How to improve access to therapy for HBV patients

Michael Manns

Dept. of Gastroenterology, Hepatology and Endocrinology, Medical School Hannover, Germany

Helmholtz Center for Infection Research (HZI), Braunschweig, Germany

Hannover Medical School
How to improve access to management (prophylaxis and therapy) for HBV patients

Michael Manns

Dept. of Gastroenterology, Hepatology and Endocrinology, Medical School Hannover, Germany

Helmholtz Center for Infection Research (HZI), Braunschweig, Germany

Hannover Medical School
Conflict of interest

Michael Manns has received financial compensation for consultancy and/or lecture activities from Abbvie, Boehringer Ingelheim, Bristol Myers Squibb, Idenix, Gilead, GlaxoSmithKline, Janssen Therapeutics, Merck, Novartis, Roche and research grants from Abbvie, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, Janssen Therapeutics, Merck, Novartis and Roche.
Acknowledgements

• Jennifer Debarry, Hannover

• Markus Cornberg, Hannover
Worldwide more than 240 million people suffer from chronic HBV infection

- only estimated 10% are diagnosed and estimated 1% actually treated

Status quo
HBV infection

Debarry, Cornberg, Manns, Liv Int 2017
Management of HBV requires:

1. Awareness and Prevention
2. Surveillance
3. Screening
4. Detection and Diagnosis
5. Treatment
Status quo
Management of HBV

Awareness and Prevention

HBV vaccine
• available since the 1980’s
• universal infant vaccination reduces HBV
HBV vaccine reduced the incidence of HCC

HBV vaccination program was launched in Taiwan in July 1984

Comparison of the incidence of liver cancer in children 6 to 14 and 0 to 5 years of age, According to birth cohort. Analysis 1997

Comparison of the incidence rates of liver cancer by age for birth cohorts born before vs after the start of the universal HBV vaccination program. Analysis 2016

Chang MH et al., Gastroenterology. 2016 Sep;151(3):472-480
Status quo
Management of HBV

Awareness and Prevention

HBV vaccine
• available since the 1980’s *
• universal infant vaccination reduces HBV

*in Germany since 1995
Answer of pupils to the question: „Have you been vaccinated against hepatitis B?“

HBV vaccination knowledge increases with education level!

Girls know better than boys their HBV vaccination status!

Mädchen kannten ihren Impfstatus signifikant häufiger als Jungen (p<0.001).
*Der Unterschiede zwischen Hauptschülern und Gymnasiasten/Realschülern war hoch signifikant (p<0.001)
Proportion of children vaccinated according to KiGGS (2003 – 2006)

Status quo
Management of HBV

Awareness and Prevention

HBV vaccine
• available since the 1980’s
• universal infant vaccination reduces HBV1

Treatment

HBV treatment options include
• alpha interferons
• nucleoside and nucleotide analogues

High virological response and low viral resistance in long term use of ETV or TDF

<table>
<thead>
<tr>
<th>Response</th>
<th>ETV</th>
<th>TDF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HBeAg+ Patients Year 51</td>
<td>HBeAg- Patients Year 32,a</td>
</tr>
<tr>
<td></td>
<td>94% (88/94)</td>
<td>95% (54/57)</td>
</tr>
<tr>
<td></td>
<td>HBeAg+ Patients Year 63</td>
<td>HBeAg- Patients Year 63</td>
</tr>
<tr>
<td></td>
<td>99% (167/169)</td>
<td>99.6% (283/284)</td>
</tr>
<tr>
<td>HBV DNA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>undetectableb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistance</td>
<td>1% (n=1)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0%</td>
</tr>
</tbody>
</table>

aETV re-treatment (relapsed <6 months post-treatment in ETV-027 study)
bTDF: HBV DNA <400 copies/mL; ETV HBV DNA <300 copies/mL

Improvement of histology after 5 years of **Tenofovir** therapy

*Marcellin et al., Lancet 2013; 381: 468-75*
Endemicity levels (HBsAg positive patients) varies widely.

Access to vaccination and treatment in high-prevalence regions

Highly-prevalent regions are mostly developing countries with low- to middle-income.

• cost and allocation of resources is a major issue

→ **NEEDED:** development of national policies and country-specific guidelines to scale-up prevention, care and treatment of hepatitis B

WHO released guidelines targeting especially those resource-poor settings.
Access to vaccination and treatment in high-prevalence regions

1. Awareness and Prevention

- awareness campaign can help reducing the risk of in-hospital infection
Use of non-sterile equipment needs to be eliminated

Fig 1 Injection equipment soaked in tepid water before reuse in the absence of sterilisation, Africa, 2000. Note the plastic syringes rinsed in the tepid water and the multidose medication vials.

Fig 2 Number of injections per person and per year and proportion of these administered with injection equipment reused in the absence of sterilisation by region, 2000.

Access to vaccination and treatment in high-prevalence regions

1. **Awareness and Prevention**

   - **awareness campaign** can help reducing the risk of in-hospital infection
   - **vaccination** of all **health-care workers** has to be priority
   - **vaccination** of all **infants within 24 hours of birth** should be implemented to reduce perinatal HBV transmission
   - **safety of blood and blood products** is crucial to lower the risk of iatrogenic transmission but requires better and affordable assays
The blood supply in low and middle income countries needs to be safe

- 25 countries still report collecting paid donations in 2012
- In low income countries, 65% of blood transfusion are given to children under 5 years of age
- In high income countries, 76% of all blood transfusions are given to adults older than 65 years old
- 25 countries are not able to screen all donated blood for HIV, HBV or HCV

<table>
<thead>
<tr>
<th></th>
<th>HIV</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-income countries</td>
<td>0.002%</td>
<td>0.02%</td>
<td>0.02%</td>
</tr>
<tr>
<td></td>
<td>(0.0004%-0.02%)</td>
<td>(0.008% - 0.24%)</td>
<td>(0.004% - 0.22%)</td>
</tr>
<tr>
<td>Middle-income countries</td>
<td>0.12%</td>
<td>0.64%</td>
<td>0.37%</td>
</tr>
<tr>
<td></td>
<td>(0.03% - 0.2%)</td>
<td>(0.19% - 2.33%)</td>
<td>(0.13% - 0.71%)</td>
</tr>
<tr>
<td>Low-income countries</td>
<td>0.85%</td>
<td>3.59%</td>
<td>1.07%</td>
</tr>
<tr>
<td></td>
<td>(0.48% - 2.0%)</td>
<td>(2.01% - 6.08%)</td>
<td>(0.63% - 1.96%)</td>
</tr>
</tbody>
</table>

WHO Fact Sheet No 279, updated June 2014
Access to vaccination and treatment in high-prevalence regions

2 Surveillance

• surveillance data for hepatitis B will help directing preventive measures and control their impact

3 Screening

• scaling-up screening activities will help to reduce disease burden by identifying asymptomatic carriers spreading the disease
• HBsAg positive mothers to be identified, with high viral load should be treated
Access to vaccination and treatment in high-prevalence regions

4 Detection and Diagnosis

- alternative **diagnostic tests**, which are **more readily available and less expensive**, need to be established

5 Treatment

- is **limited by lack of available infrastructure and high costs**
- **BUT** recent **screen-and-treat programs** showed **feasibility** with an **acceptability rate of 60-80%** and **link to care of 40-80%**

### Access to vaccination and treatment in high-prevalence regions

<table>
<thead>
<tr>
<th>Key challenges</th>
<th>Key measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lack of knowledge and awareness</strong></td>
<td>• Education of the public and targeted awareness campaign for high-risk groups</td>
</tr>
<tr>
<td><strong>Safety of blood</strong></td>
<td>• Implement policies on safety of blood and blood products</td>
</tr>
<tr>
<td><strong>Limited screening and linkage to care</strong></td>
<td>• Foster implementation of national policies on HBV screening</td>
</tr>
<tr>
<td></td>
<td>• Easy-to-use and low-cost diagnostic assays</td>
</tr>
<tr>
<td></td>
<td>• Point of care screening</td>
</tr>
<tr>
<td><strong>Lack of vaccination</strong></td>
<td>• Prioritized vaccination of high risk groups and healthcare workers</td>
</tr>
<tr>
<td></td>
<td>• HBsAg testing in mothers to prioritize active (and ideally also passive) immunization of the newborn</td>
</tr>
<tr>
<td><strong>Limited treatment</strong></td>
<td>• Increase accessibility of drugs by innovative cost models</td>
</tr>
</tbody>
</table>
Access to vaccination and treatment in intermediate- to low-prevalence regions (example Europe)

Prevalence in Europe is generally considered to be low to intermediate, BUT

• there are regional differences with prevalence increasing eastwards

• studies indicate high prevalence in certain groups and communities

→ **NEEDED:** development of national policies and programs that take into account the dynamics of HBV transmission and country-specific health-care policies

Access to vaccination and treatment in intermediate-to low-prevalence regions (example Europe)

1. **Awareness and Prevention**

- **Awareness campaign** will help increasing prevention and treatment coverage as **prejudice against risk groups is a significant barrier** in many Western and European countries.

- Adjustment of **national vaccination programs** is needed to **increase vaccination uniformity** and thereby hindering **spread of the disease**.
Immunization coverage with 3rd dose of HepB vaccines in infants, 2009

Date of slide: 27 July 2010
Access to vaccination and treatment in intermediate-to low-prevalence regions (example Europe)

2 Surveillance

- Surveillance data will help adjusting national programs to respond to new dynamics of HBV infections (e.g. HBV genotype, HBeAg status, mode of transmission)
- Southern European countries have to expect an increase in HBV-related liver diseases as the unvaccinated population comes of age
- unmask local clusters of high endemicity and infection
Access to vaccination and treatment in intermediate- to low-prevalence regions (example Europe)

3 Screening

- To reach certain sub-populations with higher prevalence but limited access to treatment, e.g. refugees, people without health insurance, people who inject drugs (PWID) or abuse alcohol, HBV management programs need to be adopted.

- Current challenge in Europe created by arrival of large numbers of refugees, prevalence must be evaluated in those populations and appropriate control strategies must be adopted.

Increase of HBV prevalence in Germany through refugees?

Seroprevalence of HBsAg (%)
HBsAg prevalence in 793 refugees

2.3% (18/793)

18 HBsAg positive patients
- 0/18 AST elevation
- 2/18 ALT elevation (58 U/l, 107 U/l)

→ PPV 0 for AST and 0.016 for ALT

Hampel, Solbach, Cornberg et al., Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2016 May;59(5):578-83.
Access to vaccination and treatment in intermediate- to low-prevalence regions (example Europe)

3 Screening

- Example Germany
  - Refugees have a higher HBsAg prevalence than the German population 2.3% vs. 0.4%
  - Especially in young age HBV immunization status is poor → „every vaccination counts“
  - Social welfare covers treatment only if life is being threatened → new transmission dynamics have to be expected

Access to vaccination and treatment in intermediate-to low-prevalence regions (example Europe)

4 Detection and Diagnosis

- **Enhance low diagnosis rate** by increasing **awareness of risk scenarios** in primary care setting
  - a recent **screening study** in Germany including >20,000 patients **revealed 85% previously unknown infections**
  - Misperception in primary care that elevated ALT levels are mainly associated with alcohol abuse

Access to vaccination and treatment in intermediate-to low-prevalence regions (example Europe)

5 Treatment

- **awareness campaigns** will help to **reduce barriers to access** in many western countries

- **declining resources and economic constraints** reduced sustainable investments in HBV management

- investments will be needed to increase proportion of HBV-infected individuals that receive treatment

---

2 Papatheodoridis et al. *J Viral Hepat.* 2016;23(Suppl 1):1-12-
## Access to vaccination and treatment in intermediate-to low-prevalence regions (example Europe)

<table>
<thead>
<tr>
<th>Key challenges</th>
<th>Key measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of knowledge and awareness</td>
<td>• evidence-based knowledge to create an appreciation of the impact of the disease</td>
</tr>
<tr>
<td>Limited screening and linkage to care</td>
<td>• Screening of risk groups (according to guidelines) to increase treatment uptake</td>
</tr>
<tr>
<td></td>
<td>• Screening of pregnant women</td>
</tr>
<tr>
<td>Lack of vaccination</td>
<td>• Implementation of universal infant vaccination</td>
</tr>
<tr>
<td>Limited treatment</td>
<td>• Better training of physicians: improve screening, optimal treatment based on guidelines, prevent reactivation</td>
</tr>
<tr>
<td>Social stigma and discrimination</td>
<td>• Increase knowledge in the general population</td>
</tr>
</tbody>
</table>
Access to vaccination and treatment in special populations: pregnant woman

**Vertical transmission** from mothers to their newborns

- is the **most common route in high prevalence regions**
- is the **route with highest rate of chronicity**

**Prevention** of vertical transmission can be reached by **active and passive immunisation** of the infant within 24 hours after birth1,2, **BUT**

- often **no access to HBlg**
- **failure of vaccination** in infants born from mothers with very high viral loads3

→ **NEEDED:** additional antiviral therapy with NUCs in pregnant women with very high viral loads 4,5

Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load.

HBsAg positive mothers with HBV-DNA levels $>200,000$ IU/mL

Access to vaccination and treatment in special populations: pregnant woman

**Proposed scenario**

- HBsAg screening of pregnant women in the first trimester
- Starting antiviral therapy at 28-32 weeks of gestation if HBV DNA is above 200,000 IU/mL

In high-income countries time-point of screening will need to be adapted, e.g. in Germany mothers are currently screened only in week 32 of gestation.

Access to vaccination and treatment in special populations: immunosuppressive therapy

HBsAg neg and HBsAg neg, anti HBc positive patients undergoing immunosuppressive therapy are at high risk
• of HBV reactivation
• and subsequent liver failure and death1

Prophylactic antiviral therapy is highly effective and current guidelines recommend screening everyone undergoing immunosuppressive treatment2, BUT

• screening rate is low, even among specialists3-5

→ NEEDED: efforts to improve screening and treatment as mortality to HBV reactivation can be prevented.

Low rates of hepatitis B virus screening at the onset of chemotherapy.


8942 not screened:  
134 unidentified HBsAg positive (1.5%)?  
662 unidentified anti-HBc positive (7.4%)?
Low rates of hepatitis B virus screening at the onset of chemotherapy.

8942 not screened:
134 unidentified HBsAg positive (1.5%)?
662 unidentified anti-HBc positive (7.4%)?
Ultimate goal: eradicating HBV

Key points

• Management of viral hepatitis should become a global health priority

• Sustainable funding will be needed to reach the ultimate goal of globally eradicating HBV
THANKS FOR YOUR ATTENTION !!