Tenofovir exposure during pregnancy and postpartum in hepatitis B mono-infected women on TDF monotherapy compared to HIV-infected women on TDF-containing antiretroviral therapy

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for the iTAP Study Team & PANNA network

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Hepatitis B Virus (HBV)

- Major cause of hepatocellular carcinoma (HCC). While treatment prevents liver cirrhosis and cancer there remains no cure.
- Mother-to-child transmission (MTCT) of hepatitis B virus (HBV) accounts for the majority of cases of chronic HBV infection. Chronic HBV infection develops in 65 to 90% of infected infants.
- Universal HBV immunization at birth has reduced the prevalence of infection. Additional use of hepatitis B immune globulin (HBIG) at birth further reduces the risk of transmission.

However, mother-to-child transmission still occurs in infants born to women with a high HBV viral load (＞200,000 IU/mL) or with HBeAg.

Antiviral prophylaxis is increasingly used for HBV mono-infected pregnant women with high HBV DNA to prevent MTCT.

# Tenofovir versus Placebo to Prevent Perinatal Transmission of Hepatitis B

## Phase 3, Multicenter, Randomized, Double-Blind, Parallel-Group Trial in Thailand

### Study Details
- **331** HBeAg-positive pregnant women
- Baby received HBV vaccine and HBlg at birth

### Results

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant’s HBsAg positivity at 6 mo</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Maternal hepatic flares</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Infant adverse events</td>
<td>27%</td>
<td>24%</td>
</tr>
</tbody>
</table>

- **Tenofovir**: 300 mg from 28 wk of gestation to 2 mo post partum
- **Placebo**: 0 mg

### P-values
- Infant’s HBsAg positivity at 6 mo: **P = 0.12**
- Maternal hepatic flares: **P = 0.29**
- Infant adverse events: **P = 0.61**

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TDF PK during Pregnancy/Postpartum

- Tenofovir disoproxil fumarate (TDF) is recommended as part of combination antiretroviral therapy (cART) to prevent MTCT of HIV

- **Absorption**
  - e.g. Gastric pH
  - Gastric emptying

- **Total body Water/Fat**

- **Plasma Proteins**

- **Drug Metabolism**
  - e.g. CYP450 activity

- **Drug Elimination**
  - e.g. GFR

*Tenofovir (TFV) exposure is reduced by about 20% during pregnancy in HIV-infected women on ART*[^1^,^2^]

*Impact of pregnancy on TFV without concomitant ARVs is unknown*

[^1^]: Colbers AP. AIDS 2013 Mar 13;27(5):739-48;
Objectives

• To assess the impact of pregnancy on the pharmacokinetics of TFV in HBV-mono-infected women

• To compare TFV exposure during pregnancy/postpartum in women receiving TDF monotherapy versus TDF with and without ritonavir boosted protease inhibitors as part of ART
Methods

• Data were combined from two clinical trials

(1) iTAP Study [ClinicalTrials.gov NCT01745822]

Mother
Active Study Arm

GA 28 Wks
3rd Trimester
2 months-PP

Tenofovir DF
Delivery
Tenofovir DF

Sparse Blood samples collected at each visit for PK analysis

TFV conc. determined using a validated LC-MS/MS assay [LLOQ 0.02 mg/L]

Data analyzed using Population PK Modeling (NONMEM VII)
Methods

- Data were combined from two clinical trials

(2) **panna Study** [ClinicalTrials.gov NCT00825929]

- PK Study of HIV-infected pregnant women, multiple **ARVs** under study

![Diagram showing drug level and sampling times](image)

[Intensive blood samples: pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24h after dosing]
Results
iTAP: TFV Population PK Model

- 166 women included: 594 tenofovir plasma concentrations

<table>
<thead>
<tr>
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<th>Pregnancy</th>
<th>Postpartum</th>
</tr>
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<tbody>
<tr>
<td>Age (Years)</td>
<td>26 (18-42)</td>
<td>-</td>
</tr>
<tr>
<td>Gestational Age (weeks)</td>
<td>35.9 (30.7-42.1)</td>
<td>-</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64 (44-108)</td>
<td>56 (39-99)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.57 (0.3-1.1)</td>
<td>0.74 (0.4-1.2)</td>
</tr>
<tr>
<td><strong>Creatinine Clearance</strong> (mL/min)</td>
<td><strong>155 (86-303)</strong></td>
<td><strong>105 (53-330)</strong></td>
</tr>
</tbody>
</table>

- 2-Compartment model (Ka fixed\(^1\)) + prop. error; TFV CL/F was influenced by CrCL
  - TFV CL/F, Vc/F, Q and Vp/F: **71.4 L/hr, 415 L, 183 L/hr, and 1130 L**, respectively.

iTAP study: TFV Exposure Pregnancy/Postpartum

<table>
<thead>
<tr>
<th>PK Parameters</th>
<th>3rd Trimester Pregnancy (3T)</th>
<th>Postpartum (PP)</th>
<th>P-value (3T vs. PP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-24}$ (mg/hr/L)</td>
<td>1.83 (1.65-2.09)</td>
<td>2.28 (2.05-2.77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>C$_{24}$ (mg/L)</td>
<td>0.040 (0.034-0.048)</td>
<td>0.056 (0.048-0.068)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Median (interquartile range)*

• In HBV-monoinfected women receiving TDF-monotherapy, TFV AUC$_{0-24}$ was 20% lower during pregnancy compared to postpartum
Demographics: iTAP versus PANNA

<table>
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<tr>
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<th>PANNA Study</th>
</tr>
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*Median (IQR); *Cockcroft-Gault formula: $\frac{(140-\text{age})(\text{weight kg})}{(72 \times \text{Scr})}$ in mL/min

**PANNA study: Concomitant ARVs [n (%)]**

| RTV-bPI regimen: | ATV/r 11 (42%); DRV/r 10 (38%); LPV/r 2 (8%); SQV/r 2 (8%); FPV/r 1 (4%) |
| NNRTI/INSTI regimen: | NVP 4 (50%); EFV 2 (25%); RAL 2 (25%) |
iTAP study: TFV Exposure Pregnancy/Postpartum

AUC 20%
- TDF alone (iTAP) pregnancy
- TDF alone (iTAP) postpartum

AUC 16%
- TDF + bPI pregnancy
- TDF + bPI postpartum

AUC 36%
- TDF + NNRTI/INSTI pregnancy
- TDF + NNRTI/INSTI postpartum
Comparison of TFV Exposure without and with concomitant ARVs

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<th>AUC (mg*hr/L) 3rd Trimester</th>
<th>PK Parameters</th>
<th>AUC (mg*hr/L) Postpartum</th>
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</thead>
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<tr>
<td>TDF Alone</td>
<td>1.83 (1.65-2.09)</td>
<td>TDF Alone</td>
<td>2.28 (2.05-2.77)</td>
</tr>
<tr>
<td>TDF + NNRTI/INSTI</td>
<td>2.15 (1.94-2.55)</td>
<td>TDF + NNRTI/INSTI</td>
<td>3.36 (2.90-3.46)</td>
</tr>
<tr>
<td>TDF + bPI</td>
<td>2.60 (2.05-2.83)</td>
<td>TDF + bPI</td>
<td>3.10 (2.82-3.63)</td>
</tr>
</tbody>
</table>
Conclusion

• TFV exposure was 20% lower during pregnancy than postpartum in HBV mono-infected women, a similar magnitude historically observed in HIV-infected women

• TFV levels were lower in HBV-infected women on TDF monotherapy vs. HIV-infected women on TDF-based ART

Discussion

• Studies have reported ↑ TFV (~20-35%) with bPIs in HIV-infected adults\textsuperscript{1,2,3}

• Impact of ↓ plasma TFV on PBMC-TFV-DP\textsuperscript{4,5,6,7} --> Hepatocytes?

• TAF approved for HBV Tx\textsuperscript{8}: ↑ TFV-DP delivered to hepatocytes vs. TDF\textsuperscript{9}
  - Use of TAF for PMTCT? Reduced TAF levels?

\textsuperscript{1}Kiser J. CPT 2008; 83:2, 265-272; \textsuperscript{2}Calcagno A. et al. AAC 2013; 57:4, 1840--3; \textsuperscript{3}Kaletra Package Insert 2017; \textsuperscript{4}Lahiri et al. AIDS 2015; 29(9) 1113-15; \textsuperscript{5}Cressey TR et al 2015; CID 2017 15;61(4):633-9; \textsuperscript{6}Pruvost A et al 2009 AAC, 53:5, 1937-43; \textsuperscript{7}Kiser J.JAIDS 2008;47:298–303; \textsuperscript{8}VEMLIDY\textsuperscript{8} Package Insert 2017; Murakami et al 2015 AAC; 59:6
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