Introduction of Perinatal Transmission of Hepatitis B

Viral Hepatitis Prevention Board Meeting

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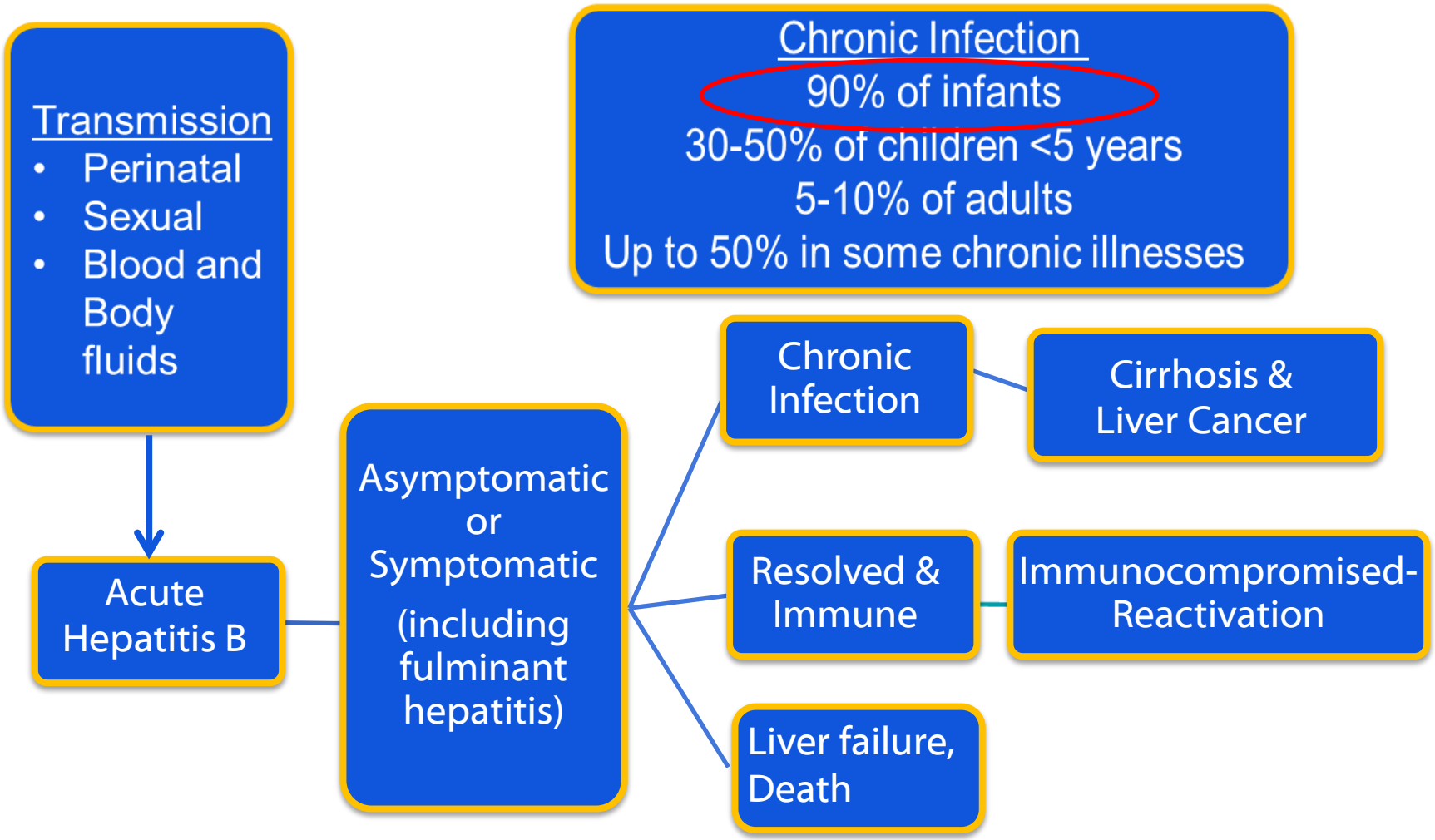
Perinatal Transmission - Epidemiology

- Global:
  - In 2015, WHO estimates that 257 million people are chronically infected with HBV, and 887,00 people died from complications of HBV-related liver
    - Of the 257 million people infected, 9% (22 million) knew their diagnosis; treatment coverage was only 8% (1.7 million)
    - Mother-to-child transmission (MTCT) is responsible for more than one third of chronic HBV infections worldwide
- United States:
  - In the United States, 850,000–2.2 million persons are estimated to be living with HBV infection
  - Approximately 25 000 infants are born annually to hepatitis B infected pregnant women

WHO. Hepatitis B. Available at: http://www.who.int/mediacentre/factsheets/fs204/en/. Accessed May 31, 2017.
Roberts H, et al. Prevalence of chronic hepatitis B virus (HBV) infection in U.S. households: NHANES, 1988-2002. Hepatology 2016; 63(2):388-97.
Kowdley KV, et al. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. Hepatology 2012;56(2):422-33.

Natural History of Hepatitis B Virus (HBV) Infection



Mother-to-child Transmission

- Approximately 90% of infants of HBsAg-positive/ HBeAg positive women and 5%–20% of infants of HBsAg-positive/ HBeAg-negative women become infected without intervention

- The most important risk factor for MTCT is the maternal HBV DNA level

- Most MTCT infant PEP failures occur at thresholds of maternal HBV DNA levels of 10^6 to 10^8 copies/mL

Nelson NP, Jamieson DJ, Murphy TV. Prevention of Perinatal Hepatitis B Virus Transmission. J Pediatric Infect Dis Soc. 2014 Sep;3(Suppl 1):S7-S12.

Nelson NP, Easterbrook PJ, McMahon BJ. Epidemiology of Hepatitis B Virus Infection and Impact of Vaccination on Disease. Clin Liver Dis. 2016 Nov;20(4):607-628.

Pre-embryonic and Assisted Reproductive Therapy

- HBV has been detected in sperm, oocytes, and embryos
- Limited data suggest HBV transmission can occur in germline cells
- The risk of HBV transmission from persons with chronic HBV during assisted reproductive therapy is unknown; transmission possible
- Storage of cryopreserved sperm and embryos in the nitrogen vapor state, sperm washing, and double-sealing cryocontainers are suggested methods for reducing the possible risk of transmission

Prenatal

- The rate of intrauterine transmission is unknown but considered to be low
- The presence of maternal HBeAg (associated with higher HBV DNA levels) associated with prenatal transmission
  - HBeAg, only structural HBV protein that can pass through the placenta
- Transmission via amniocentesis has been reported at high HBV DNA levels
  - Not generally considered a risk factor

Intrapartum

- MTCT during delivery is most common
  - Exposure occurs through micro-transfusion or hematologic leaks of mother's blood to the fetus during contractions, or through inoculation of mucosal membranes or breaks in the skin (e.g., scalp electrodes)
  - Most studies find no difference in MTCT among babies delivered by operative/spontaneous vaginal delivery or caesarean section when the infants receive PEP
  - Caesarian section is not recommended for reducing MTCT in the US

Breastfeeding

- Markers of HBV are detectable in breast milk and colostrum from HBsAg-positive women
- Reported rates of HBV-infection among breastfed and non-breastfed infants are similar, although some studies did not account for maternal HBV DNA levels
  - Considerations: cracked or bleeding nipples

Strategies for Prevention

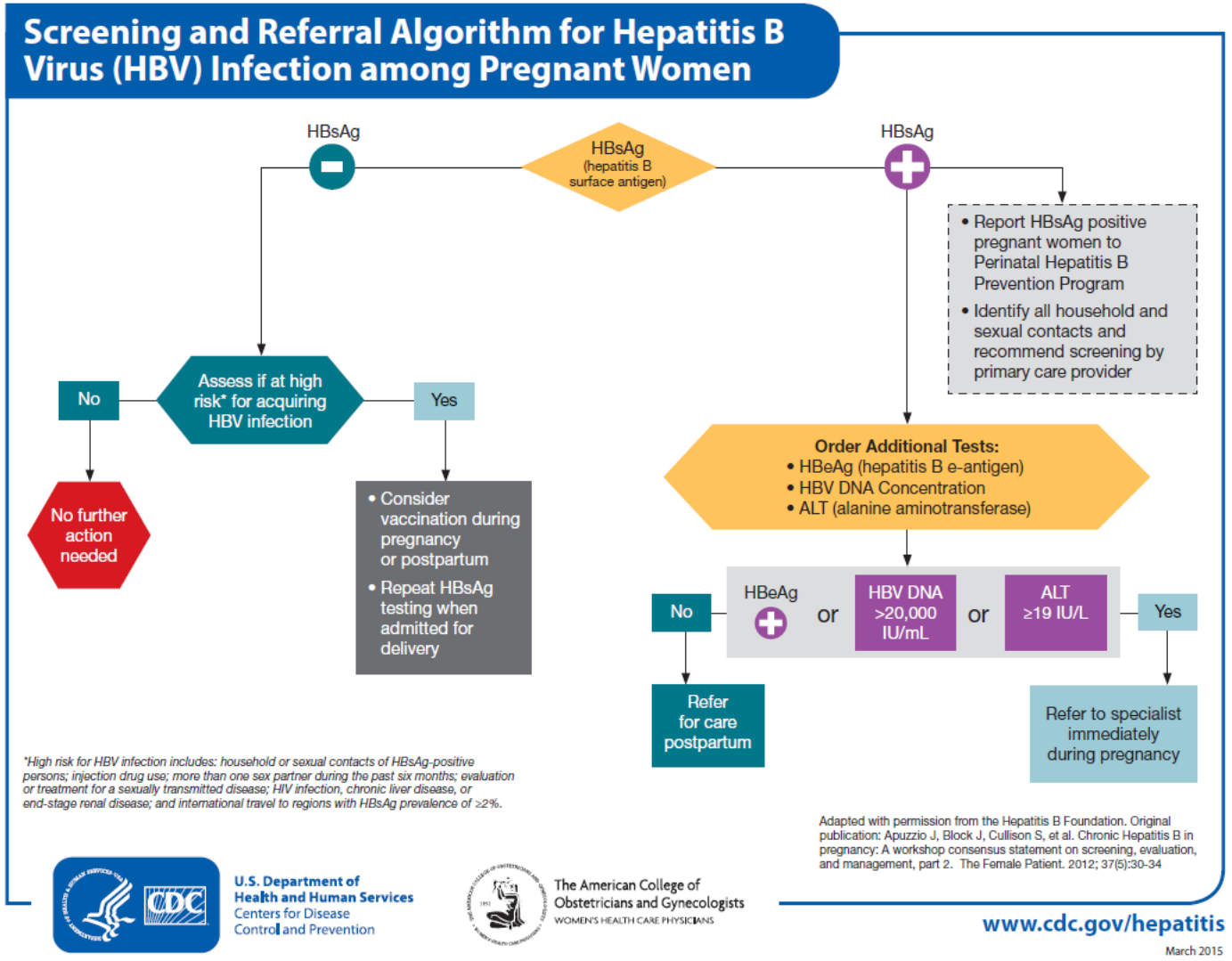
- Maternal screening
- Hepatitis B (HepB) vaccination at birth (with passive immunoprophylaxis [HBIG]) and completion of HepB vaccine series
- Use of antivirals for high risk HBV-infected pregnant women

Maternal Screening

- Advisory Committee on Immunization Practices (ACIP) recommends screening pregnant women (including women previously vaccinated or previously tested) for HBsAg during the first prenatal visit of each pregnancy
- Retest mother at or prior to delivery if HBsAg-negative earlier in pregnancy but presents for delivery with a risk factor identified
  - >1 sex partner in previous 6 months
  - Evaluation or treatment for STD
  - Injection drug use
  - HBsAg-positive sex partner
  - Diagnosed with clinical hepatitis since last test

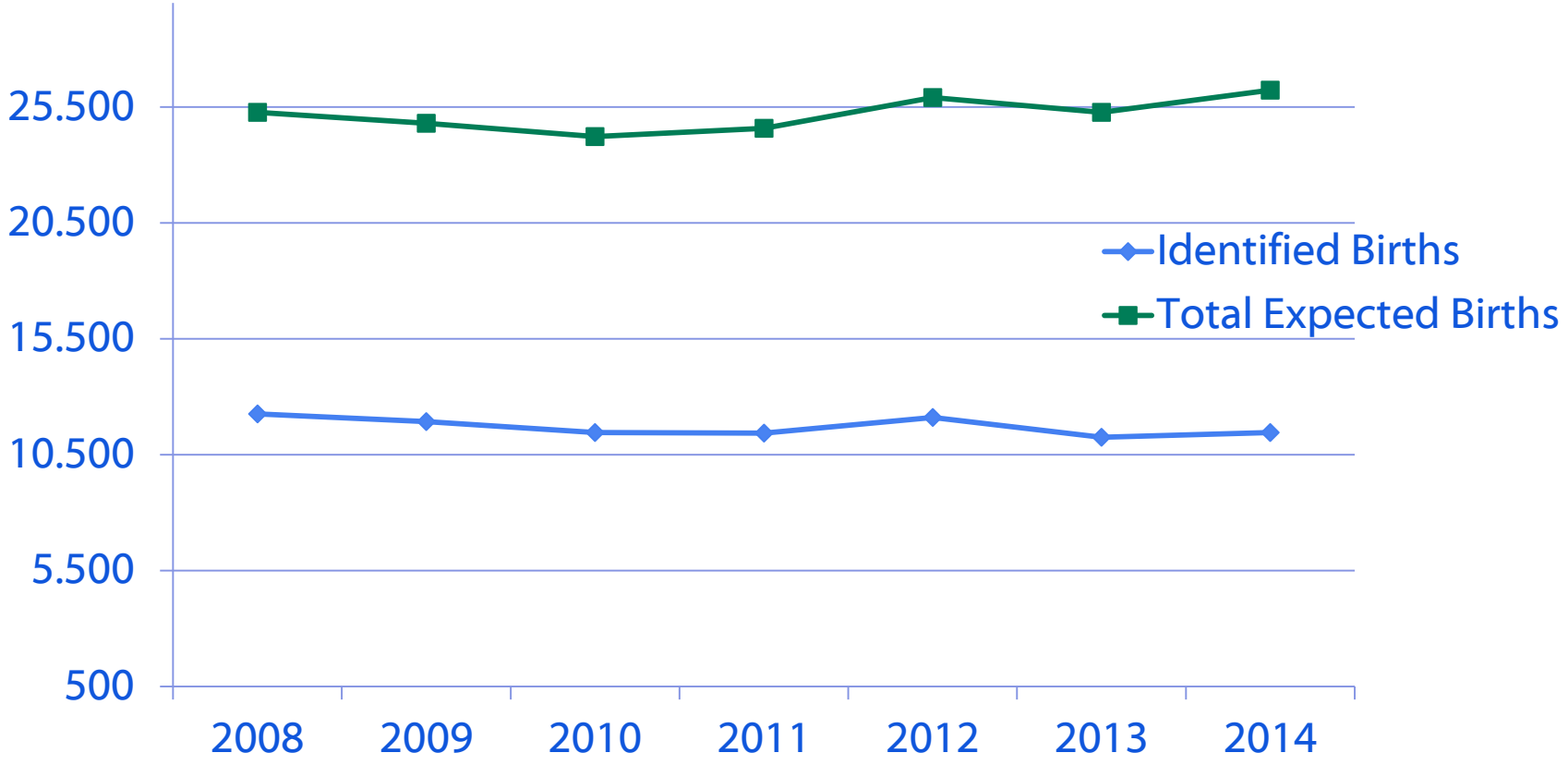
Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep 2005;54:1–31.

Pregnant Women Screening Algorithm



Identified U.S. births to Total Expected Births 2008-2014

- 2008-2014 Expected Birth Tables, DVH/NCHHSTP



2008-2014 Expected Birth Tables, DVH/NCHHSTP

Post-exposure Prophylaxis (PEP)

- Prevention of MTCT by PEP, consisting of administering HBIG and a monovalent HepB vaccine within 12 hours of birth, followed by completion of the vaccine series, has 85%-95% efficacy
- HBIG (passive immunoprophylaxis) provides a short-term increase (i.e., 3-4 months) in anti-HBs which might improve protection until the infant responds to vaccine
- WHO recommends HBIG as an adjunct to HepB vaccine starting within 24 hours of birth, although the added benefit of HBIG is less clear among term infants of HBsAg-positive, HBeAg-negative women
  - Worldwide, administration of HBIG might not be feasible, because of supply, safety, or cost issues
- PEP success relies on timely completion of a 3-dose HepB vaccine series

Universal Birth Dose

- Global: WHO recommends the use of monovalent HBV vaccination within 24 hours of birth, regardless of HBsAg status of the mother, followed by completion of the HBV vaccine series within 6 to 12 months as the most cost-effective strategy for the prevention and control of hepatitis B

- United States: ACIP recommends birth dose within 12 hours for infants born to HBsAg positive mothers
    - 24 hours for all infants born to HBsAg-negative mothers (ACIP approved)

Birth Dose – Safety Net

- The birth dose provides a “safety net” for
  - Infants of HBsAg-positive women not identified for post-exposure prophylaxis (PEP) because of:
    - Medical errors in interpreting or documenting maternal screening results
    - Failure to test women at delivery who are admitted without prenatal HBsAg test results
  - Infants who have contact with a HBsAg-positive caretaker or household member
  - Infants at risk for exposure after the perinatal period

Mast, E.E., et al., MMWR, 2005. 54(RR-16): 1-32
Willis, B.C., et al., Gaps in hospital policies and practices to prevent perinatal transmission of hepatitis B virus. Pediatrics, 2010. 125(4): p. 704-11.

HBIG and Hepatitis B Vaccine Efficacy

- For prevention of MTCT of hepatitis B virus the efficacy* of
  - HBIG and HepB vaccine combined is ~94%
  - HBIG alone is ~71%
  - Hepatitis B vaccine alone is ~75%

*Based on infants of mothers HBsAg-postive and HBeAg-positive

- MTCT occurs in 5%–15% of infants despite timely prophylaxis

Beasley RP, Hwang LY, Lee GC, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet. Nov 12 1983;2(8359):1099-1102.

Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. BMJ. Feb 11 2006;332(7537):328-336.

Hepatitis B Vaccine Coverage

- Global
  - In 2015, Birth dose coverage of hepatitis B vaccine, 39%
  - Three dose coverage of hepatitis B vaccine, 84%

- United States
  - In 2015, Birth dose coverage of hepatitis B vaccine, 72.4%
  - Three dose coverage of hepatitis B vaccine, 92.6%

Treatment During Pregnancy and Delivery

- The AASLD suggests antiviral therapy to reduce the risk of perinatal transmission of hepatitis B in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL
  - Quality/Certainty of Evidence: Low
  - Strength of Recommendation: Conditional

Terrault NA, et al.. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016 Jan;63(1):261-83.

Clinical Trials

- Pan et al. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load
  - Enrolled 200 women with HBV DNA level >200,000 IU/mL
  - Non-breastfed infants received HBIg at birth and at week 4, and vaccine at birth, week 4 and week 24

- Jourdain et al. TDF To Prevent Perinatal Hepatitis B Virus Transmission: A Randomized Trial (iTAP)
  - Placebo-controlled, double-blind
  - Infants received hepatitis B vaccine (10 ug) at birth, 1, 2, 4 and 6 months, HBIg at birth

Pan CQ, Duan Z, Dai E, et al. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. N Engl J Med 2016;374(24):2324–34.

TDF Trial Conclusions (Pan et al.)

- At delivery, 68% of the mothers in the TDF group (66 of 97 women), as compared with 2% in the control group (2 of 100) had an HBV DNA level <200,000 IU/ml (P<0.001).
- At postpartum week 28, the rate of MTCT was significantly lower in the TDF group than in the control group
  - intention-to-treat analysis (transmission 5% of infants [5 of 97] vs. 18% [18 of 100], P = 0.007)
  - per-protocol analysis (transmission 0 vs. 7% [6 of 88], P = 0.01)
- The maternal and infant safety profiles were similar in the TDF group and the control group

Pan CQ, Duan Z, Dai E, et al. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. N Engl J Med 2016;374(24):2324–34.

TDF Trial Conclusions (iTAP)

- 331 women (168 TDF, 163 placebo) enrolled
  - HBV DNA load at enrollment: 8.0 log10 IU/mL (7.1, 8.5)
  - HBV DNA load at delivery: 3.9 log10 IU/mL (3.0, 4.8) on TDF, versus 7.8 log10 IU/mL (6.8, 8.5) on placebo
- 322 (97%) on-study deliveries (85 Cesarean, 26%)
- 323 live births
  - 320 (99%) infants received HBIg a median of 1.3 hours after birth
  - 322 (>99%) HB vaccine a median of 1.2 hours after birth
- In the primary complete case analysis at 6 months, 0/147 infants had HBV infection in the TDF arm versus 3/147 (2.0%) in the placebo arm (p=0.12)
- All 3 infected infants' mothers had HBV DNA >7.8 log10 IU/mL at delivery

http://www.croiconference.org/sites/default/files/posters-2017/584LB_Jourdain.pdf; Jourdain G, et al. BMC Infect Dis. 2016 Aug 9;16:393.

Elimination

- Perinatal transmission might be controlled or eliminated in regions with a combined strategy of:
  - Maternal screening,
  - Maternal antiviral treatment and
  - Infant post-exposure prophylaxis

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