1	**Multi-drug treatment : direct -acting and host-targeting drugs**	Decrease HBV viral loads below the level of detection
Step 2	**Immune modulators:** **Cytokines, therapeutic vaccines, adjuvants**	Induce immune-mediated cccDNA elimination/control
Step 3	**Therapeutic vaccination**	Produce long-term immune control of HBV

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Adapted from John Tavis

The way forward……

- Coordinate efforts in order to have a global approach to curing chronic hepatitis B
- Determine the optimal combination therapies
- Establish the end-points of therapy
  - Biomarkers
  - New animal models
  - *In vitro* study systems

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

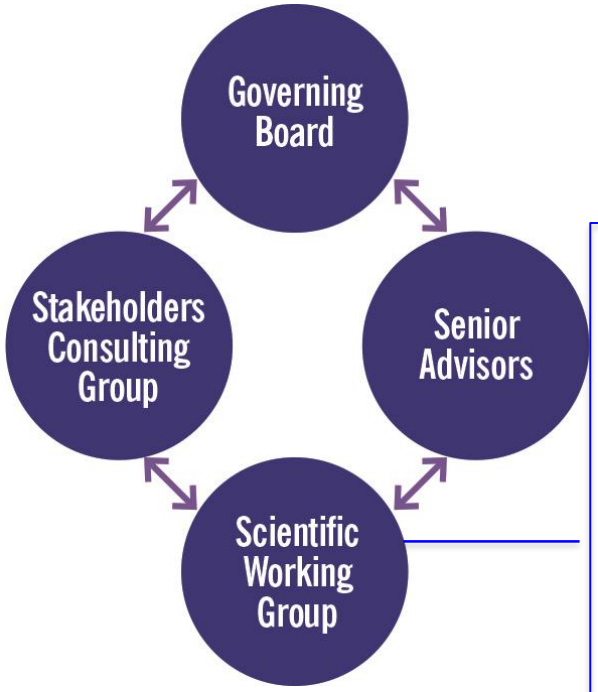
ICE-HBV was formed in 2016 and aims to fast-track the discovery of a safe, effective, affordable and scalable cure to benefit all people living with CHB, including children and people living with HCV, HDV and HIV co-infection. ICE-HBV intends to contribute to the elimination of CHB as a global public health challenge.

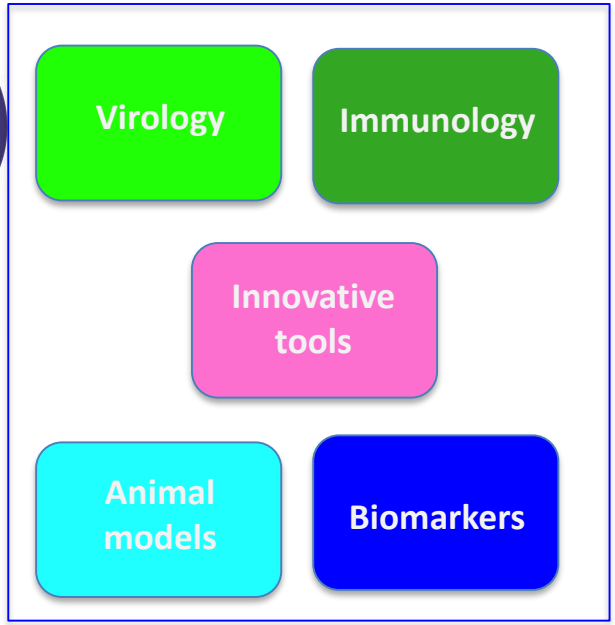
ICE-HBV Structure

- Governance structure established
- Developed resources to fund the initiative

- Community representatives
- Research agencies
- Global Health Organizations
- Foundations
- Pharmaceutical Industry

www.ICE-HBV.org





ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

ICE-HBV Strategy

Immediate and future actions required to achieve HBV Cure

I — **INCREASE** funding for individual and collaborative cure-related research projects by governmental and private funding agencies and philanthropic benefactors

C — **CONCENTRATE** on the discovery of interventional strategies including direct acting/host-directed and immuno-modulatory

E — **ESTABLISH** repositories of standardized HBV reagents and protocols and facilitate access to all researchers globally and support the development of animal models

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

ICE-HBV Publications

Lancet Gastroenterol Hepatol. 2019 Jul;4(7):545-558

Health Policy

A global scientific strategy to cure hepatitis B

Peter A Revill, Francis V Chisari, Joan M Block, Maura Dandri, Adam J Gehring, Haitao Guo, Jianming Hu, Anna Kramvis, Pietro Lampertico, Harry L A Janssen, Massimo Levrero, Wenhui Li, T Jake Liang, Seng-Gee Lim, Fengmin Lu, M Capucine Penicaud, John E Tavis, Robert Thimme, Members of the ICE-HBV Working Groups*, ICE-HBV Stakeholders Group Chairs*, ICE-HBV Senior Advisors*, Fabien Zoulim

Nat Rev Gastroenterol Hepatol. 2018 Sep;15(9):517-518

COMMENT

ELIMINATING VIRAL HEPATITIS

The hepatitis B epidemic and the urgent need for cure preparedness

Jeffrey V. Lazarus[1]*, Timothy Block[2], Christian Bréchot[3], Anna Kramvis[4], Veronica Miller[5], Michael Ninburg[6], Capucine Pénicaud[7], Ulrike Protzer[8], Homie Razavi[9], Laura A. Thomas[10], Jack Wallace[11] and Benjamin C. Cowie[10,12]

ICE-HBV
International Coalition to Eliminate HBV

PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

ICE-HBV 2019 Activities

- NIAID HBV resources repository ✓
- ICE-HBV Open Access Protocols Database on www.ICE-HBV.org ✓
- cccDNA standardization, serum biomarkers, POC diagnostics
- HBV elimination messaging & media engagement & scientific workshops
- EASL-ICE Think Tank on HBV Cure- Vienna, April 2019 ✓
- Strategy Paper Launch – EASL, Vienna, April 2019✓
- HBV cure workshop – ANRS, Paris, May 13, 2019✓
- HBV & HIV Cure Forum at IAS, Mexico, July 20-21, 2019✓
- ICE-HBV Webinar June 2019✓
- **HBV Cure Science 101 – COLDA 2019, Cairo, 7 September 2019**
- ***In vivo* models working group and workshop, Melbourne, 1 October 2019**
- **HBV Public Forum, Melbourne, 4 October 2019**
- **HBV Cure Symposium, Melbourne, 5 October 2019**
- **Global Fund Replenishment Conference – Lyon, 8 October 2019**
- **HepFree Asia Conference, Hong Kong, November 2019**

ICE-HBV
International Coalition to Eliminate HBV

PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

There is always something new coming out of Africa

Aristotle 384 –322 BC

It's time to end HIV/AIDS, Viral Hepatitis and other Infectious Diseases.

It's time to UNITE.

UNITE

Global Parliamentarians Network to End HIV/AIDS, Viral Hepatitis and other Infectious Diseases

unitenetwork@unitenetwork.org

www.unitenetwork.org

@UniteMPNetwork

@UNITE.Parliamentarians.Network

@unite-parliamentarians-network

@unite_mp_network

ICE-HBV

International Coalition to Eliminate HBV

PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Acknowledgements

WITS UNIVERSITY

Doherty Institute

anrs France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

HBV INTERNATIONAL MEETING

Australian Academy of Science

ACH2

AUSTRALIAN CENTRE FOR HEPATITIS VIROLOGY

ICE-HBV
International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH