The State of HBV in the World

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Disclosures

- I personally have no conflict of interests for this talk

Outline of Talk

- Epidemiology: Challenges in uncovering the Global Burden of Liver Disease
- HBV in the USA
- Prevention of chronic HBV: Where are we succeeding and Where are We Falling Behind?
- Other considerations in LIC and MIC
  - Screening for HBV: How can it be done?
  - Management of Chronic HBV: What is needed?

Challenges in uncovering the Global Burden of Liver Disease

- This is important in targeting not only where emphasis on implementation of guidelines should go but also determining impact of programs
- Accurate estimates of cirrhosis death and Epidemiology of cirrhosis and HCC linked to HBV
- Where prevalence and incidence data is lacking

Global Burden of Liver Disease Model*

BMC Medicine 2014;12:145-158 and 159-65

- Global estimates of 1 million cirrhosis deaths in 2010:
  - For 39/187 (31%) countries there was no data
  - For another 39% estimated deaths were likely substantially underreported
- An additional 1 million deaths estimated due to hepatocellular carcinoma and acute hepatitis

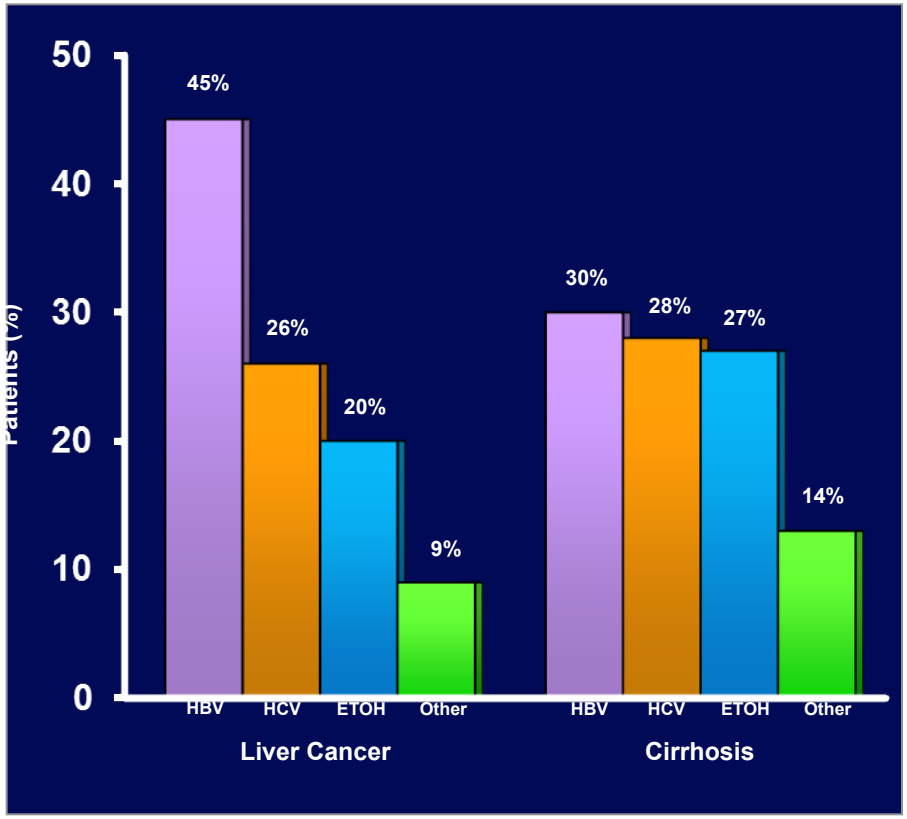
*Collaboration coordinated by the Institute of Health Metrics and Evaluation, University of Washington, Seattle

Epidemiology of HBV and HCC: Major Gaps

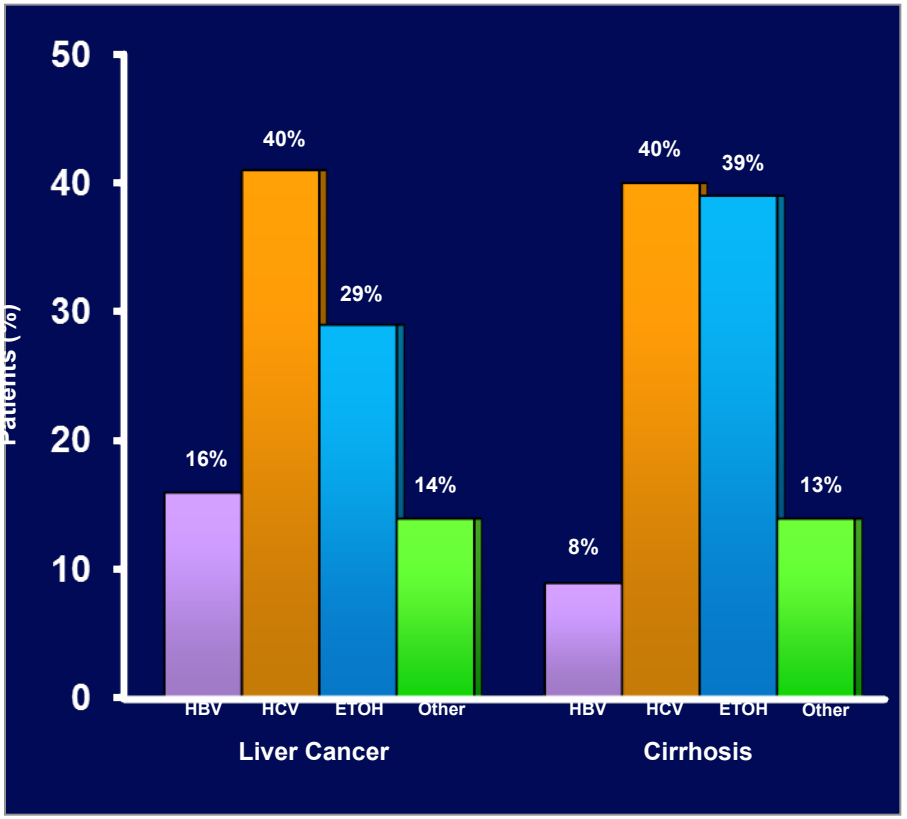
- WHO estimates HCC is 3rd leading cause of cancer death in world: http://www.iarc.fr/en/media-centre/pr/2014/pdfs/pr224_E.pdf
- There are major gaps on prevalence and incidence of HBV and HCC especially in sub-Sahara Africa
  - For example data from the Global Burden of Disease Project, using available published data, found the annual incidence of HCC in East Africa was similar to incidence in US
    - Whereas incidence for China was more than four times higher

Global Burden of Disease Study 2010: Causes of Death From Chronic Liver Disease

Global 2010



USA 2010



Antivir Ther. 2013;18(8):953-4. doi: 10.3851/IMP2654. Epub 2013 Jun 11.

Need for Better Data on HBV and HCC Epidemiology

- Large gaps in prevalence and incidence of chronic HBV as well as HBV associated cirrhosis and HCC
- More accurate data is need to assists both WHO and Country Health Departments set prioritizes for HBV programs

Chronic HBV in USA

- Prevalence of HBV is high in immigrants born in endemic regions of the world
- How much screening of these high risk persons in US is unknown
- Both providers and persons born in endemic countries need to be aware of the importance of one time screening

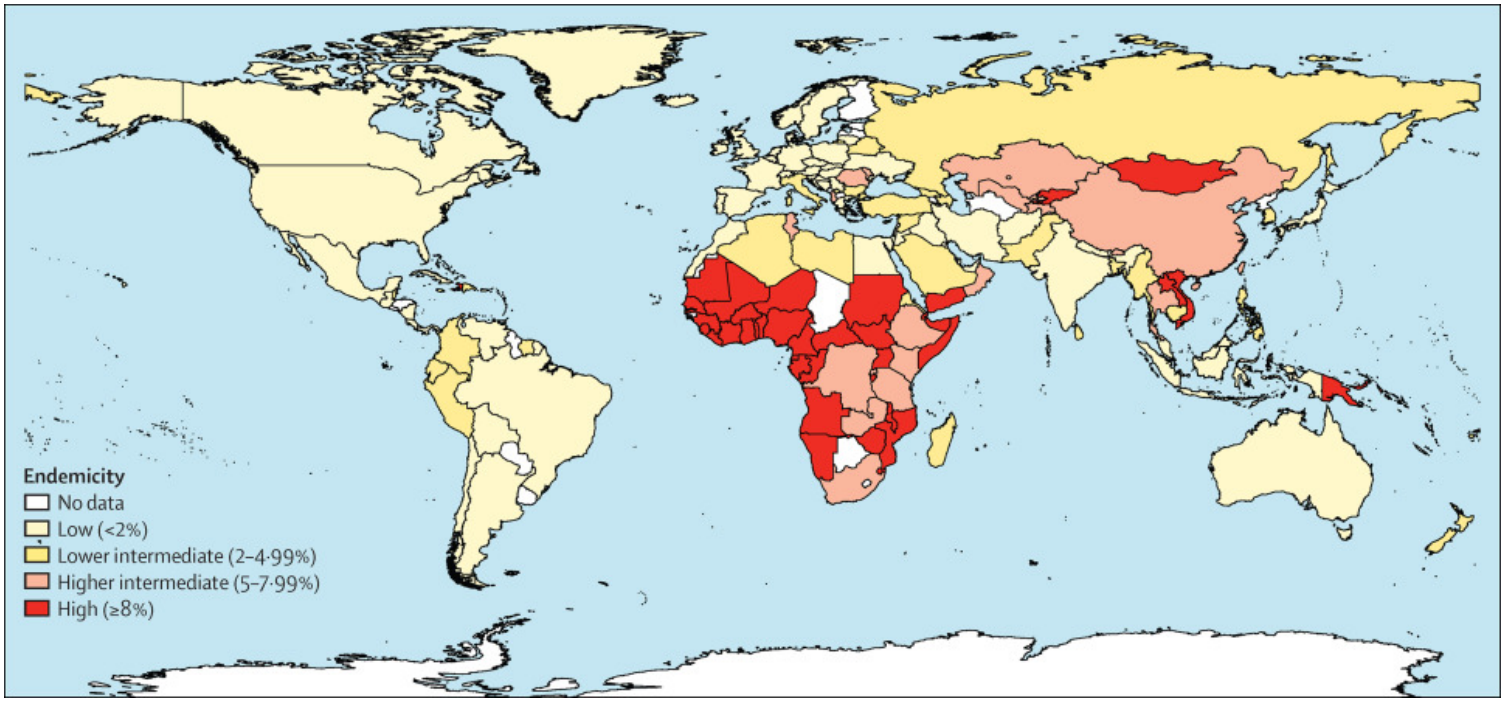


Figure 2. Global HBsAg endemicity (1957–2013)

Aparna Schweitzer, Johannes Horn, Rafael T Mikolajczyk, Gérard Krause, Jördis J Ott

Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013

null, Volume 386, Issue 10003, 2015, 1546–1555

http://dx.doi.org/10.1016/S0140-6736(15)61412-X

Persons with Chronic HBV and Linkage to Care

- Most patients with chronic HBV are not linked to providers who know how to care for them
  - The proportion who are is largely unknown
- The Hepatitis B Foundation Algorithm for screening, diagnosis and management of chronic HBV for primary care providers
- AASLD has updated guideline for the management of chronic HBV at aasld.org/ practice guidelines/hepatitis B

Challenges for Identifying Persons with Chronic HBV

- Screening strategies
- In HIC, screening is usually recommended in persons born in endemic areas with prevalence of HBsAg > 2%
  - How well are these recommendations working?
  - Almost all LMIC have HBsAg prevalence >2%: Screening the entire populations is impractical

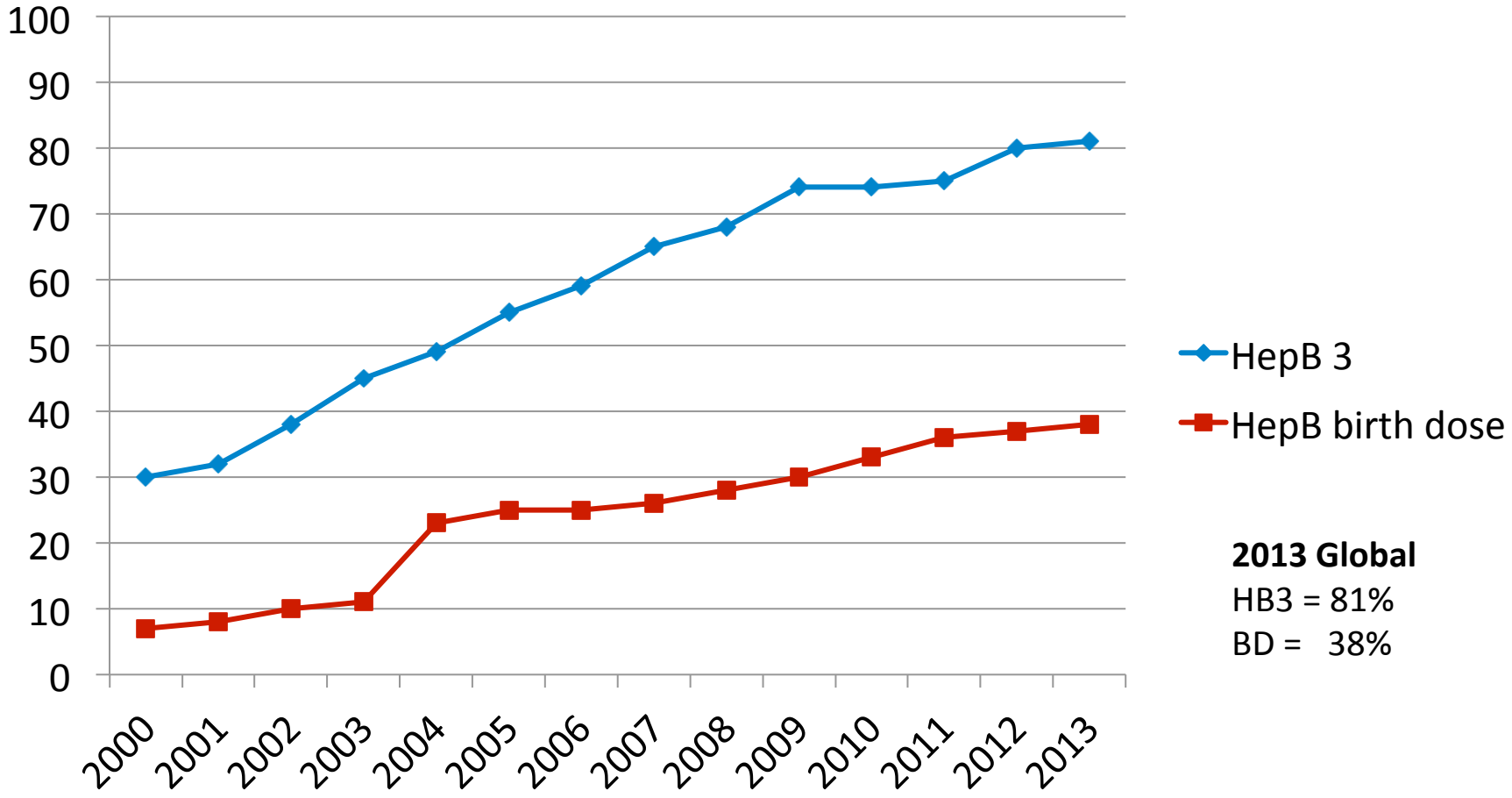
Challenges for Identifying Persons with Chronic HBV in LMIC

- Where is screening currently being done?
  - Blood donors in blood banks and hospitals funded by Global HIV Program
- Where could screening be expanded
  - Household and sexual contacts of HBsAg+ persons identified by current screening
  - Piggybacked onto screening programs for HIV (including HCV)
  - Healthcare workers coupled with vaccination programs
  - Patients with liver disease or abnormal LFT

Global Programs for Vaccination Against HBV

- Global Alliance for Vaccination Initiative (GAVI) provides HBV vaccine in combination vaccine preparations
- Birth dose is not a part of GAVI
  - Thus omission of birth dose in infants of HBsAg positive women will not work in those who are also HBeAg-positive or have high viral levels of HBV DNA.
  - Two obstacles to overcome
    - Most LIC/MIC are currently not paying for birth dose
    - Many babies are not born in hospital

Where are we now?
Global HepB3 & BD coverage, 2000-2013



Source: WHO/UNICEF coverage estimates 2013 revision. July 2014
Immunization Vaccines and Biologicals, (IVB), World Health Organization.
194 WHO Member States.

Barriers to Birth Dose

- In some countries a large proportion of births do not take place in a hospital
- GAVI will not provide birth dose of HBV vaccine requiring country to pick this up
  - GAVI only supplies HBV vaccine in combination with other childhood vaccines
  - Some countries feel they can't afford cost of birth dose
  - It may be that GAVI not supplying birth dose has negative impact on countries implementing it

Birth Dose of HBV Vaccine

- Examples of countries doing well
  - US, Singapore, Taiwan (reduction in the prevalence of HBsAg in Children has been reduces to <1%.
- Examples of countries where birth dose is not routine
  - Most countries in sub-Saharan Africa, many regions of Asia
- Reduction of HBsAg in children not receiving birth dose
  - In countries where 50% of pregnant women are HBeAg-positive (e.g. Korea, Vietnam, China or wherever else genotype C predominates)
    - 50% reduction (e.g. 10% to 5%)
  - In countries where 15% to 30% of women are HBeAg-positive (e.g. Africa or where genotypes A and D predominate
    - 70%-90% (e.g. 10% to 1-3%)

Impact of HBV Vaccination

- For Goal to eradicate chronic HBV in children: 3 components are required
  - Universal administration of HBV vaccine starting at birth (not at 2-4 months with DPT)
  - HBIG if possible at birth for infants of HBeAg+ mothers
  - Antiviral therapy in 3rd trimester (TDF or other) in infants of HBeAg+ mothers with high viral load

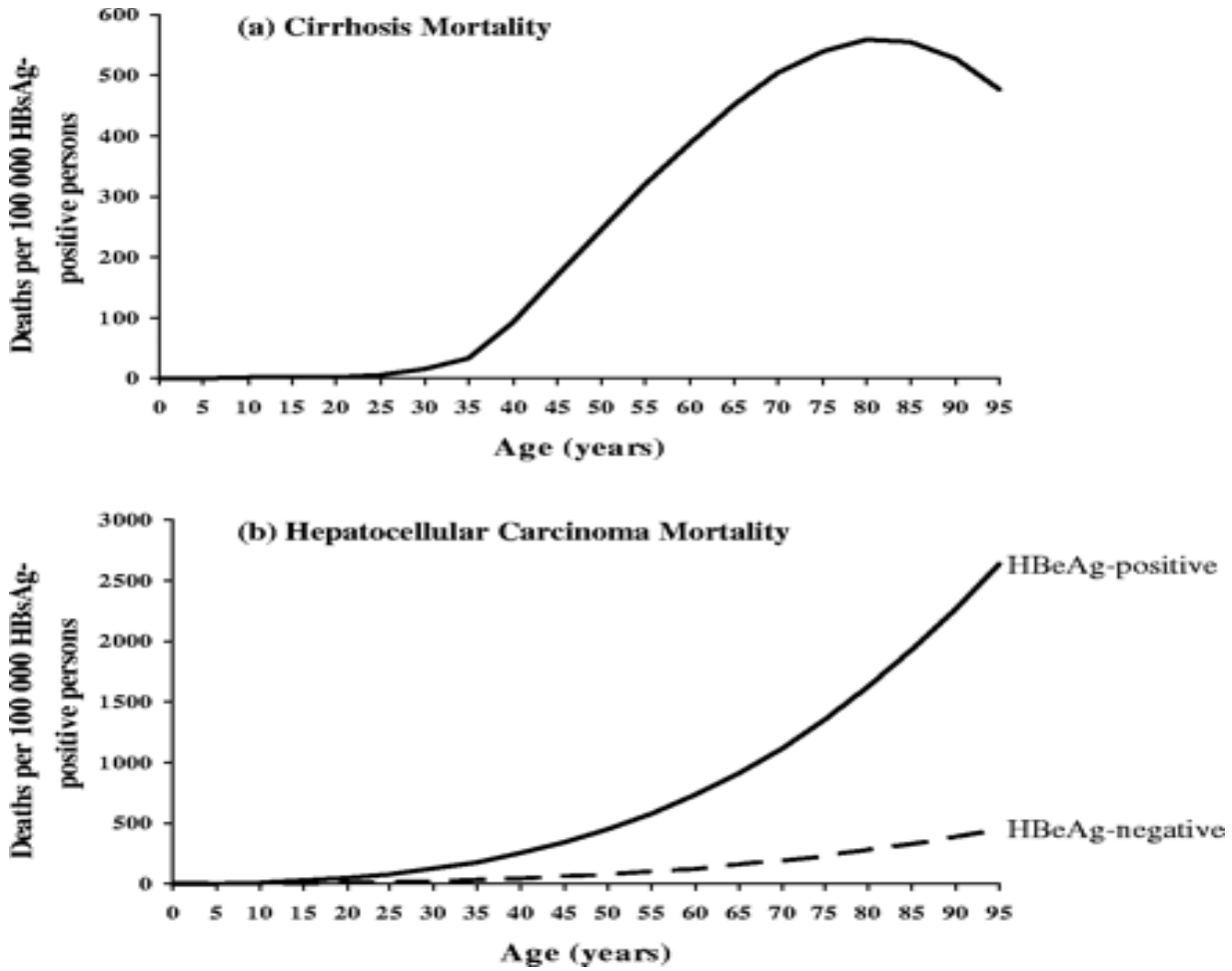
Long-term Protection from HBV Vaccination

- Evidence of long-term protection from vaccination
  - Studies from Alaska have found that evidence of humeral immunity in persons vaccinated >6 months of age last for at least 30 years
  - For those vaccinated as newborns, duration of protection lasts at least 18 years
    - Duration only needed 1st 5 years of life to have greatest impact on reduction of chronic HBV
  - Need for more serosurveys from MIC/LIC countries in children 5-years post infant vaccination

Impact of Reduction of Prevalence of HBV in Children on the Incidence of HCC

- 3-4 decade lag time in overall reduction of HCC incidence in countries once successful vaccination programs in newborns have been introduced

Mathematical Model: Age-specific hepatitis B-related cirrhosis and HCC mortality



Goldstein Int J Epidemiol 2005;34;1329-39

WHO HBV Guidelines: General Background

- Guidelines were developed by a panel of experts from all regions of the world
- The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Framework was followed. PICO questions were chosen
- A systemic review of the literature and meta-analysis was performed by two established Methodology groups
- The quality of evidence was ranked as high, moderate, low or very low for each recommendation:
- The Committee then gave their recommendation as strong or conditional

WHO Guidelines for Treatment of Chronic HBV in LMIC

- WHO Guidelines for Management of Chronic HBV were unveiled at APASL 2015 meeting: http://www.who.int/hiv/events/hepB-guidelines-APASL/en/
- In general, two recommendations for treatment candidates; both assume liver biopsy are unavailable
  - Areas where HBV DNA testing is not established
    - Persons with clinical evidence of cirrhosis
    - Persons with evidence of cirrhosis by non invasive tests
  - Areas where HBV DNA testing is available
    - In addition to above, persons >30 years with persistently elevated ALT and HBV DNA>20,000 IU/ml
  - WHO will recommend only tenofovir or entecavir be used for antiviral treatment (though Peg-IFN is an alternate)

WHO Hepatitis B Guidelines

- Recommendation for Non-Invasive Assessment of Liver Disease Stage at Baseline and during Follow-up:
  - Use of non-invasive tests (NIT) was recommended including APRI >2, Fibrotest or other commercial tests, FibroScan to identify persons with advanced fibrosis
    - Sensitivity 40%-50%, Specificity 80%-90% for APRI and serologic tests
    - Sensitivity 80-90%, Specificity 80%-90% for transient elastography

What is Needed to Implement WHO Guidelines

- For recommendation on non-invasive assessment:
  - Only platelet count and AST are need to calculate APRI
  - Since sensitivity for cirrhosis for APRI is low, inexpensive and serologic markers with better sensitivity are needed (commercial markers are not that much better)
  - Inexpensive equipment for transient elastography (e.g. FibroScan)

Persons with HBV/HIV co-infection

- All HIV patients should be screened for HBV
- HIV/HBV co-infection: All persons should be treated with TDF based therapy

Which Drugs to Choose for Treatment

- Only tenofovir (TDF) and entecavir (ETC) should be used in previously untreated patients
- Persons on other antiviral medications if antiviral resistance is suspected or found should be switched to 1st line drugs

When to Stop Treatment

- Treatment should lifelong in those with cirrhosis
- Discontinuation of antiviral therapy maybe considered in persons with APRI < 2
  - After an additional one year of antiviral therapy in persons with HBeAg seroconversion
    - Plus normalization of ALT and undetected HBV DNA in HBV DNA testing is available
  - If HBV DNA testing not available, loss of HBsAg after additional 1-year of therapy
  - Treatment in persons with APRI >2 should be lifelong

Monitoring

- Annually: ALT, AST platelets, APRI HBsAg, HBeAg and HBV DNA levels as appropriate plus evaluation for clinical evidence of cirrhosis
- On drug therapy for toxicity: All of above plus baseline and yearly renal function

Who to Screen for HCC

- Surveillance for HCC: US
  - Implemented only in regions where surgical or ablative therapy is available
  - Persons with cirrhosis,
  - Family history of HCC
  - Persons over 40 years depending on regional incidence of HCC
  - Not effective for children <20 with the exception of those infected with HBV genotype F
    - Gounder et al. J of Pediatrics under review

Prevention

- Vaccination: Birth dose followed by full vaccination
- Antiviral therapy in pregnancy: no recommendation
- HIV pregnancy and breastfeeding
  - TDF + lamivudine or emtricitabine + efavirenz in 1st trimester and continue if breast feeding

What is Needed to Threat Persons Recommended by Guidelines

- Where HBV DNA levels are not available, only those with evidence of cirrhosis would qualify but persons with persistently elevated ALT levels could be considered
  - Inexpensive platforms and reagents for HBV DNA testing are needed to be developed and introduced
  - Training of laboratory persons to perform serology and HBV DNA testing and providers to care for HBV infected persons are crucial

What is Needed for Antiviral Therapy for HBV

- Cost of ETC and TDF need to be reasonable as treatment duration is long
- Appropriate training of providers on following Guideline to know which patients meet criteria, when to start, when to stop and how to monitor
- Ultimately, better antiviral drugs are needed that target multiple sites in viral replication and have potential for short term duration of treatment and at least functional cure of HBV

What is Needed to Implement the HCC Recommendations

- Diagnostic Criteria for HCC in LIC and MIC where CT and MRI not available
- Expertise for ablative therapy with alcohol injection
  - Inexpensive radiofrequency ablation equipment and expertise
- Surgical expertise to resect small tumors

Implementation Considerations for National Programs

- Key Principals
  - Considering national response to HBV care within broader health contexts
    - Most countries are now developing National hepatitis B and C programs
  - Ensuring human rights, ethical principles of fairness, equity and urgency
  - Defining program needs
  - Financial resources and political support

Key Considerations to Support Country Planning

- Infrastructure
  - Leadership and advocacy
  - Human Resources: Training of HCW and specialists
  - Laboratory and radiology capabilities
    - HBV serologies, HBV DNA, US, CT, MRI
  - Drug supply
  - Cost: Who pays for all of this?
  - Monitoring and evaluation
  - Implementation plan

Other Considerations in the Implementation of WHO Guidelines in LMIC

- Training programs and materials for providers
- Developing the widespread capacity for HBV DNA testing as well as reliable serology tests
  - Needed inexpensive platforms and reagents
- Establishing clinics of excellence to manage patients with HBV infection
- Instituting programs for HCC surveillance in areas where facilities able to treat early tumors with resection or local ablation are available.

Conclusions

- Better data on epidemiology of HBV related cirrhosis and HCC are needed to help plan programs for care
  - In much of Africa and many other countries
- Better Birth dose coverage of vaccine is needed
- WHO Practice Guidelines for HBV are now published and provide impetus to planning management of HBV in MIC and LIC
- Innovation strategies to develop programs to follow WHO Guidelines in LMIC are needed


Thank you