HBV Cure Science 101
Anna Kramvis, BScHons, PhD
ICE-HBV Governing Board Member

Research Professor/Director
Hepatitis Virus Diversity Research Unit
University of the Witwatersrand
South Africa
## Disclosure

<table>
<thead>
<tr>
<th>Relations that could be relevant for the meeting</th>
<th>Company names</th>
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<tbody>
<tr>
<td>Sponsorship or refund funds</td>
<td>• ICE-HBV (non-profit)</td>
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<td>• Wits (non-profit)</td>
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<td>Payment or other financial remuneration</td>
<td>• None</td>
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<td>Shareholder rights</td>
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<td>Other relations</td>
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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………. 

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

https://hbr.org/2018/01/the-art-of-strategy-is-about-knowing-when-to-say-no
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.
2 billion/7.3 billion exposed to HBV

3.9% (95% [UI] 3.4–4.6) HBsAg+ve

20%–30% FH, cirrhosis, HCC

886 000 Annual deaths

257 million HBV carriers

25 million (10%) diagnosed

4.8 million of 94 million (5%) received AVT

HBV Diagnosis/Treatment Cascade

Global

- HBsAg+ve: 350,000,000
- Diagnosed: 10%
- Eligible: 5%
- Treated: <1%

Central Europe

- HBsAg+ve: 250,000
- Diagnosed: 25%
- Eligible: 3%
- Treated: <1%

SSA

- HBsAg+ve: 8,000,000
- Diagnosed: 10%
- Eligible: 5%
- Treated: <1%

Greece

- HBsAg+ve: 250,000
- Diagnosed: 42%
- Eligible: 51%
- Treated: <1%

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, telbivudine, 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
Accelerate Reduction of HBV Incidence

New cases of chronic HBV carriage per year (millions)

- Status quo
- Infant vaccination
- Infant vaccination + birth dose vaccination
- Infant vaccination + birth dose vaccination + PPT
- Infant vaccination + birth dose vaccination + PPT + treatment
- Infant vaccination + birth dose vaccination + PPT + treatment + cure

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

## Decrease Risk of Hepatocellular Carcinoma

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<th>Serological Markers</th>
<th>Unadjusted OR (95%CI)</th>
<th>Adjusted* (95%CI)</th>
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<td><strong>HBV DNA</strong></td>
<td><strong>Anti-HBc</strong></td>
<td><strong>HBsAg</strong></td>
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* adjusted for age group, sex, anti-HCV, country and province of birth and HIV

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**ICE-HBV**

International Coalition to Eliminate HBV

Promoting Global Collaboration in HBV Cure Research

Decrease the morbidity of ESLD and HCC

![Graph showing the impact of different vaccination strategies on HBV deaths. The strategies include status quo, infant vaccination, infant vaccination + birth dose vaccination, infant vaccination + birth dose vaccination + PPT, and infant vaccination + birth dose vaccination + PPT + treatment + cure.](image-url)

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**ICE-HBV**

International Coalition to Eliminate HBV

**PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH**

Decrease the cost of reaching WHO targets

![Graph showing cost of combined interventions](image)

- Global
- Global (with cure)
- LICs and LMICs only
- LICs and LMICs only (with cure)

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PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

*Nagayam et al. Lancet Infect Dis 2016; 16: 1399-1408*
Molecular Virology of HBV

- Genome: partially double stranded DNA
- Capsid: HBcAg
- Polymerase
- Envelope: L-HBsAg, S-HBsAg, M-HBsAg
- X protein HBeAg
- Non-particulate proteins
The HBV Replication Cycle

- **Viral entry**
- **NTCP Receptor**
- **Uncoating**
- **NUCLEUS**
  - Repair
  - **rcDNA**
  - **cccDNA**
  - **Transcription**
  - **pgRNA**
  - **mRNA**
  - **Translation and synthesis**
  - **DNA (-)**
  - **DNA (+)**
  - **(+ strand synthesis)**
  - **Encapsidation of the pgRNA and synthesis of -ssDNA, then +ssDNA within the nucleocapsid**
- **CYTOPLASM**
  - **HBeAg secretion**
- **Budding virion**
- **Non-infectious spherical and filamentous subviral particles**
- **sodium-taurocholate cotransporting polypeptide**
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.

Revill et al. [www.thelancet.com/gastrohep](http://www.thelancet.com/gastrohep). Published April 10 2019

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
cccDNA : Public Enemy #1

• 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

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

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 Immune Modulatory Agents

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

Adapted from John Tavis

Hillary Vos 2019; Masters Dissertation, University of the Witwatersrand
Example of Direct-acting Antiviral

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

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
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

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

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 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

Virology
Immunology
Innovative tools
Animal models
Biomarkers
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
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 Levero, 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

The hepatitis B epidemic and the urgent need for cure preparedness

Jeffrey V. Lazarus1,2 *, Timothy Block3, Christian Bréchet3, Anna Kramvis3,4, Veronica Miller5, Michael Ninburg5, Capucine Pénicaud6,7, Ulrike Protzer8, Homie Razavi9, Laura A. Thomas10, Jack Wallace11 and Benjamin C. Cowie10,12
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
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.

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

unitenetwork@unitenetwork.org
www.unitenetwork.org
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@unite-parliamentarians-network
@unite_mp_network

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Acknowledgements