Towards the Elimination of Hepatitis B: Challenges in implementing the WHO vision by 2030

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Global Burden of Disease

Global Burden of Disease study: 1990-2013 (183 countries)

- Viral hepatitis is responsible for approximately 1.45 million deaths/yr
  - Cirrhosis, liver failure and liver cancer
- HIV/AIDS: 1.3 million deaths/year
- Malaria: 0.9 million deaths/year
- Tuberculosis: 1.4 million deaths/year

Viral hepatitis is now the 7th leading cause of mortality worldwide

- Mortality due to viral hepatitis has increased by 63% since 1990
- Persistent lack of global awareness of the severity of the problem
- Lack of commitment to combat and ultimately eliminate the disease

Viral hepatitis kills more than 1.4 million people a year, yet there is a remarkable lack of global awareness and action to combat the disease.

- Mortality and morbidity mainly due to hepatitis B and C infections
  - 96% of mortality and 91% of morbidity in 2013
- 95% unaware of their infection
- Do not benefit from clinical care and treatment or interventions designed to reduce onward transmission (1% access Rx)

Data from 183 countries: Mortality increased from 890,000 deaths in 1990 to 1.45 million deaths in 2013
Leading causes of mortality and Trends 2013
Global burden of Viral Hepatitis 190-2013 (Lancet 6 July 2016)
Africa Mortality rates ranging from:

- < 10 000 per 100 000 per year (South Africa)
- 10 - 33.49 per 100 000 per year (Central and Eastern Africa)
- ≥ 33 - 50 per 100 000 per year (West Africa)
Proposed WHO targets for reducing new infections and stopping deaths

**Hepatitis B and C**
- 80% people eligible for treatment being treated
- Requires identification and linkage to care
WHO: Elimination of Viral Hepatitis by 2030

WHO strategy: Key targets to eliminate Hepatitis B and C as a public health threat

- 90% infants receive a hepatitis B birth dose vaccination
- 100% blood donations screened
- 90% injections are safe
- 90% people aware of their illness
- 80% people treated

Saving 7.1 million lives
Elimination of Hepatitis B in sSA

Many sSA countries in the process of developing Viral Hepatitis Management Guidelines and Strategic plans to achieve these elimination goals

Major challenges to the elimination of Hepatitis B in sSA

• Effective prevention of mother to child transmission

• Access to affordable diagnostics: Identify HBV-infected individuals and link to care

• Addressing social stigmas associated with the diagnosis of HBV and screening of contacts

HBV and its associated complications of cirrhosis, liver failure & HCC

VACCINE PREVENTABLE
Hepatitis B

Effective vaccines since 1981 & effective antiviral therapy

• Hepatitis B remains a global health problem
• 2 billion people have serologic evidence of past or ongoing HBV infection
• 350-400 million people with chronic HBV infection
• 1 million people die annually from HBV & its associated complications
• Life-time risk of cirrhosis, liver failure & HCC: 15-40%
• Recent systematic review based on observational studies (1965-2013)
   ❖ Africa: 8.83% HBsAg seroprevalence (75.6 M): high endemicity
• Chronicity determined by age of acquisition
  ❖ 90% after neonatal infection and 20-50% with childhood infection < 5 years
HBV endemicity is established in early childhood with HBsAg seroprevalence studies showing no difference between children aged 5-9 years and adults.

Lancet 2015; 386: 1546-55
70% of global 36 million people with HIV live in sSA

Increased mortality & morbidity

**HIV co-infection promotes:**

- Increased HBV replication & rates of HBV reactivation
- HBV MTCT 2.5 fold
- Increased rates of occult HBV
- Chronicity of newly acquired HBV infections
  - *Progression to fibrosis and cirrhosis – 5x faster*
  - *HCC - occurs at a younger age and is more aggressive*

Globally, up to 10% of HIV-infected individuals have HBV co-infection

- 4-6 M HIV/HBV co-infected individuals

HBV endemic countries up to 25% HIV/HBV co-infected

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Hepatitis B Epidemiology

- HBV infection rates largely reflect a failure of maternal and child healthcare programmes to prevent HBV MTCT and early childhood transmission

sub-Saharan Africa
- Horizontal transmission - early childhood <5 years old
- Lower prevalence of HBeAg positive mothers
- Close household contacts, medical or traditional scarification procedures
- 30-50% risk of chronic infection

Impact of HIV/HBV co-infection in pregnancy
- Pregnant women 3 x more likely to test positive for HBV DNA, higher HBV DNA
- Twice as likely to test positive for HBeAg
- Increased risk of HBV MTCT
Elimination of Hepatitis B

Prevention of Mother-to-child-transmission (MTCT) of HBV

- **Identify:** Maternal HBsAg screening
  - Not routine in many sSA countries

- **Incorporate Birth dose HBV vaccine into EPI schedule**
  - Administration within 24 hours of delivery

- **Assess the need for Tenofovir in 3rd trimester of pregnancy**
  - Most women are immune tolerant or immune control phase - not candidates for treatment
  - Risk of MTCT if HBV DNA >200 000 IU/ml
  - HBIG and HepB-BD: 80-95 % effective in preventing MTCT
  - HBIG expensive and not routinely available

- **Ensure full HBV3 vaccine coverage**
Universal HBV Vaccination

World Health Organization (WHO) recommended its incorporation into the Expanded Programme of Immunization (EPI) in 1991

• Most effective way to reduce global burden of HBV

• 194 countries worldwide and 45 in WHO Africa region have incorporated hepatitis B vaccination into EPI

• **Systemic review (1990-2005):** HBV seroprevalence has decreased in many regions of the world

• **Estimated to have prevented more than 1.3 million deaths**

  In 2009, WHO recommended HBV Birth dose vaccine for all countries, even those with low HBV prevalence

2014: only 96/194 countries (49%) reported offering HepB-BD as part of their national immunization programmes and <38% of babies born worldwide received HepB-BD within 24 hours after birth.
HBV Vaccination :sSA

HBV Vaccine schedule 6,10 and 14 weeks

• Prevent childhood acquisition between 6 months and 5 years
• Based on acquisition being mainly horizontal
• Concerns in HIV era of increased risk of perinatal MTCT of HBV
• HBV monovalent vaccine is thermostabile and can be administered at same time as polio and BCG
  ❖ Innovative approaches are required in settings of home deliveries

Chinese government in partnership with GAVI
(Vaccine 2013;31(Suppl 9):J29-J35)

• Free birth dose vaccine
• Upscaling of full vaccine schedule, improved maternal screening
• Utilising village lay healthcare workers
• HBsAg seroprevalence now 0.96% in children < 5yrs (9.67% in 1992)
Implementation: HBV Birth dose vaccine

- Births take place in two main settings
  - Formal healthcare facilities or in the ‘home’ delivery setting
- Integrate birth dose vaccination with newborn care policies & practice
- Assign responsibility for administering the birth dose
- Build capacity for vaccine storage, administration, reporting & recording
- **Formal healthcare facilities:** HBV Vaccine in or adjacent to delivery room
- **Home deliveries:** Educating mothers and other caregivers, during the antenatal period: Importance and timing of HepB-BD vaccine
- **Antenatal visits are a key opportunity for education**
  - 74% pregnant women in WHO African Region had at least one antenatal care contact
  - Community health workers and other antenatal care providers should be trained to include HepB-BD in counselling
- Auxiliary health workers or community health workers can be trained to administer vaccines at home
  - Single-dose vials or compact pre-filled auto-disposable devices (CPADs)
Implementation: HBV Birth dose vaccine

Pregnancy tracking to improve HepB-BD vaccine coverage

**Vietnam** *(Vaccine 2008;26(11):1411)*

Established strategy for tracking pregnant women in order to increase timely HepB-BD coverage

- In two districts where 20 - 36% of newborns were born at home
  - **Community health workers** tracked pregnancies by recording names, addresses and expected delivery dates of pregnant women
  - **Village health workers** informed community health workers of births to further ensure that HepB-BD was administered
- This system helped districts to achieve **90 - 97% coverage with HepB-BD vaccine**
HBV Birth dose vaccine

**Indonesia** *(Vaccine 2007;25(32):5985)*

- >90% of births occur at home
- **1990s:** Programme training village midwives in use of CPADs
  - Allowed to store CPADs out of the cold chain in their homes
- HepB-BD immediately available when midwife was called to a delivery
- Both village midwives and mothers preferred use of CPADs
- Successful use of CPADs was expanded nationwide
- Facility delivery rates still low: **HepB BD vaccine coverage is now 84%**

Compact pre-filled auto-disposable device (CPAD)
### HBV Birth dose vaccine

**MONOVALENT HEPATITIS B VACCINE MUST BE USED FOR THE BIRTH DOSE**

<table>
<thead>
<tr>
<th>NAME OF DOSE</th>
<th>3-DOSE SCHEDULE</th>
<th>4-DOSE SCHEDULE**</th>
</tr>
</thead>
<tbody>
<tr>
<td>HepB-BD</td>
<td>As soon as possible after birth (≤24 h)</td>
<td>As soon as possible after birth (≤24 h)</td>
</tr>
<tr>
<td>HepB1</td>
<td>HepB1 is not given (i.e. not counted*)</td>
<td>As per combination vaccine schedule</td>
</tr>
<tr>
<td>HepB2</td>
<td>4 weeks minimum after HepB-BD</td>
<td>As per combination vaccine schedule</td>
</tr>
<tr>
<td>HepB3</td>
<td>4 weeks minimum after HepB2</td>
<td>As per combination vaccine schedule</td>
</tr>
</tbody>
</table>

* Not counting HepB1 is recommended as a standard to allow for reporting coverage of Hep-B-D and HepB3 when using a 3-dose schedule.

** In the 4-dose schedule, the second dose is still called HepB1 in order to avoid confusion with DTP1/Pentavalent1.

- Monovalent HBV birth dose improves immunogenicity of penta/hexavalent vaccines
- 4 dose schedule does not immunologically compromise infants who do not access Hep-BD
- **Risk of chronic HBV infection, despite HepB-BD, is 3.74x higher if interval between 1st and 2nd vaccine dose >10 weeks**

Vaccine 2009;27:6110–6115
Global and regional infant vaccination rates

Taiwan
- Incomplete vaccination is an important predictor for HCC
- HR 2.52 after correction for maternal HBsAg status

WHO/UNICEF estimates of third dose of HBV vaccine coverage 1989-2010

Thurz et al Nature Gastro 2012 ; 9; 492-494
Efficacy: Universal HBV Vaccination


• Universal vaccination in 1984, together with
  - Catch-up vaccination programme
  - Improved maternal screening

• HBsAg seroprevalence in children <15 years decreased
  - 9.8% in 1984 to 0.7% in 1999 to 0.3% in 2009

• Infection rate (anti-HBc seropositive rate): children 15-20yrs after programme decreased from:
  - 38% in 1984 to 16% in 1999 to 4.6% in 2009
Efficacy: Universal HBV Vaccination


### HCC incidence in children decreased, esp in boys

- Average annual incidence in children 6-14 years of age
  - 0.70 per 100,000 children in 1981-1986
  - 0.57 per 100,000 children in 1986-1990
  - 0.36 per 100,000 children in 1990-1994

5.2 cases/million population (1984) to 1.3 cases/million in 1st vaccination cohort

Incomplete immunisation most important risk predictor for HCC

- HR 2.52 after correction for maternal HBsAg status *(Hepatology 2014;60:125)*
Efficacy: Universal HBV Vaccination


- Age-standardised HCC incidence rate among males decreased
  - 27.8 per 100,000 per year during 1978 -1982
  - 19.0 per 100,000 per year during 1988 -1992

Khon Kaen, Thailand *(Asian Pac J Cancer Prev 2008;9:507)*

- Age-standardized HCC incidence rates in children >10 years
  - Non-vaccinated: 0.88 per million
  - Vaccinated children: 0.07 per million

Alaska Natives *(Hepatology 2011;54:801)*

- 25 years after Universal HBV vaccination & mass screening
- HCC incidence in adolescents <20 years decreased
  - 3 per 100 000 in 1984 -1988
  - 0 per 100 000 in 1995 -1999
- **No cases of HCC documented since 1999**
Efficacy: Universal HBV Vaccination

Rural China: Qidong province: Neonatal HBV vaccination


- Reduces infant fulminant hepatitis mortality rate: 69% efficacy (95% CI 34-85%)
- Reduces end stage liver disease mortality rates: 70% efficacy (95% CI 15-89%)
- Reduces HCC incidence rate: 84% efficacy (95% CI 23-97%)
Efficacy: Universal HBV Vaccination

- SA introduced universal HBV vaccination in April 1995
  - Added to existing 6, 10 and 14 week EPI schedule, now 18 month booster
  - Hexavalent vaccine

- Pre-HIV era epidemiological studies
  - sSA: Mothers predominantly HBeAg negative
  - Lower risk of perinatal transmission: lower HBV replication

- No birth dose, no catch-up programme & no formal policy of screening mothers for HBsAg

- Overall HBsAg seroprevalence declining from 12.8% to 3% in some studies

- Recent SA studies suggest that there is a potential problem
  - Recent HBsAg seroprevalence rates vary between 3-25%
  - Highest rates in HIV infected individuals

Efficacy: Universal HBV vaccination

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SA : Impact of HIV : Maternal Transmission

**Western Cape** (9 355 pregnant women from antenatal clinics comparing HIV-positive and negative women) Vaccine 2013;31(47):5579

- Low HBsAg prevalence region in SA
  - HBsAg 3.4% (53/1 543 HIV pos) v. 2.9% (44/1 546 HIV neg)
- HBeAg 18.9% (10/53 HIV pos) v. 17.1% (7/41 HIV neg)
- HBV DNA levels were much higher in HIV positive women
  - $9.72 \times 10^7$ IU/ml v. $1.19 \times 10^6$ IU/ml
- One in six HBV-infected pregnant women, irrespective of HIV status is HBeAg seropositive
- Neonates remain unprotected for first 6 weeks of life
SA : Impact of HIV : Maternal Transmission


- **Retrospective cross-sectional study:** July 2011 to December 2011
- 322 study samples from discarded residual dried blood spot samples following routine infant diagnosis of HIV

**10% overall HBsAg seroprevalence**
- HIV-positive infants: 21/161 infants HBV positive: 13.0%; 95% CI 6.8-19.9
- HIV-negative infants: 12/161 HBV positive: 7.5%; 95% CI 2.5-13.7
- Not statistically significant

**Concern**
- High prevalence of HBV infection in children despite HBV vaccination
- Independent of HIV status
Prevention of Mother to Child Transmission

Prevention of HBV MTCT is critical step towards the eradication of HBV & reduction in the incidence of HCC

- Universal HBV vaccination including HepB-BD decreases HBsAg seroprevalence
- Immunoprophylaxis fails in 10 to 30% of infants born to mothers with HBV DNA level >6 log_{10} copies/ml
- HBIG expensive and not easily accessible

Third trimester prophylaxis

- AASLD now suggest Tenofovir 300mg daily at 28-32 weeks of pregnancy if HBV DNA >200 000 IU/ml to further reduce risk of perinatal transmission
- EASL suggests antiviral therapy in 3\textsuperscript{rd} trimester if HBV DNA >10^{6-7} IU/ml
- WHO: no formal recommendation for routine use of antiviral therapy

Prevention of Mother to Child Transmission

China: 5 geographic regions – Pan et al, NEJM 2016;374:2324

- HBeAg-positive mothers HBV DNA >200 000 IU/ml
- 300 mg TDF: 30 to 32 weeks of gestation until postpartum week 4
- Infants: 200 IU HBIG & 10ug HBV vaccine within 12hrs, HBV vaccine & HBIG repeated at 1 month and HBV vaccine at 6 months
- All mother–infant dyads: evaluated at postpartum weeks 4, 12, 24 & 28
- 68% TDF-treated mothers (66/97) vs 2% (2/100) - target HBV DNA level < 200 000 IU/ml at delivery
- Week 28, rate of MTCT (HBV DNA >20 IU/ml or HBsAg positive at 28 wks)
  - ITT analysis: 5% infants (5/97) in TDF vs. 18% (18/100), p= 0.007
  - Per-protocol analysis 0% infants in TDF vs. 7% (6/88), p= 0.01
  - No difference in maternal HBV serological outcomes
- No difference in birth defects - 2% (2/95) vs 1% (1/88)
Prevention of Mother to Child Transmission

Need to identify highly viraemic mothers

- HBeAg and HBV DNA quantification (expensive with limited access)
- Shared diagnostic platforms for viral loads: HIV and HBV

**HBsAg quantification: Taiwan: Wen et al, Hepatology epub**

- Maternal HBV DNA viral load > 6 - 7 log_{10} IU/ml or HBsAg >4 to 4.5 log_{10} IU/ml: substantial risk of perinatal transmission

- Estimated perinatal infection rates at maternal HBsAg levels:
  - 4 log_{10} IU/ml (10,000 IU/ml): 2.4%
  - 4.5 log_{10} IU/ml (30,000 IU/ml): 8.6%
  - 5 log_{10} IU/ml (100,000 IU/ml): 26%

- Optimal cut-off of maternal HBsAg level to predict perinatal infection: 4.1 log_{10} IU/ml (12,500 IU/ml): 100% sensitivity, 71% specificity
Prevention of adult acquisition and transmission

• Ideally all individuals should be vaccinated – no catch-up programmes

**Essential to identify and vaccinate high risk groups**

- Health-care workers
- All laboratory staff working with clinical specimens
- Policemen, firemen and members of the armed forces
- Persons with endstage renal disease requiring dialysis
- Persons with chronic liver disease
- Residents and staff of facilities for the developmentally disabled
- Patients receiving frequent transfusions of blood or blood components
- Transplant candidates before transplantation

**Dependent on ability to:**

- Screen high risk individuals: HBsAg and anti-HBs
- Administer HBV Vaccine

At all levels of care
Diagnosis and Linkage to Care

It is essential to identify HBV-infected individuals in order to assess the need for treatment and appropriate frequency of follow-up

- Upscaling diagnosis and improving linkage to care
- **Accurate WHO accredited HBV point of care testing that can be easily administered at primary levels of care**
- Shared diagnostic platforms for viral quantification: HIV, HBV and HCV
- Establish clear pathways of referral for follow-up and treatment
- **Educate clinicians that HBV is a silent disease:** often only clinically presenting when life-threatening complications arise
- **Most HBV-infected individuals in sub-Saharan Africa** do not fit the clinical profile for Interferon-based therapy and will usually require **lifelong treatment with nucleos(t)ide analogues**
- Tenofovir is the preferred antiviral
- **Ensure access to antivirals for management of HBV mono-infection**
Elimination of Hepatitis B: Conclusions

- **Hepatitis B is endemic in sub-Saharan Africa**
  - Despite Universal HBV vaccination, estimated overall HBsAg seroprevalence remains high at 8.83%.

**Achieve WHO vision to eliminate hepatitis B by 2030 in sSA**

- Development and Implementation of National Guidelines for the Prevention and Treatment of Viral Hepatitis.

- Actively implement a number of elimination strategies
  - Effective prevention of HBV MTCT
    - Tenofovir in 3rd trimester if HBV DNA >200,000 IU/ml
    - Birth dose vaccine
  - Ensure full HBV vaccine coverage
  - Upscale diagnosis and treatment of HBV-infected individuals
    - Accurate and affordable diagnostics
    - Ensure access to Tenofovir for mono-infected individuals

- Commitment from Governments and National Departments of Health.
Health Disparities: Sub-Saharan Africa

Burden of liver disease in Sub-Saharan Africa is substantial.

Challenges:

- Lack of data to accurately establish disease prevalence
- Lack of access to health facilities - diagnostic and interventional
- Access and cost of medications

Apply similar programmes to HIV/AIDS to combat liver disease in SSA:

- PEPFAR
- Global Fund to Fight AIDS, TB and Malaria
  → brought medication at affordable prices to SSA
Kwazulu-Natal, South Africa
- September to December 2014
- Screened for HBsAg, anti-HBs, anti HBc
- 183 HIV infected vs. 108 HIV uninfected children bet 5-15 years
- HBsAg positive in 2.1% vs. 0% in HIV + vs. HIV negative children
- anti-HBs response to immunization: 15.8% (HIV+) vs 61.1% (HIV-) children

<table>
<thead>
<tr>
<th>TABLE I. Serologic Markers of Past and/or Ongoing Infection in the HIV-Infected and Uninfected Cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected</td>
</tr>
<tr>
<td>5–10 years</td>
</tr>
<tr>
<td>Ongoing infection</td>
</tr>
<tr>
<td>0/103 (0%)</td>
</tr>
<tr>
<td>1/80 (1.3%)</td>
</tr>
<tr>
<td>1/183 (0.5%)</td>
</tr>
<tr>
<td>Past infection</td>
</tr>
<tr>
<td>2/103 (1.9%)</td>
</tr>
<tr>
<td>1/80 (1.3%)</td>
</tr>
<tr>
<td>3/183 (1.6%)</td>
</tr>
<tr>
<td>HIV-uninfected</td>
</tr>
<tr>
<td>5–10 years</td>
</tr>
<tr>
<td>0/74 (0%)</td>
</tr>
<tr>
<td>0/34 (0%)</td>
</tr>
<tr>
<td>0/108 (0%)</td>
</tr>
<tr>
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</tbody>
</table>

HIV-infected children remain at risk of infection

<table>
<thead>
<tr>
<th>TABLE II. Comparison of the Immunity Against HBV in the HIV-Infected and Uninfected Cohorts According to the Age Subgroup of the Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected</td>
</tr>
<tr>
<td>5–10 years</td>
</tr>
<tr>
<td>Presence of anti-HBs</td>
</tr>
<tr>
<td>21/103 (20.4%)</td>
</tr>
<tr>
<td>8/80 (10%)</td>
</tr>
<tr>
<td>29/183 (15.8%)</td>
</tr>
<tr>
<td>HIV-uninfected</td>
</tr>
<tr>
<td>5–10 years</td>
</tr>
<tr>
<td>49/74 (66.2%)</td>
</tr>
<tr>
<td>17/34 (50%)</td>
</tr>
<tr>
<td>66/108 (61.1%)</td>
</tr>
</tbody>
</table>
Treatment of CHB
Inhibition of HBV replication &
Clinical Impact : Disease progression and HCC
Risk factors: Disease progression & HCC in patients with CHB

<table>
<thead>
<tr>
<th>Host factors</th>
<th>Viral factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (duration of infection?)</td>
<td>HBV DNA levels</td>
</tr>
<tr>
<td>Sex (males&gt;females)</td>
<td>HBsAg levels</td>
</tr>
<tr>
<td>Genes (polymorphisms)</td>
<td>HBeAg status</td>
</tr>
<tr>
<td>Body mass index</td>
<td>HBV genotype (C/D&gt;A/B)</td>
</tr>
<tr>
<td>Cofactors of liver disease (alcohol, NAFLD, Iron overload)</td>
<td>Basal core promotor mutations pre-core promoter mutations</td>
</tr>
<tr>
<td>Dietary factors (aflatoxin, coffee)</td>
<td>Pre-S deletions</td>
</tr>
<tr>
<td>Disease severity (decompensation&gt;compensated cirrhosis&gt;CHB&gt;carrier state)</td>
<td>Protein X</td>
</tr>
<tr>
<td>Smoking?</td>
<td></td>
</tr>
</tbody>
</table>

Non-modifiable factors - Modifiable factors

NAFLD: non-alcoholic fatty liver disease
REVEAL demonstrated the association between HBV DNA levels and cirrhosis

Cumulative incidence of cirrhosis (n=3582)

Baseline HBV DNA level (copies/mL)
- ≥1.0 x 10^6
- 1.0–9.9 x 10^5
- 1.0–9.9 x 10^4
- 300–9.9 x 10^3
- <300

P-value for log rank test <0.001

Cumulative incidence of liver cirrhosis (%)

No patient had cirrhosis at baseline
REVEAL demonstrated the association between HBV DNA levels and HCC

Entire cohort (n=3653)

Baseline HBV DNA level (copies/mL)
- ≥1.0 x 10^6
- 1.0–9.9 x 10^5
- 1.0–9.9 x 10^4
- 300–9.9 x 10^3
- <300

Cumulative incidence of HCC (%)

Year of follow-up

No patient had cirrhosis at baseline; HCC: hepatocellular carcinoma
Undetectable HBV DNA is a key goal as it is associated with the lowest risk of HCC

Histological outcomes with ETV in patients with undetectable on-treatment HBV DNA levels

- NA naïve, HBeAg+ or HBeAg- patients with HBV DNA <300 copies/mL on ETV
  - N=57 had paired biopsies available
  - 86% had normal ALT
  - N=4 with cirrhosis
- Median interval 6 years
  - Range 3-7 years
  - 96% had histological improvement
  - 88% had improvement in fibrosis score

Ishak fibrosis score at baseline and treatment at Week 48 and Year 6

3 yr cumulative ETV therapy in Phase 3 studies & long term rollover studies

Histological outcomes with TDF treatment: liver fibrosis regression and cirrhosis reversal

- TDF vs ADV for 48 weeks then open-label TDF in HBeAg- and HBeAg+ patients (Studies 102 and 103)
  - N=348 had biopsies at baseline and Year 5
  - N=96 with cirrhosis
- 87% (304/348) - histological improvement
- 74% (71/96) had reversal of cirrhosis
- Only low BMI was associated with fibrosis regression at Year 5
- Baseline BMI, diabetes at baseline & on-treatment ALT level associated with cirrhosis reversal

ETV treatment in cirrhotic patients

All hepatic events

Hepatocellular carcinoma

Liver-related mortality

All-cause mortality

Wong GL et al. Hepatology 2013;58:1537
651 patients (98 percent Asian and 85% male)

• Study was terminated after median duration of treatment of 32.4 months (range, 0 to 42)
  - clear benefit of lamivudine in preventing disease progression and liver related death

HCC: 3.9 % in lamivudine group & 7.4% in placebo group (Hazard Ratio, 0.49; P=0.047)

Cumulative HCC risk scores: Asian CHB pts

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>Alb (g/L)</th>
<th>TBil (µmol)</th>
<th>ALT (U/l)</th>
<th>HBeAg status</th>
<th>HBV DNA (cp/mL)</th>
<th>Cirrhosis</th>
<th>AUROC</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAG-HCC²</td>
<td>In years</td>
<td>M: 16 F: 0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>3 × log</td>
<td>Yes: 33 No: 0</td>
<td>5yr: 0.87 10yr: 0.88</td>
</tr>
<tr>
<td>CU-HCC³</td>
<td>≤50: 0 &gt;50: 3</td>
<td>NA</td>
<td>≤35: 20 &gt;35: 0</td>
<td>≤18:1.5 &gt;18:1.5</td>
<td>NA</td>
<td>NA</td>
<td>&lt;4 log: 0 4–6 log: 1 &gt;6 log: 4</td>
<td>Yes: 15 No: 0</td>
<td>5yr: 0.76 10yr: 0.78</td>
</tr>
</tbody>
</table>

Cirrhosis 5yr: 0.7 10yr: 0.65

AUROC for HCC prediction: Caucasian pts with compensated CHB treated with ETV/TDF

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</thead>
<tbody>
<tr>
<td>GAG-HCC²</td>
<td>0.76</td>
<td>CU-HCC: 0.62</td>
<td>REACH-B: 0.61</td>
<td></td>
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</tr>
</tbody>
</table>

*The risk score attributed to HBV DNA ≥10⁶ copies/mL was less than that for HBV DNA of 10⁵–<10⁶ copies/mL because most patients with HBV DNA ≥10⁶ copies/mL were also HBeAg-positive, thus sharing the associated higher score for this category.

Risk of HCC is predicted to be decreased with longterm TDF therapy

- 7.4 year longterm follow-up from pivotal TDF studies (N=641) compared with predicted rate of HCC from 3 new models
- **Risk models predicted similar scores that were consistently higher** than the 14 cases of HCC that occurred during follow-up (n=404)
- Despite viral suppression by TDF there is still risk of HCC
  - Need for constant monitoring for HCC

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**Graph Description**

- **Cumulative no. of HCC cases** vs **Years**
- **Observed**, **REACH-B**, **CU-HCC**, **GAG-HCC**, **PAGE-B**

**Legend**

- **REACH-B**: Risk Estimation for HCC in CHB-developed in non-cirrhotic patients only and may underestimate risk in cirrhotic pts
- **CU-HCC**: Chinese University HCC score
- **GAG-HCC**: Guide with Age, Gender, HBV DNA, Core promoter mutations and Cirrhosis
- **PAGE-B**: Platelets, Age and Gender in CHB
USA STUDY: 841 patients - 646 male (65%) - multicentre
- 84% Asian, median age 47 yrs, 36% HBeAg positive
- 9.4% with cirrhosis

Median follow-up of 4 years
- 17 (2.6%) HCC
- 8/61 (13.1%) with cirrhosis
- 9/585 (1.5%) without cirrhosis

17 HCC pts: 53 yrs vs 47 yrs and more likely to have cirrhosis at 47.1% vs. 8.4%

REACH-B prediction model

Max follow-up time of 8.2 years: Significantly lower than predicted HCC incidence was noted with an SIR of 0.56 (95% confidence interval: 0.35–0.905)
Risk of HCC predicted to be decreased antiviral therapy: ETV and Tenofovir

Validation of PAGE-B (age, gender and platelets)

• 1815 Caucasians with CHB & no HCC at baseline: ETV/TDF ≥ 12 mnths
• Using data from eight centers (derivation dataset, n = 1325): HCC risk score

NONE OF THE HCC RISK SCORES VALIDATED IN AFRICA

40% HCC occur in young non-cirrhotic patients

≥18: 17% in derivation & 16% invalidation dataset

PAGE-B: Simple & reliable score for prediction of 5-yr HCC risk in Caucasian CHB patients under ETV/TDF

J Hepatol 2016;64;800
Towards the Elimination of HBV and HCC

- **Hepatitis B and its associated complications are vaccine preventable**
- Implement WHO recommendations of HBV Birth dose vaccine
  - Full impact of birth vaccination will take 2-3 decades
- Ensure full coverage of HBV vaccination
- Maternal HBsAg screening and consider Tenofovir in 3rd trimester if HBV >200 000 IU/ml
- Vaccinate high risk groups
- Identify HBV-infected individuals and link to appropriate care & follow-up
- Antivirals have had an impact on development of cirrhosis & risk of HCC
  - Improving liver-related and all cause mortality
- Have not eliminated HCC risk: Antiviral Rx & monitoring usually lifelong
- **NEED A CURE AIMED AT ERADICATION OF cccDNA**
Worldwide Prevalence of Hepatitis B and Incidence of Hepatocellular Carcinoma

sSA: HBV causes 80% HCC and cirrhosis only present in 60% HCC

- Highest in Mozambique - 101.7 per 100,000 persons/yr

Can J Gastroenterol 2000;14:703; WHO HBV Vaccines 2003
Efficacy: Universal HBV Vaccination

South Korea *(Korean J Intern Med 2013;28:413)*
- Overall HBsAg seroprevalence:
  - 4.61% in 1998 and 2.98% in 2010
- Adolescents (10-19 years):
  - 2.2% in 1998 to 0.12% in 2010

American Samoa
- HBsAg seroprevalence decreased amongst children: 7.5% to 0%

Gambia
- HBsAg seroprevalence: 10.3% to 0.6%

Italy
- HBsAg seroprevalence: 3.4% to 0.9%

Saudi Arabia
- HBsAg seroprevalence: 6.7% to 0.3%
Efficacy: Universal HBV Vaccination


- Universal vaccination in 1984, together with
  - Catch-up vaccination programme
  - Improved maternal screening

- HBsAg seroprevalence in children <15 years decreased
  - 9.8% in 1984 to 0.7% in 1999 to 0.3% in 2009

- Infection rate (anti-HBc seropositive rate): children 15-20yrs after programme decreased from:
  - 38% in 1984 to 16% in 1999 to 4.6% in 2009

  - 2002: 6602 individuals and followup in 4088 individuals in 2007
  - HBsAg seroprevalence 13.7% & 68.46% anti-HBc positive
  - None of vaccinated cohort became HBsAg positive: durability of vaccination
  - Backlog of substantial HBV infection in Taiwan
Elimination of Hepatitis B

- Many sSA countries in the process of developing Viral hepatitis Management Guidelines and Strategic plans to achieve these elimination goals

**Major challenges to the elimination of Hepatitis B in sSA**

- Effective prevention of mother to child transmission
  - Maternal HBsAg screening
  - HBV Birth dose vaccine – implementation
  - Universal HBV vaccination with full coverage of vaccine

- Access to affordable diagnostics: Identify HBV-infected patients and link to care

- Addressing social stigmas associated with the diagnosis of HBV
Cost-effectiveness analysis: Additional birth dose of HBV vaccine

Mozambique (Vaccine 2012,31(1):252)

- Cost-effectiveness of an additional birth dose of Hepatitis B (HBV) vaccine administered by professional birth attendants in medical settings

- **Markov model**: analyse costs and effects associated with avoiding perinatal transmission of HBV through a birth dose vaccination in addition to existing vaccination schedule (2008 birth cohort of 2008)

- **Comparator intervention** - existing vaccination 6-10-14 week schedule

- Low-income setting - main outcome measure was disability-adjusted life years (DALYs) averted

- Found incremental cost-effectiveness ratio (ICER) for the additional birth dose of 250.95 US$ per DALY averted

- Assuming a willingness-to-pay threshold of 441 US$ (GDP per capita for Mozambique in 2008)

  Additional birth dose was highly cost-effective