What is new about hepatitis B?
From novel biomarkers to innovative cure strategies

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King’s College London
Conflict of Interest

I have a part-time role as Head of Virology Early Development at Roche Pharma Research & Early Development (Basel Campus) and in this role I am researching novel biomarkers and cure strategies for chronic hepatitis B.

I collaborate with Roche diagnostics on biomarker research.
The high burden of HBV-related disease

HBsAg seroprevalence (1993-2013)\(^1\)

- 1.5 million new infections (59% M)
- 2.7 million people live with HIV and HBV (2015)\(^2\)
- \(820^k\)
- \(296^m\)
- \(2019^2\)
- \(<10%\) have been diagnosed

### Chronic HBV Infection: Targets vs. Status

<table>
<thead>
<tr>
<th>Target</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% ↓ in <strong>new chronic infections</strong> by 2020, 90% by 2030</td>
<td>1,500,000 new infections in 2019</td>
</tr>
<tr>
<td>10% ↓ in <strong>deaths</strong> by 2020, 65% by 2030</td>
<td>820,000 deaths in 2019</td>
</tr>
<tr>
<td>90% <strong>vaccine</strong> coverage (3rd dose) by 2020</td>
<td>85% coverage in 2019</td>
</tr>
<tr>
<td>50% coverage of <strong>MTCT</strong> prevention by 2020, 90% by 2030</td>
<td>43% coverage for timely birth dose in 2019</td>
</tr>
<tr>
<td>95% of <strong>blood donations</strong> screened in a quality-assured manner by 2020, 100% by 2030</td>
<td>97% in 2015</td>
</tr>
<tr>
<td>50% of <strong>injections</strong> administered with safety-engineered devices in &amp; out of health facilities by 2020, 90% by 2030</td>
<td>3.9% reuse of injection equipment in 2017</td>
</tr>
<tr>
<td>200 sterile <strong>needles &amp; syringes</strong> provided per IDU person per year by 2020, 300 by 2030</td>
<td>33 sets per person per year in 2017</td>
</tr>
<tr>
<td>30% of chronic infections <strong>diagnosed</strong> by 2020, 90% by 2030</td>
<td>30.4 M knew of diagnosis in 2019</td>
</tr>
<tr>
<td>80% of eligible people with chronic infection <strong>treated</strong> by 2030</td>
<td>6.6 million received treatment in 2019</td>
</tr>
</tbody>
</table>

**MTCT**= Mother to child transmission; **IDU**= Injecting drug using

*WHO. Global progress report on HIV, viral hepatitis and sexually transmitted infections 2021*
Chronic HBV infection: Successful prevention programmes, massive gaps in diagnosis and treatment

• Supported by childhood immunization and prevention, the reduction in HBV incidence is one of the few Sustainable Development Goals health targets on track to be achieved => HBsAg prevalence <1% among children <5 years by 2020

• Sustained and regionally focused scale-up of birth dose vaccination and maternal antiviral treatment required to achieve impact by 2030

• Massive gaps in diagnosis and treatment, including among the populations most severely affected and at higher risk

296M living with chronic HBV infection  ▶▶▶  ~10% diagnosed  ▶▶▶  ~22% accessing antiviral therapy
Chronic HBV infection in the future

The unmet need for all populations

- Diagnose a larger proportion of patients
- Prevent transmission and liver disease progression
- Offer earlier treatment to a larger number of eligible patients
- Fight stigma and barriers to care
- Find novel treatment options to improve functional cure rates

New HBV infections in 2019

10,000
REGION OF THE AMERICAS

19,000
EUROPEAN REGION

140,000
WESTERN PACIFIC REGION

WHO. Global progress report on HIV, viral hepatitis and sexually transmitted infections 2021
## HBV in the UK

<table>
<thead>
<tr>
<th>Routine infant immunisation programme started in 2017&lt;sup&gt;1&lt;/sup&gt;</th>
<th>~98% uptake of antenatal screening&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual incidence of acute infection 0.7 / 100,000 people (1.5 / 100,000 in men aged 45-54 years)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Sentinel surveillance (2018): HBsAg seroprevalence 0.3% among 133,236 women attending for antenatal care</td>
</tr>
</tbody>
</table>
| Estimated prevalence of chronic infection <1%
<sup>1</sup> | HCC incidence ↑ ~ 3-fold in the last 2 decades<sup>3</sup> |
| NICE 2013: targeted screening<sup>2</sup> | 80% of chronic HBV infections undiagnosed<sup>1</sup> |

Born or brought up in countries with HBsAg prevalence ≥2%, past or current IDU, close HBV contact, prisoners, in residential care, MSM, at risk via unprotected sexual exposure (e.g., multiple sexual partners, STIs)

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IDU = Injecting drug use; HCC = Hepatocellular carcinoma
HBsAg seroprevalence in GP records in England

- 6,975,119 records extracted from the RCGP Research & Surveillance Centre (2008-2019)
- HBsAg seroprevalence **0.12%** (95% CI 0.11-0.12)
- Mostly located in London and in socio-economically deprived neighbourhoods

**Disease of poverty**

- Increased adjusted odds of HBsAg seropositivity:
  - Asian 5-fold, Black 9-fold (vs. white)
  - MSM 7-fold (vs. men lacking an MSM record)
  - IDU history 11-fold*  
    *vs. no record
  - Close HBV contact 12-fold*
  - People with a diagnosis of*
    - Syphilis 6-fold
    - HCV 40-fold
    - HIV 13-fold

*IDU= Injecting drug use

Geretti et al. Unpublished data
How shall we protect patients living with HIV?

Co-infection among people living with HIV:
10-25% in Asia, Africa; 4-17% in North America, Europe, Australia

- Screen for HBsAg, anti-HBc, anti-HBs at HIV diagnosis
- **HBsAg+:** Stage the infection, assess liver disease, enquire about close contacts, offer life-long antiviral treatment, usually tenofovir (TDF or TAF) as part of ART
- **HBsAg-, anti-HBc+:** Manage risk of reactivation in case of immunosuppression
- **HBsAg-, anti-HBc-, anti-HBs-:** Vaccinate => assess initial response => monitor and boost appropriately *(see BHIVA Guidelines)*
- **HBsAg-, anti-HBc-, anti-HBs+:** Enquire about vaccination history, if in doubt boost or even revaccinate (according to risk and immune status)
- Non responder to vaccination: Consider tenofovir as part of ART (prophylaxis)

1. Sun et al. World J Gastroenterol 2014
# Stages of chronic HBV infection: Definitions

<table>
<thead>
<tr>
<th></th>
<th>HBeAg&lt;sup&gt;Pos&lt;/sup&gt; chronic infection</th>
<th>HBeAg&lt;sup&gt;Pos&lt;/sup&gt; chronic hepatitis</th>
<th>HBeAg&lt;sup&gt;Neg&lt;/sup&gt; chronic infection</th>
<th>HBeAg&lt;sup&gt;Neg&lt;/sup&gt; chronic hepatitis</th>
<th>‘Functional’ Cure</th>
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<tr>
<td><strong>Previous terminology</strong></td>
<td>Immunotolerant</td>
<td>Immunoactive</td>
<td>Inactive</td>
<td>Immunoactive</td>
<td></td>
</tr>
<tr>
<td><strong>HBV DNA levels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALT levels</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum HBsAg</td>
<td>+++++</td>
<td>+++++</td>
<td>+</td>
<td>++</td>
<td>Undetectable</td>
</tr>
<tr>
<td>Liver cccDNA</td>
<td>+++++</td>
<td>+++++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>LLOQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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**LLOQ= Lower limit of quantification**

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Fanning et al. Nat Rev Drug Discovery 2019
Stages of chronic HBV infection: Treatment

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<tr>
<th>Previous terminology</th>
<th>HBeAg^Pos chronic infection</th>
<th>HBeAg^Pos chronic hepatitis</th>
<th>HBeAg^Neg chronic infection</th>
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<td>Immunoactive</td>
<td>Inactive</td>
<td>Immunoactive</td>
<td></td>
</tr>
<tr>
<td>HBV DNA levels</td>
<td>Poor response to available therapies</td>
<td>NUCs (peg-IFNα)</td>
<td></td>
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<td></td>
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<td>Serum HBsAg</td>
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LLOQ= Lower limit of quantification; NUCs= Nucleos(t)ide analogues

Fanning et al. Nat Rev Drug Discovery 2019
Chronic HBV infection: Host-virus interactions are complex
Multifaceted immune dysfunction in chronic HBV infection

Characteristics of immune-dysfunction

↓ innate and adaptive antiviral immunity

↑ suppressive cell subsets and inhibitory molecules (e.g., IL-10, TGF-β)

↑ PD-1, CTLA-4, TIM-3 on antiviral immune cells

Progressive exhaustion of HBV-specific T cells and B-cell dysfunction

Key drivers of immune-dysfunction in chronic HBV infection

Persistently high antigenic expression

Increased expression of inhibitory signalling, primarily PD-L1, on hepatocytes, non-parenchymal liver cells (e.g., Kupffer cells) and intra-hepatic and circulating APCs

Direct suppressive role also proposed for high levels of serum HBsAg

Characteristics of chronic HBV infection

- Immunotolerant liver environment
- Ineffective T-cell and B-cell responses
- Chronic high levels of HBV antigens
HBsAg in chronic HBV infection

HBsAg circulates in large amounts within viral and subviral particles

- 3 components (L, M, S)
- Encoded by episomal HBV cccDNA
- Encoded by integrated HBV sequences
- Proposed to have immunosuppressive role

Why is HBsAg loss the desirable endpoint of therapy?

HBsAg loss allows discontinuation of treatment and predicts significantly improved clinical outcomes.

HBsAg seroclearance and clinical outcomes

Meta-analysis of 28 studies with ~90,000 patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver decompensation</td>
<td>0.28</td>
<td>0.13</td>
<td>0.59</td>
<td>0.001</td>
</tr>
<tr>
<td>HCC</td>
<td>0.30</td>
<td>0.20</td>
<td>0.44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transplant/Death</td>
<td>0.22</td>
<td>0.13</td>
<td>0.39</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Composite first clinical event</td>
<td>0.31</td>
<td>0.23</td>
<td>0.43</td>
<td>&lt;0.001</td>
</tr>
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HBsAg loss with standard of care therapy

HBeAg-positive chronic hepatitis B, 1 year

<table>
<thead>
<tr>
<th></th>
<th>peg-IFNα</th>
<th>ETV</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg loss</td>
<td>29-32%</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>HBsAg loss*</td>
<td>3-7%</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

* ~10-12% after 5-8 years of ETV or TDF; ~11% with peg-IFNα in long-term follow-up¹

HBeAg-negative chronic hepatitis B, 1 year

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<th>peg-IFNα</th>
<th>ETV</th>
<th>TDF</th>
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<tr>
<td>HBsAg loss</td>
<td>0-4%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

<3% with prolonged therapy

¹ Buster et al. Gastroenterology 2008 and 2009
Risk of hepatocellular carcinoma in NUC-treated patients

- Systemic review of 21 studies
- 3881 people treated with NUCs for ≥24 months vs. 534 untreated patients

**HCC incidence** over 46 months (range 32-108 months) of observation:
- 2.8% in NUC treated vs 6.4% in controls (p=0.003)
- In treated patients, 2.3% if virologically suppressed vs. 7.5% if viraemic (p<0.001)

*Papatheodoridis et al. J Hepatol 2010*
Pathways towards a HBV cure

Core assumptions

- Combination of antiviral(s) & immunomodulator(s) required to achieve high cure rates
- Restoration of antiviral immunity likely to be required to ensure sustained responses
- HBV antigen suppression necessary (but not sufficient) to enable immune restoration
- Pathways to immune restoration may include direct stimulation and removing inhibition
Host-virus interactions offer several points of possible attack
HBV siRNA induces suppression of HBsAg

Phase 1b/2a Study DCR-HBVS-101, NUC-suppressed CHB patients, 4 monthly doses, 3 dose levels

Yuen et al. AASLD 2020
HBV therapeutic vaccines in clinical development

<table>
<thead>
<tr>
<th>Platform</th>
<th>Antigens</th>
<th>CD8 T cells</th>
<th>Anti-HBs</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChAd-MVA-Protein</td>
<td>C, S</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>ChAd-MVA</td>
<td>C, P, S (preS1, pre-S2)</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>DNA</td>
<td>C, P</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>PICV-LCMV</td>
<td>C, P, S</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

Ad, adenovirus; MVA, modified vaccinia virus Ankara; PICV, pichinde virus; LCMV, lymphocytic choriomeningitis virus
HBV biomarkers old and new

pgRNA = pregenomic RNA; rcDNA = relaxed circular DNA; cccDNA = covalently closed circular DNA

Fanning et al. Nat. Rev. Drug Discovery 2019
HBsAg quantification

Natural history
- HBsAg levels predict HCC risk in patients with low HBV DNA
- HBsAg levels <1000 IU/ml discriminate true inactive carriers among HBeAg-negative patients

Treatment decisions
- HBsAg decline at 12 and 24 weeks predicts response to peg-IFNα (response-guided therapy)
- HBsAg <100 IU/ml predict low risk of relapse after NUC discontinuation

What else could guide NUC discontinuation in the future?

- HBsAg <100 IU/ml (routine assay, incomplete availability)
- HBeAg negative (routine assay)
- Undetectable serum HBV DNA (ultrasensitive assays in the future?)
- Undetectable serum HBV RNA (research-use assays at present)
- Serum CrAg <3 log_{10} U/ml (Fujirebio assay for research applications)
- Anti-HBc levels ≥1000 IU/mL (commercial assay with limited availability)

HBV: Takeaway messages for clinical care

- In the UK, most **patients with HIV and HBV** are likely to do well through systematic screening and effective antiviral therapy as part of ART; however, needs do not end with tenofovir
  - Initial assessment of liver disease stage to define overall risk and monitoring plan
  - Ongoing monitoring for liver cancer, regardless of effective HBV DNA suppression
  - No simplification to regimens containing 3TC or FTC as the sole anti-HBV agents
  - Do not forget to test for HDV co-infection
- Patients with a past HBV infection remain at risk of **reactivation** and should be managed accordingly
- Non-immune patients require **vaccination** with augmented schedules or using novel adjuvanted vaccines due to reduced responsiveness
- Patients who do not mount a response to **vaccination** may benefit from antiviral prophylaxis through ART (tenofovir generally preferred over 3TC or FTC)
- Patients may soon become eligible to join HBV cure studies; meanwhile studies are needed to guide any consideration around stopping or deescalating anti-HBV treatment
Thank you!