Strategies for the elimination of mother-to-child transmission (MTCT) of hepatitis B virus

Moving from Hepatitis Discovery to Elimination
A webinar series by NIH and the Coalition for Global Hepatitis Elimination (CGHE)
6th Webinar: “Protecting Moms and Infants from Hepatitis B and C“
October 14, 2021

Gonzague Jourdain, MD, PhD
French National Research Institute for Sustainable Development, France (IRD)
Chiang Mai University, Thailand (CMU)
Disclosures

• Sanofi equities
• Gilead Science grant: organization of a symposium at Chiang Mai University, Thailand (2019)
• Gilead Science provided study drugs for a clinical trial (2013-2017)
Contents

• Background and context of our research
• Evolution of research questions and guidelines
• iTAP-1
• iTAP-2
• Sub-studies
• Unanswered questions
Some Facts

• **Perinatal acquisition** of hepatitis B virus (HBV) remains the main source of chronic HBV infection worldwide.

• **No cure for HBV infection in 2021**

• **Infants born to HBV chronic carrier mothers are exposed to HB viruses in utero, intra partum and during early life**

• **Main risk factor:** high maternal HBV viral load. HBeAg is a marker of high replication. HBeAg transmitted to the fetus may increase infant tolerance to HBV.

• **Mutants** may “escape” from vaccine and HBIG, explaining some transmissions (**escape mutants**).
MTCT of HBV in the 2010’s

- HBV Epidemic in Southeast Asia and in Western Pacific
  - Prevalence in pregnant women
  - Viral loads
  - HBeAg
  - Persisting MTCT of HBV
- Vaccine birth dose
- In case of high maternal viral load, infant HBIG + vaccine prevent most MTCT but not all
- Future of HB immune globulin?
- Use of antiviral inspired by the success of PMTCT of HIV

- Uncertainties about safety of discontinuing antivirals
- No antiviral approved by FDA for PMTCT
- Several clinical studies with significant methodological issues
- Unclear recommendations by the associations for the study of the liver and no WHO recommendations
- Cohorts of HIV infected pregnant on TDF
- Best antiviral in this setting?
- Timing (when to start, when to stop)
- Breastfeeding?
CTU established in Chiang Mai

Data Management

Quality Management Systems

Inhouse Information Technology Tools

Network of ~40 Clinical Sites in Thailand & Lao PDR

Onsite Monitoring

Management of Study Drugs

Laboratories

Admin, Finance, and Support
iTAP Studies

Efficacy?
Maternal safety?
Standardize, Simplify
Base for PMTCT without HBIg?

Diagnosis of HBV & Risk of MTCT

Maternal Antiviral
28 weeks GA to 2 months PP

Infant Immunization
0-6 months
**Mother**

**Antepartum**

- GA 28 Wks.
- 3rd Trimester
- Placebo
- Tenofovir DF

**Placebo**

**Delivery**

- Placebo
- Tenofovir DF

**Postpartum**

- 2 months
- Follow-up until 12 months postpartum

---

**Infant**

**Birth to 12 months**

**Target sample size:** 328 women with HBeAg+ and normal ALT and their infants (17 sites in Thailand)

**Primary endpoint:** HBV infection status at 6 months of age (HBsAg positive, confirmed by HBV DNA)

**HBV vaccine at birth, 1, 2, 4 and 6 months* plus HBIg at birth**

**Follow-up**

* following Thai national guidelines
Tenofovir vs. Placebo to Prevent Perinatal Transmission of Hepatitis B

PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PARALLEL-GROUP TRIAL IN THAILAND

331 HBeAg-positive pregnant women
Baby received HBV vaccine and HBIG at birth

Tenofovir

- 300 mg
- From 28 wk of gestation to 2 mo post partum

Placebo

Infant’s HBsAg positivity at 6 mo

- Tenofovir: 0% (P = 0.12)
- Placebo: 2% (P = 24%)

Maternal hepatic flares

- Tenofovir: 6% (P = 0.29)
- Placebo: 3%

Infant adverse events

- Tenofovir: 27% (P = 0.61)
- Placebo: 24%

The NEW ENGLAND JOURNAL of MEDICINE
Jourdain et al. 2018
Two TDF trials with No Infant Infections

Pan's Study
- No intervention: 7%
- TDF: 0%
- Placebo: 2%

iTAP-1 Study
- TDF: 0%

6 of 88 vs. 0 of 92
3 of 147 vs. 0 of 147

TDF 6-Month Efficacy

Pan, NEJM, 2016
Jourdain, NEJM, 2018
Deliveries and Pregnancy Outcomes

- 319 singleton live births, 2 live-born twin pairs (TDF) and 1 stillbirth (TDF)
- 85 Cesarean deliveries:
  - TDF: 38, 23%
  - Placebo: 47, 29%
- Median gestational age at delivery: 38.9 weeks
- Preterm newborns: 21 (7%) (8 TDF, 13 placebo)
- Median birth weight:
  - TDF: 3028 g
  - Placebo: 3061 g
  No significant differences between arms
- Median HBV DNA load at delivery:
  - TDF: $3.9 \log_{10} \text{IU/mL}$
  - Placebo: $7.8 \log_{10} \text{IU/mL}$

Safety

Time to Maternal First Grade 3/4 Event or SAE

![Graph showing time to maternal first grade 3/4 event or SAE](image)

Time to First Maternal ALT >300 U/L from Study Treatment Discontinuation to 12 Months postpartum

![Graph showing time to first maternal ALT >300 U/L](image)

- TDF: 9/155 women (5.8%)
- Placebo: 6/157 women (3.8%)

Fisher's exact p-value: 0.44

All Maternal ALT Elevations (from enrollment to 12-month postpartum visit)

- No ALT elevations were symptomatic and no women restarted double-blind treatment based on protocol specifications.
- One woman (placebo arm) started antiviral treatment more than 6 months after delivery.
Bone Mineral Density (BMD)

**Design of Parent Study (NCT01745822)**

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mothers</strong></td>
<td>71</td>
<td>69</td>
<td>140</td>
</tr>
<tr>
<td><strong>Infants</strong></td>
<td>70</td>
<td>67</td>
<td>137</td>
</tr>
</tbody>
</table>

Hologic Discovery A DXA machine
Software Version: 4.0.2

Salvadori N et al, CID 2019
Is it possible to omit immune globulin if maternal TDF prophylaxis?

iTAP-2 clinical trial
Primary Objective

To demonstrate that

Risk of MTCT if Maternal TDF + Infant Vaccine

<

Minimal Risk observed with Vaccine + HBIG (2%)

in infants born to HBeAg positive mothers who take an antiviral from 28 weeks gestation to 2 months postpartum
Specifically:

To demonstrate that the risk of HBV infection at 6 months of age is lower than 2% in infants who
- receive active immunization but no HBIG,
- are born to HBeAg positive mothers with satisfactory virological response on tenofovir disoproxil fumarate (TDF) 300 mg per day from 28 weeks gestation to 2 months postpartum.
Tenofovir-DF 300mg OD

HBsAg +  HBeAg +

Birth

28w 32w 36w

M1 M2  M4  M6  M9  M12  M18

Immunization

Single arm clinical trial
Study population

• **499 pregnant women/infants**
• 15 sites in Thailand and 9 sites in Lao PDR

• **Inclusion criteria**
  • Pregnant women aged ≥18 years,
  • Positive for HBsAg and HBeAg,
  • Negative for HIV antibodies

• **Exclusion criteria**
  • Contraindication to TDF
If no significant decrease in DNA level and still > 200,000 IU/mL:
- Reinforce adherence
- Consider HB Ig at birth
Infant’s close contacts

If someone else than the mother is to be in close contact with the infant, and if this person is HBV infected there may be a risk of HBV transmission

• To prevent risk of horizontal transmission, all close contacts will be proposed before the birth of the infant:
  ▪ Counseling about routes of HBV transmission
  ▪ Blood sample for HBsAg test

• If a relative is diagnosed with HBV infection, referral to a gastroenterologist for further follow up and evaluations.
Progress

- 504 pregnant women enrolled
- 496 deliveries in the study
- 502 infants born in the study (6 pairs of twins)
- Collection of infant 6-month endpoints expected by the end of 2021
- Primary analysis results expected beginning of Q2-2022

- Moderate impact of the COVID-19 pandemic on participants’ follow up
Revision of WHO Guidelines in 2019

- Epidemiological and modelling studies suggest that infant vaccination alone would be insufficient to reach the 0.1% HBsAg prevalence goal in children by 2030.

- The Group acknowledged that most clinical trials had also included the use of HBIG in both arms. However, it was concluded that the efficacy of antiviral prophylaxis could reasonably be extrapolated to settings in which HBIG is not available.

- The Group noted that trials are under way to provide an evidence base for the efficacy of tenofovir to prevent mother-to-child transmission among women whose infants did not receive HBIG.
PMTCT of HBV, Priorities and Context

- HBV genotypes (replication)
- HBeAg prevalence in pregnant women
- Immunization schedule (birth dose)

Prevalence of HBsAg in children under 5 years

Global: 1.3%, African Region: 3%, South-East Asia and Western Pacific Regions: 0.5%-0.6%

LSHTM WHO 2017 Hepatitis Global Report
Need for Further Research

• Monitoring adherence to TDF during pregnancy
• Predictors of ALT flares
• Antiviral in infants?
• Place of TAF and new drugs for PMTCT?
• Monoclonal antibodies in the future?
Acknowledgements

Women and infants in the studies
Collaborators, in particular Nicole Ngo-Giang-Huong
Site investigators
CTU Team

Sponsors
iTAP-1: NICHD + CDC (U01HD071889)
BMD & EKIM: NICHD
R03HD096131
iTAP-2: NICHD (R01HD09527)