

# Viral Hepatitis Prevention Board

## **Prevention and control of perinatal transmission of hepatitis B and C**

**VIENNA, AUSTRIA**

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# Objectives

- To provide an overview of the current epidemiology of mother-to-child transmission of hepatitis B and C
- to discuss the impact of perinatal transmission on the achievement of the goals for elimination of viral hepatitis
- to review the scientific evidence for the prevention and control of perinatal HBV transmission through birth dose active vaccination and treatment with HBIg and other means and for improving the prevention and control of perinatal HBV transmission through maternal antiviral treatment
- to examine the scientific evidence on perinatal transmission of HCV
- to examine the coverage, impact verification and scientific relevance of birth dose vaccination
- to identify challenges and objectives for improving prevention of perinatal transmission of HBV and HCV and securing success in attaining the goals for elimination by 2030
- to present examples of prevention, discuss lessons learned and identify opportunities

# Rationale and context

- Global and regional strategies aim to eliminate viral hepatitis as a public health threat by 2030; prevention of mother to child transmission of hepatitis B and C virus is an integral intervention in achieving that goal
- Despite progress, core measures need further work, especially in areas of universal HBV vaccination of all babies and babies at risk (including birth dose), diagnosis, infection control, treatment and harm reduction; broad regional and national differences in rates of disease prevalence and HBeAg positivity, and many cases of chronic HB not detected or reported
- Number of children still being born with HBV despite measures such as active vaccination and administration of HBIG (where available); overall, mother-to-child transmission accounts for more than 30% of chronic HBV infections globally
- Factors associated with transmission include mothers' HBeAg positivity and high viral load: 90% of infants born to HBeAg<sup>+</sup> mothers and 5-20% of those born to HBsAg<sup>+</sup>/HBeAg<sup>-</sup> mothers become infected
- Overall 5% of children born to chronically HCV-infected mothers are infected, with high rates of chronicity but mostly mild liver injury during childhood; rates of 20-25% of spontaneous viral clearance seen; some extrahepatic manifestations and non-organ specific autoantibodies seen. Estimates indicate about 13 million children (1-15 years) infected with HCV worldwide

# Rationale and context (continued)

- When HBV or HCV infection is detected, there is often poor linkage and referral to care systems with poor reporting and recording systems
- Concern exist about high prevalence rates of hepatitis B in Africa and Asia; although perinatal transmission of HBV is less frequent in Africa than Asia it is responsible for two thirds of HBV-related liver disease in Africa, where mother-to-child transmission of HBV is a neglected problem
- Concern also generally about high prevalence rates in groups at risk such as people who inject drugs: three-fold increase in acute HCV infection over past decade after years of decrease and increasing number of children exposed to or being born with HCV (e.g. in USA: 1700 infected children a year) – increase in new infections is real and not just due to better ascertainment. Also demographic changes, with waves of movement within Europe and of immigration into Europe
- Low rates in Latin America may offer an opportunity for further prevention (including triple prevention – of HIV, hepatitis B and syphilis and also Chagas disease)
- Current antiviral treatment for chronic hepatitis B is based on suppression of HBV-DNA but is not curative; in contrast, treatment with the new direct acting antiviral agents (DAAs) for HCV is apparently curative
- The advent of safe and effective DAAs to cure HCV infections has radically changed thinking about prevention and control of hepatitis C in adults, although safety in children and pregnant women is not yet established and cost remains an issue

# Strategies

## **General considerations for strategies to prevent mother-to-child transmission of viral hepatitis**

- Policies for prevention and control for perinatal HBV transmission exist in some countries but are not always put into practice, leading to dissonance. Policies are needed to guide prevention of perinatal HCV
- Actions are within health system strategic approach and will need monitoring and verification

## **For hepatitis B**

- Existing measures (not always implemented) comprise:
  - timely administration of birth dose HBV vaccine
  - antenatal HBV screening of pregnant women with linkage to care and follow up of infants (if affordable and feasible)
  - Timely administration of HBIG (within hours of birth to babies born to HBsAg/HBeAg-positive mothers and no later than 24 h post-partum) to reduce incidence (if affordable and feasible)
  - antiviral treatment of HBsAg-positive pregnant women with a high viral load (i.e. with tenofovir) (if affordable and feasible)
- All the above measures may be presented as a pyramid in which the base consists of universal active immunization against HBV and regardless of HBsAg /HBeAg/HBV-DNA status of the individual pregnant woman

# Strategies for chronic hepatitis B

## **Hepatitis B (continued)**

- Timely administration of HB birth dose and a full course of vaccination form the centrepieces of prevention of HBV infection in young children and infants
- Use of antivirals (alone or in combination) may soon be considered increasingly in women with high viral loads, but currently are only suppressive and not curative
- In some areas, HBV antivirals might be more readily available than HBIg; studies are needed to determine if antivirals can be used to augment the effects of hepatitis B vaccination for babies born to HBsAg+ mothers

## **Universal hepatitis B vaccination**

- It is essential to ensure the completion of at least three scheduled doses as part of routine immunization programmes
- More than 180 countries in the world report having policies in place, but questions exist about the reliability of data and the efficiency of some programmes. There are serious concerns about coverage rates and the reach of vaccination programmes, with reports of considerable percentages of people being missed by vaccination, especially among immigrants, in various European countries

# Strategies for chronic hepatitis B(cont'd)

## **Timely administration of birth dose of HBV vaccine**

- Current recommendations indicate administration of the birth dose within 12 or 24 hours of birth, but more aggressive policies are in place in some countries, e.g. within 6 hours or even 1 hour of birth
- Early administration (within 6 h) may also reduce occult HBV infection (not readily detectable through routine HBsAg and anti-HBs testing)
- The coverage of the birth dose of vaccine is only 38% globally; it is not well implemented in Africa and not universally practised in Europe. There are issues of feasibility, for instance in Africa where only some 50% of births may take place in health facilities but nearly 80% of pregnant women attend an antenatal clinic at least once (thus generating an opportunity to raise awareness). A new community-based intervention is being launched in three African countries to improve coverage of timely birth dose
- Knowledge of health care workers and parents about the role of timely birth dose administration of vaccine is often limited, and communication between health care teams should be enhanced
- Ensure that post-vaccination serological testing for HBsAg and anti-HBs (and for anti-HBc and HBsAg when required) is done at an appropriate age (for instance, 9-12 months)

# Strategies for chronic hepatitis B (cont'd)

## **Antenatal screening of pregnant women**

- Policies for maternal HBV screening vary by country (e.g. Denmark where pregnant women have been screened for HBV since 2005)
- In most countries screening and preventive measures for HBV were reported to be cost-effective (testing for HBsAg followed by HBV DNA is more cost-effective than HBsAg followed by HBeAg and then HBV DNA, but HBV DNA testing needs to be available, of high quality and affordable)
- Continuing debate and different views about whether universal or risk factor-based screening for HBV is best and most cost-effective; many risk factors are not disclosed or remain unknown, and previous use of lists of risk groups/behaviours (e.g. in HIV/AIDS) failed
- Questions about when in pregnancy to test (e.g. first trimester and then retest), diagnosis and diagnostics (PCR detecting more low-level infections), availability of rapid and point-of-care tests, and about improving collection of data for immigrants with information about country of origin
- Reference was made to criteria for screening (see outcomes of previous VHPB meetings on screening, e.g. chronic hepatitis (Budapest 2010) – available at [www.vhpb.org/meetings](http://www.vhpb.org/meetings))

# Strategies for chronic hepatitis B (cont'd)

## **Administration of HBIg**

- Early studies from Taiwan suggested that administration of HBIg in combination with timely active vaccination is effective; concerns about emergence of envelope protein mutant viruses in HBIg recipients do not seem to have materialized
- Divergent policies and views about recommendation for the administration of HBIg, however, including considerations of availability, cost, and limited added value in newborns to HBsAg-positive/HBeAg-negative mothers; HBIg is no longer used and available only in limited quantities or not available at all in some countries
- Role of HBIg is controversial, especially as it has biological functions
- Concern about emergence of envelope protein mutant viruses in HBIg recipients
- Measure is not practical in Africa owing to cost and limited supply

# Strategies for chronic hepatitis B (cont'd)

## Antiviral treatment during pregnancy

- Cited data for tenofovir, a nucleoside analogue antiviral, refer to tenofovir disoproxil fumarate but that affects renal function and lowers bone density; tenofovir alafenamide fumarate is a prodrug that is less toxic but it has not been tested on HBV-infected women post-partum
- The safety of treatment with tenofovir has been repeatedly confirmed in HIV-infected pregnant women and their newborns
- Critical review of literature provides only a qualified affirmative response to the question of whether HBV-positive pregnant women should be treated
- High-quality evidence for effectiveness of nucleos(t)ide analogues in prevention of mother-to-child transmission of HBV is limited to two randomized controlled clinical trials conducted in China and Taiwan; most data relate to genotype C
- Guidelines exist for clinical management and treatment of chronic hepatitis B - EASL, AASLD and WHO; AASLD and EASL recommend use of antivirals in all pregnant women with viral loads greater than 200,000 IU/ml and WHO concluded that the indications for their treatment were the same as for adults, but a critical review of literature provides only a qualified affirmative response to the question of whether HBV-positive pregnant women should be treated: high quality evidence is limited and most data relate to genotype C

# Strategies for chronic hepatitis C

## **Antenatal screening of pregnant women**

- Advent of new safe and effective DAAs might represent an additional justification for screening for HCV infection markers
- Policies for maternal HCV screening vary by country (e.g. recommended in the USA)
- Continuing debate and different views about whether universal or risk factor-based screening for HCV is best and most cost-effective; many risk factors are not disclosed or remain unknown, and previous use of lists of risk groups/behaviours (e.g. in HIV/AIDS) failed
- Discussion of where to focus resources, e.g. whether to screen PWIDs and prisoners as well as pregnant women for HCV infection; more cases are likely to be found in the first two groups
- Reference was made to criteria for screening, in particular for HCV infections (see outcomes of previous VHPB meetings on screening (on chronic hepatitis generally (Budapest 2010) and on HCV (Split 2013) – available at [www.vhpb.org/meetings](http://www.vhpb.org/meetings))

# Strategies for chronic hepatitis C (cont'd)

## **Antiviral treatment**

- Guidelines exist for clinical management and treatment of chronic hepatitis C (EASL and WHO), recommending use of antivirals (DAAs), but a critical review of literature showed that high-quality supporting evidence for treatment of pregnant women and infected children is limited
- Nevertheless, uncertainties surround treatment of HCV-positive pregnant women, such as when to start, and optimal regimens for treatment of children
- For treatment of HCV in pregnant women and HCV-infected children issues include unknown safety, although limited data are now available for 6-11 year olds with no evidence of adverse effects
- Use of antivirals (alone or in combination) may soon be considered for use in women with high HCV viral loads

# Virology, genotypes and transmission

- Correlation between high maternal HBV load and risk of infection of neonate; maternal viral load is considered the most relevant risk factor for mother-to-child transmission of HCV
- Possible association of between infected peripheral blood monocytes and vertical transmission of both HBV and HCV was described
- It is not yet known whether occult HBV infection represents a risk factor in mother-to-child transmission of HBV
- Different hepatitis B disease and transmission patterns are possibly due to variety of HBV genotypes
- Maternal risk factors for HCV transmission include invasive obstetric practices and prolonged rupture of the membranes, but neither Caesarian section nor breastfeeding increase risk of transmission
- Data suggest that HCV infection increases risk of comorbid conditions during pregnancy

# Policy development

- WHO developing an incremental approach for prevention of mother-to-child transmission building on progress and experience in regional frameworks, including for triple elimination; revised position paper on hepatitis B vaccines in draft form for publication in July 2017
- WHO European Region: considerable regional progress being made in implementing policies and action plans towards hepatitis B elimination targets, but still gaps and weaknesses in data (including only 8 countries routinely collecting data on screening pregnant women for HBsAg)
- CDC: several ongoing HBV programmes, active response to recent increases in hepatitis B and hepatitis C in PWID, and ACIP statement on hepatitis B vaccine being revised; a national strategy for hepatitis B and hepatitis C elimination was recently released and a recent summit of stakeholders committed to the elimination of hepatitis B and C in the USA was recently convened
- ECDC: incomplete data on chronic hepatitis B and C in pregnancy, especially HBV, and reporting biases; great variations in antenatal screening of pregnant women for HBsAg and reporting in EU/EEA; need for better information to produce standardized advice on preventing mother-to-child transmission
- EASL: issuing revised clinical practice guidelines on prevention of transmission of HBV and HCV, which cover screening of pregnant women, administration of HBIG and vaccine, antiviral therapy
- A critical review of the literature underlined the importance of credible evidence for decisions about care of patients, immunoprophylaxis (and response to failures) and antiviral therapy; discussion highlighted the need to take medicolegal considerations of guidelines and recommendations, the status of which differs between countries. Once sufficient evidence is available, countries should formulate or approve new guidelines that are adapted to local conditions

# Needs

- Better epidemiological and programmatic data especially HBV and HCV prevalence rates in pregnant women and children, with better analyses as well as verification of data (e.g. coverage rates); better access to and use of data, including innovative approaches using new concepts and techniques to access and use data such as data mining and big-data IT/AI applications
- Improved communication between databases and other sources of information (e.g. diagnostic laboratories, cancer registries, birth registries and other demographic databases)
- Refine epidemiological models of hepatitis B to take account of different genotypes (e.g. GT1)
- Agreed standard case definition for perinatal infection (US Council of State and Territorial Epidemiologists' decision due imminently), with criteria for laboratory diagnosis and epidemiological data
- Recommendations for screening pregnant women for HCV infection, in particular in high prevalence areas/regions: the discussion should be started (involving high-level decision-makers)
- Development of rapid and point-of-care tests as well as affordable tests for HB and HC viral load
- Long-term follow up of both HBV-positive as well as HCV-infected children for consequences of infection/natural history
- Evaluation and/or confirmation of effectiveness and most importantly of safety of the new tenofovir derivative (tenofovir alafenamide) in pregnant women and children, which reportedly has a superior safety profile (renal toxicity and bone density) in adults as compared to tenofovir disoproxil fumarate currently used for reduction of viral load in pregnant women in some countries

# Needs (continued)

- Better document effectiveness of antiviral treatment of HBV in pregnant women
- HCV treatment: define age for optimum treatment with DAAs of children with HCV infection; obtain approval for use of antivirals in pregnant women; development and implementation of policies should follow quickly thereafter
- Monitoring and evaluation – how to incentivize countries to evaluate implementation of existing policies and adherence to guidelines?
- Raise awareness of and knowledge about HBV and HCV transmission and infection and health consequences – among pregnant women and health care providers; general practitioners and nurses have a large role in diagnosis, referral and prevention but are largely unprepared; obstetricians and gynaecologists and paediatricians also need to be closely involved
- Health system strengthening is vital not only in general but also for making progress towards viral hepatitis elimination targets set out in global and regional health sector strategies for viral hepatitis
- Provision of materials and interpreters in appropriate languages (including for migrants from endemic regions)

# The way forward

- Continue to work to raise and sustain political commitment at national and regional levels (including the European Commission)
- Urge countries to evaluate existing programmes and policies for HBV and HCV, for instance through seroepidemiological surveys
- Carefully review the results of holistic and integrated approaches, for instance by building on the agreement in three WHO regions to work towards triple elimination of hepatitis B, HIV and syphilis (quadruple in the Americas with inclusion of Chagas disease) and a focus on incremental introduction of antenatal screening of pregnant women for HBsAg, timely birth dose of vaccine and other measures such as administration of HBIg and antivirals; promote antenatal screening of pregnant women and work towards integration with screening programmes for HIV and syphilis
- Integrate screening for HBC and HCV into other existing screening programmes in antenatal care
- Recommend obtaining more robust evidence for treatment of HBsAg positive mothers

# The way forward (continued)

- Recommend that WHO should include a consistent statement regarding its position on screening of pregnant women for HBsAg in its position paper which is currently being revised, with references to the need to consider degree of endemicity, and to clarify its position with regard to screening for HCV in pregnant women
- Benefits of universal screening of pregnant women for HCV infection appear to outweigh the risks, but for many countries conditions (cost-effectiveness, availability of DAAs and human resources) need to be fulfilled before it can be introduced
- Continue educating, informing and engaging health care professionals, especially obstetricians, gynaecologists and family physicians, paediatricians and nurses
- Involve patients and families in awareness campaigns and families in counselling;
- Consider policies on who can prescribe antiviral treatments for HBV and HCV
  
- The clear message to emerge is that the **timely administration of the birth dose of hepatitis B vaccine does prevent mother-to-child transmission of hepatitis B virus** and VHPB expects WHO to issue clear guidance on the importance of timeliness and how to achieve it