Review: Safety of Tenofovir PrEP in Pregnant and Breastfeeding HIV-Uninfected Women and Their Infants

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Several Systematic Reviews Have Evaluated TDF Safety in Pregnant Women with Chronic Hepatitis B (HBV)

- *Brown RS et al. Hepatology 2016;63:319-33*: search to 11/2014 in women with chronic HBV receiving antiviral therapy; 26 studies, only 3 included TDF (141 pt, 1 RCT, 2 observational).
  
  "TDF showed improvement in HBV DNA suppression at delivery; no significant differences in PP hemorrhage, CS or elevated creatinine kinase."

- *WHO Systematic Review for HBV 2015 Guidelines (Appendix)*: search to 2/2014 on most effective antiviral therapy during 3rd trimester to reduce HBV MTCT; 35 studies, only 1 included TDF (observational, also included in Brown):
  
  "Conclusions should be drawn with extreme caution on the efficacy of TDF as only 1 observational study was identified and the quality of the evidence was low."
"In pregnant women with HBV infection who are candidates for maternal antiviral therapy, we suggest tenofovir as a first-line agent (2B – weak recommendation, moderate quality evidence).

Women who are pregnant or breastfeeding

“Offer tenofovir disoproxil to women with HBV DNA greater than 10^7 IU/mL in the third trimester to reduce the risk of transmission of HBV to the baby…they may continue antiviral treatment while breastfeeding.”

“Telbivudine, lamivudine or tenofovir may be used for prevention of perinatal and in utero HBV transmission in the last trimester of pregnancy in HBsAg-positive women with high levels of viremia (serum HBV DNA >10^6-7 IU/mL)….it may be discontinued within the first 3 months after delivery (C1)…”

“The GDG considered that tenofovir is a drug that is highly potent, and would be permissible for use in pregnancy as in the HIV field…..no evidence suggesting harms associated with breastfeeding during treatment in the mothers.”
Several Systematic Reviews Have Evaluated TDF Safety in Pregnant Women with HIV

- **Wang L et al. CID 2013;57:1773:** search to 8/2013; 16 studies (15 HIV, 1 HBV) but 3 not relevant (eg, TDF gel, no outcomes), 4 with comparative data (other case rpt, PK, sdTDF)
  - “Although information is limited, TDF appears to be safe during pregnancy.”

- **Ehrhardt S et al. CID 2015:60:275-8:** 8 studies (4 in Wang), 2 breast milk.
  - “Exposure to the drug [TDF] is lower from breastfeeding than in utero exposure. Thus the data do not support the contraindication to use in breastfeeding.”

  - “Data on TDF-based ART in pregnancy were reassuring…although data remain limited and few studies addressed maternal toxicity or infant growth and bone effects..”

- **Fonner G. Update on WHO 2015 Review re: TDF and reproductive outcomes:** Updated 4/2015-3/2016 on PrEP and reproductive health outcomes; 2 studies identified on pregnancy outcomes (1 in Nachega).
  - “No differences reported across all outcomes between study arms.”
Current Review TDF in Pregnancy

- Prior 5 reviews represent 23 unique papers.
- Search: Pub Med: tenofovir and pregnancy, tenofovir and breastfeeding, tenofovir and breast milk; reviewed abstracts from prior review papers; CROI 2014-2016 and IAS 2014-2015; Clinicaltrials.gov; Gilead communication.
  - 265 citations; after review 56 relevant papers + 3 reviews identified = 33 comparative studies (23 overlap prior reviews)
  - 27 papers on TDF ART in HIV+ pregnant women
    - 26 comparative, 2 randomized trials
  - 6 PK studies on TDF ART in HIV+ pregnant women
  - 8 studies of single dose (sd)TDF (7 PK)
  - 4 “case reports” in HIV+ pregnant women on TDF ART
  - 7 papers on TDF in HBV+ (HIV-) pregnant women
    - 5 comparative, 1 randomized trial
  - 4 papers on TDF PrEP in women who become pregnant
    - 2 comparative, 2 randomized trials
TDF in Pregnant Women: 33 Comparative Papers Most Providing Data in Inconsistent Ways

- Exclusions from 265 citations:
  - Duplicates, non-English citations
  - General reviews/commentaries
  - Animal and in vitro studies
  - No pregnancy or safety outcomes (or TDF outcomes not separated)
  - Non-oral TDF studies (eg, TDF gel)

- Of 33 comparative TDF papers in primary analysis, pregnancy/infant outcomes were inconsistently reported:

<table>
<thead>
<tr>
<th>Preg incidence</th>
<th>Spont. Abortion/Stillbirth</th>
<th>Preterm</th>
<th>Low Birth Weight</th>
<th>Small for Gestational Age</th>
<th>Birth defects</th>
<th>Neo/Infant death</th>
<th>Infant Growth</th>
<th>Infant Bone/Renal</th>
<th>Maternal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>11</td>
<td>12</td>
<td>8</td>
<td>4</td>
<td>12</td>
<td>8</td>
<td>14</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>
Caveats on Comparative Studies Re: PrEP

- **HIV comparative studies** reflect 3 drugs (vs 1-2 drug PrEP), most started during 2\textsuperscript{nd}/3\textsuperscript{rd} trimester; of \(\sim 20,000\) exposures, 1059 (5\%) specifically state started before pregnancy and additional 4469 (22\%) state 1\textsuperscript{st} trimester exposure. Pregnancy outcomes are worse among HIV+ than HIV-uninfected pregnant women even in ART era.

- **HBV comparative studies** all enrolled HBV+/HIV-uninfected pregnant women with high HBV DNA (\(>10^{6-7}\)).
  - 5 with comparison groups
  - Primarily 3\textsuperscript{rd} trimester initiation of TDF alone:
    - GA at initiation ranged from 18-32 weeks
    - Only 5 of \(\sim 280\) (1.8\%) had TDF received from conception

- **PrEP comparative studies** all enrolled HIV-uninfected non-pregnant women
  - When become pregnant, stop TDF (median 1-2 mo GA)
  - PrEP adherence low, so how much reflects exposure unclear
What Do Pharmacokinetic Studies Demonstrate?
PK TDF ART in Pregnancy

- TFV has lower AUC (↓ by 20-33%) and trough (↓ by 18-37%) levels during pregnancy compared to postpartum or non-pregnant individuals.
- However, it is felt that “standard TDF doses appear to be adequate for most women (dose adjustment may be needed in women with body weight >90 kg).”

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>N</th>
<th>Comparison</th>
<th>AUC</th>
<th>Cmax</th>
<th>Ctrough</th>
<th>CL/F</th>
<th>Vdistrib</th>
<th>T1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benaboud/2011</td>
<td>46</td>
<td>Pop PK on TDM spec; preg/non-preg</td>
<td>33%↓</td>
<td>-</td>
<td>37%↓</td>
<td>39%↑</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Colbers/2013</td>
<td>34</td>
<td>3rd trimester/6-12 wkPP</td>
<td>23%↓</td>
<td>19%↓</td>
<td>21%↓</td>
<td>30%↑</td>
<td>-</td>
<td>30%↑</td>
</tr>
<tr>
<td>Best/2015</td>
<td>37</td>
<td>3rd trimester/6-12 wkPP</td>
<td>20%↓</td>
<td>NS</td>
<td>18%↓</td>
<td>25%↑</td>
<td>60%↑</td>
<td>28%↑</td>
</tr>
</tbody>
</table>
TFV Levels in Amniotic Fluid and Cord Blood

- TFV appears to concentrate in amniotic fluid.
- TFV has excellent transplacental passage and reaches levels in the cord blood near or higher than mother.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>N</th>
<th>TDF dose (mg)</th>
<th>Cord/Maternal Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AMNIOTIC FLUID</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeh/2009</td>
<td>1</td>
<td>ART</td>
<td>158.2</td>
</tr>
<tr>
<td>Mirochnick/2014</td>
<td>24</td>
<td>ART</td>
<td>1.69</td>
</tr>
<tr>
<td><strong>CORD BLOOD</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flynn/2011</td>
<td>13</td>
<td>600 (single dose)</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>900 (single dose)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hirt/2009</td>
<td>32</td>
<td>600 (single dose)</td>
<td>0.71 (0.8, 1.01)</td>
</tr>
<tr>
<td>Mirochnick/2014</td>
<td></td>
<td>600 (single dose)</td>
<td>0.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>900 (single dose)</td>
<td>0.59</td>
</tr>
<tr>
<td>Colbers/2013</td>
<td>14</td>
<td>ART</td>
<td>0.82 (0.64-1.1)</td>
</tr>
<tr>
<td>Yeh/2009</td>
<td>3</td>
<td>ART</td>
<td>6.0 (3.5, 7.2)</td>
</tr>
<tr>
<td>Best/2015</td>
<td>28</td>
<td>ART</td>
<td>0.88 (0.76, 1.03)</td>
</tr>
</tbody>
</table>
TFV Levels in Breast Milk

- TFV has low bioavailability; TDF is water soluble di-ester prodrug of active drug TFV and is rapidly converted TDF to TFV in blood.
- Since TFV is form in blood, would expect minimal penetration into breast milk compartment and to BF infant, which is what seen.

<table>
<thead>
<tr>
<th>Author/yr</th>
<th>N</th>
<th>TDF dose</th>
<th>Breast milk</th>
<th>Infant levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benaboud 2011</td>
<td>5</td>
<td>TDF/FTC (single dose + 7 d PP)</td>
<td><em>TDF</em>: med max 14.1 ng/mL, min 6.8 ng/mL &lt;br&gt; <em>FTC</em>: med max 679 ng/ml, min 177 ng/mL</td>
<td><em>TDF</em>: est. 0.03% infant dose &lt;br&gt; <em>FTC</em>: est. 2% infant dose</td>
</tr>
<tr>
<td>Mirochnick 2014</td>
<td>25</td>
<td>TDF (single dose)</td>
<td>Detectable 3/4 samples at 2d (6.3-17.8 ng/mL) &lt;br&gt; Detectable 1/21 samples at 4-6d (15.7 ng/mL), then BLQ</td>
<td>-</td>
</tr>
<tr>
<td>Palombi 2016</td>
<td>47</td>
<td>TDF ART</td>
<td><em>TDF</em> BM/plasma ratio: 0.07-0.08</td>
<td><em>TDF</em> age 6 mo: med 24 ng/mL 12 mo: BLQ</td>
</tr>
<tr>
<td>Mugwanya 2016</td>
<td>50</td>
<td>TDF/FTC PrEP</td>
<td><em>TDF</em>: med max 3.2 ng/mL (2.3-4.7); BM/plasma ratio: 0.03 &lt;br&gt; <em>FTC</em>: med max 212.5 ng/mL (140-405); BM/plasma: 0.63</td>
<td><em>TDF</em>: 94% BLQ; ~ &lt;0.01% infant dose &lt;br&gt; <em>FTC</em>: 96% detectable, med 13.2 ng/mL; ~ 0.5% infant dose</td>
</tr>
</tbody>
</table>
Comparative Studies of Pregnancy Outcome and Infant Growth
Pregnancy Incidence, HIV-Infected Women on ART and HIV-Uninfected Women on PrEP

- **Maskew 2012 Africa**
  - TDF ART: 4.9
  - Non-TDF ART: 5.2

- **Mugo 2014 Africa Partners PrEP**
  - TDF ART: 11.9
  - Non-TDF ART: 8.8
  - TDF/FTC2: 10.0
  - Placebo: 7.4

- **Bunge 2015 Africa VOICE PrEP**
  - TDF ART: 7.4
  - Non-TDF ART: 8.0
  - TDF/FTC2: 7.9

- **RR 0.95**
  - (0.72-1.24)

- **P=0.22**
- **P=0.39**
Stillbirth, HIV-Infected Women
HIV ART Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>TDF ART</th>
<th>Non-TDF ART</th>
<th>AZT/sdNVP</th>
<th>% Stillbirth</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibb 2012 Africa</td>
<td>8.0%</td>
<td>4.0%</td>
<td></td>
<td></td>
<td>251</td>
</tr>
<tr>
<td>Moodley 2016 Africa</td>
<td>2.2%</td>
<td>4.2%</td>
<td>1.8%</td>
<td></td>
<td>1666</td>
</tr>
<tr>
<td>Fowler 2016 Africa</td>
<td>2.0%</td>
<td>1.0%</td>
<td>2.0%</td>
<td></td>
<td>341</td>
</tr>
</tbody>
</table>

P-values:
- P = 0.19
- P = 0.80
- P = 0.041
- P = 0.79
Stillbirth, HIV ART Studies, by Time ART Starts: ART Start Preconception vs During Pregnancy

- Preconception: 4.9% (TDF ART), 6.4% (Non-TDF ART), N=165, N=2006
- During Pregnancy: 1.7% (TDF ART), 4.9% (Non-TDF ART), N=1054, N=243

P=NS for both categories.
Spontaneous Abortion, Stillbirth, HIV-Uninfected Women

HBV Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Year</th>
<th>0%</th>
<th>5%</th>
<th>10%</th>
<th>15%</th>
<th>20%</th>
<th>25%</th>
<th>30%</th>
<th>35%</th>
<th>40%</th>
<th>45%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celen 2013</td>
<td>Turkey</td>
<td>2013</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>4.2%</td>
<td>0%</td>
</tr>
<tr>
<td>Greenup 2014</td>
<td>Australia</td>
<td>2014</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Chen 2015</td>
<td>Taiwan</td>
<td>2015</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Kochaksaraei 2016</td>
<td>Canada</td>
<td>2016</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Pan 2016</td>
<td>China</td>
<td>2016</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>1.0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

N=21 24 58 52 20 62 56 23 146 97 100
Pregnancy Loss or Stillbirth, HIV-Uninfected Women
PrEP Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Pregnancy Loss</th>
<th>Abortion</th>
<th>Stillbirth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mugo 2014</td>
<td>27.7%</td>
<td>15.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>PartnersPrEP</td>
<td>32.3%</td>
<td>19.0%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Bunge 2015</td>
<td>20.0%</td>
<td>20.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>VOICE</td>
<td>P=NS all</td>
<td>P=NS all</td>
<td>P=NS all</td>
</tr>
</tbody>
</table>

Pregnancy Loss, Abortion, Stillbirth

N=112  N=80  N=96  N=65  N=104  N=100  N=65  N=104  N=100
Preterm <37 Weeks, HIV-Infected Women
HIV ART Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>TDF ART N</th>
<th>Non-TDF ART N</th>
<th>AZT/sdNVP N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibb 2012 Africa</td>
<td>111</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Ransom 2013 US</td>
<td>630</td>
<td>1395</td>
<td></td>
</tr>
<tr>
<td>Fowler 2016 Africa</td>
<td>335</td>
<td>346</td>
<td>341</td>
</tr>
<tr>
<td>PROMISE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moodley 2016 S Africa</td>
<td>1666</td>
<td>907</td>
<td>974</td>
</tr>
</tbody>
</table>

% Preterm <37 week

- Gibb 2012 Africa: 7.2% (TDF) vs. 12.9% (Non-TDF), P=0.69
- Ransom 2013 US: 18.6% (TDF) vs. 16.6% (Non-TDF), P=0.26
- Fowler 2016 Africa PROMISE: 18.5% (TDF) vs. 19.7% (Non-TDF), P=0.09
- Moodley 2016 S Africa: 21.1% (TDF) vs. 24.5% (Non-TDF), P=0.32

P-values indicate no significant difference between groups.
Preterm <37 Weeks, HIV ART Studies, By Time ART Starts: ART Start Pre-Conception vs During Pregnancy

### Zash 2016 Africa
- **PRE-CONCEPTION**
  - TDF ART: 28.0% (N=165)
  - Non-TDF ART: 31.0% (N=2006)
  - **P=NS**

- **DURING PREGNANCY**
  - TDF ART: 18.2% (N=1054)
  - Non-TDF ART: 19.8% (N=243)
  - **P=NS**

### Malaba 2016 Africa
- **PRE-CONCEPTION**
  - TDF ART: 20.1% (N=572)
  - Non-TDF ART: 18.4% (N=922)
  - **P=0.10**

- **DURING PREGNANCY**
  - TDF ART: 31.0% (N=146)
  - Non-TDF ART: 19.8% (N=2006)
  - **P=NS**

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*Note: N values represent sample sizes.*
Very Preterm <34 Weeks, HIV-Infected Women
HIV ART Studies

Fowler 2016 Africa PROMISE
- TDF ART: 6.0% (N=335)
- Non-TDF ART: 2.6% (N=346)
- AZT/sdNVP: 3.2% (N=341)

Zash 2016 Africa
- TDF ART: 10.0% (N=165)
- Non-TDF ART: 12.0% (N=2006)

- **P=0.036**
- **P=0.10**
- **P=NS**

(data for preconception start only)
Preterm <37 Weeks, HIV-Uninfected Women HBV and PrEP Studies
Low Birth Weight <2500 g, HIV-Infected Women

HIV ART Studies

- Gibb 2012 Africa: 15.0% (N=130), 19.0% (N=69)
- Siberry 2012 US: 19.5% (N=426), 19.1% (N=1156)
- Pintye 2015 Africa: 10.0% (N=89), 7.0% (N=188)
- Fowler 2016 Africa PROMISE: 16.9% (N=301), 20.4% (N=319)
- Moodley 2016 Africa: 13.5% (N=1666), 15.3% (N=907)

P-values:
- Gibb 2012 vs. Siberry 2012: P=0.44
- Siberry 2012 vs. Pintye 2015: P=0.87
- Siberry 2012 vs. Fowler 2016: P=0.45
- Fowler 2016 vs. Moodley 2016: P=0.004
- Gibb 2012 vs. Moodley 2016: P=0.59

N: Sample size
Low Birth Weight <2500 g, HIV ART Studies, By Time ART Starts: ART Start Pre-Conception vs During Pregnancy

P = 0.57
Very Low Birth Weight <1500 g, HIV-Infected Women

HIV ART Studies

- TDF ART
- Non-TDF ART
- AZT/sdNVP

Fowler 2016 Africa PROMISE

% Very Low Birth Weight

- TDF ART: 2.0% (N=301)
- Non-TDF ART: 0.6% (N=319)
- AZT/sdNVP: 0.3% (N=315)

P-values:
- TDF ART vs. Non-TDF ART: P=0.17
- TDF ART vs. AZT/sdNVP: P=0.063

N=301, N=319, N=315
Low Birth Weight <2500 g, HIV-Uninfected Women
HBV Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>TDF</th>
<th>3TC</th>
<th>No drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celen 2013 Turkey HBV</td>
<td>4.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greenup 2014 Australia HBV</td>
<td>3.4%</td>
<td>1.9%</td>
<td>0%</td>
</tr>
<tr>
<td>N= 21</td>
<td>23</td>
<td>58</td>
<td>53 20</td>
</tr>
</tbody>
</table>

P=NS
Small For Gestational Age (SGA), HIV-Infected Women
HIV ART Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>TDF ART</th>
<th>Non-TDF ART</th>
<th>AZT/sdNVP</th>
<th>% Small for Gestational Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siberry 2012 US</td>
<td>8.3%</td>
<td>8.6%</td>
<td></td>
<td>16.9%</td>
</tr>
<tr>
<td>Moodley 2016 Africa</td>
<td>8.0%</td>
<td>9.2%</td>
<td>7.5%</td>
<td>24.7%</td>
</tr>
</tbody>
</table>

P-values:
- Siberry 2012 US: P=0.85
- Moodley 2016 Africa: P=0.80
- Moodley 2016 Africa: P=0.52

Sample sizes:
- Siberry 2012 US: N=1666, N=907, N=974
- Moodley 2016 Africa: N=426, N=1156
SGA, HIV ART Studies, By Time ART Starts: ART Started Pre-Conception vs During Pregnancy

Adjusted OR
0.3 (0.1-1.0)  0.5 (0.3 to 0.8)

% Small for Gestational Age

P=0.59

Zash 2016 Africa
PRECONCEPTION
13.0% 32.0%
N=165 N=2006

Zash 2016 Africa
DURING PREGNANCY
19.2% 25.5%
N=1054 N=243

Malaba 2016 Africa
PRECONCEPTION
9.3%
N=572

Malaba 2016 Africa
DURING PREGNANCY
10.2%
N=922

TDF ART  Non-TDF ART
Birth Defects, HIV-Infected Women
HIV ART Studies

<table>
<thead>
<tr>
<th>Study</th>
<th># defects</th>
<th># exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibb 2012</td>
<td>4</td>
<td>141</td>
</tr>
<tr>
<td>Floridia 2013</td>
<td>5</td>
<td>173</td>
</tr>
<tr>
<td>Phiri 2014</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>Sibiude 2014</td>
<td>30</td>
<td>823</td>
</tr>
<tr>
<td>Williams 2015</td>
<td>33</td>
<td>431</td>
</tr>
<tr>
<td>Fowler 2016</td>
<td>34</td>
<td>332</td>
</tr>
<tr>
<td>APR 2016</td>
<td>61</td>
<td>2779</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>167</strong></td>
<td><strong>4707 (3.5%)</strong></td>
</tr>
</tbody>
</table>
Birth Defects, HIV-Uninfected Women HBV and PrEP Studies

- Greenup 2014 Australia HBV: 1.7% (N=58)
- Chen 215 Taiwan HBV: 0% (N=53)
- Kochaksaraei 2016 Canada HBV: 0% (N=20)
- Pan 2016 China: 0.7% (N=65)
- Mugo 2014 Africa PrEP: 4.9% (N=56)

PrEP:
- TDF: 8.5% (N=24)
- TDF/FTC: 7.6% (N=146)
- 3TC: 3.8% (N=95)
- No drug: 1% (N=88)

Statistical significance:
- p=0.51
- p=0.86
Neonatal Death (Age <14 Days), HIV-Infected Women
HIV ART Studies

Gibb 2012 Africa
- TDF ART: 4.0%
- Non-TDF ART: 1.0%
- AZT/sdNVP: 3.2%
N=141 (P=0.40)

Fowler 2016 Africa PROMISE
- TDF ART: 4.4%
- Non-TDF ART: 0.6%
- AZT/sdNVP: 3.2%
N=341 (P=0.001)
N=346 (P=0.43)
N=349
Infant Death (Age >14 Days), HIV-Infected Women

HIV ART Studies

% Infant Death

<table>
<thead>
<tr>
<th></th>
<th>TDF ART</th>
<th>Non-TDF ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibb 2012 Africa median FU 25 mo</td>
<td>6.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Taha 2016 Africa 12 month mortality</td>
<td>1.2%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

P=0.42

N=111 N=62 N=1220 N=1211

Gibb 2012

Taha 2016

P=0.72
Neonatal/Infant Death, HIV-Uninfected Women
HBV and PrEP Studies

% Neonatal (<14 Days)/Infant Death

Greenup 2014
Australia HBV

Chen 2015
Taiwan HBV

Kochaksarrei 2016 Canada
HBV

Pan 2016
China

Mugo 2014
Africa PrEP

TDF
TDF/FTC
3TC
No drug

P=0.17
P=0.49

0% 0% 0% 1% 1.2%
10.6%
6.1%

* Mugo PrEP:
overall infant mortality to 12 mo:
TDF: 1/81, 1.2% (p=0.17 vs PL)
TDF/FTC: 5/46, 10.6% (p=0.49 vs PL)
Placebo: 4/65, 6.1%
Birth Weight for Age Z-Score, HIV ART Studies

- Gibb 2012, Africa: $P=\text{NS}$, TDF ART $-0.97$, Non-TDF ART $-1.22$
- Siberry 2012, US: $P=0.77$, TDF ART $-0.58$, Non-TDF ART $0.59$
- Ransom 2013, US: $P=0.90$, TDF ART $0.14$, Non-TDF ART $0.14$
- Siberry 2015, US: $P=0.38$, TDF ART $-0.71$, Non-TDF ART $-0.48$
Birth Length and Head Circumference for Age Z-Score, HIV ART Studies

Gibb 2012 Africa
Siberry 2012 US
Siberry 2015 US
LeRoux 2016 Africa

LAZ HCAZ

Z-score

-3.00 -2.00 -1.00 0.00 1.00 2.00 3.00

LAZ HCAZ

-2.22 -0.25 -0.66 -0.41

-0.65 +0.07

+0.29 -0.16 -0.18

P=0.03 P=NS P=0.29 P=0.83 P=0.26

P=0.79 P=0.53 0.23 0.30

<12 wk TDF 12-22 wk TDF >22 wk TDF

Duration TDF Exposure During Pregnancy

TDF ART Non-TDF ART TDF-ART Non-TDF-ART

LAZ HCAZ

P=0.03 P=NS P=0.29 P=0.83 P=0.26

Gibb 2012 Africa
Siberry 2012 US
Siberry 2015 US
LeRoux 2016 Africa

LAZ HCAZ

-2.22 -0.25 -0.66 -0.41

-0.65 +0.07

+0.29 -0.16 -0.18

P=0.03 P=NS P=0.29 P=0.83 P=0.26

P=0.79 P=0.53 0.23 0.30

<12 wk TDF 12-22 wk TDF >22 wk TDF

Duration TDF Exposure During Pregnancy

TDF ART Non-TDF ART TDF-ART Non-TDF-ART

LAZ HCAZ

-2.22 -0.25 -0.66 -0.41

-0.65 +0.07

+0.29 -0.16 -0.18

P=0.03 P=NS P=0.29 P=0.83 P=0.26

P=0.79 P=0.53 0.23 0.30

<12 wk TDF 12-22 wk TDF >22 wk TDF

Duration TDF Exposure During Pregnancy

TDF ART Non-TDF ART TDF-ART Non-TDF-ART
Weight for Age Z-Score at Age 6-12 Months, HIV ART Studies

P=0.62

P=0.61

P=0.31

P=0.003

WAZ-score

-3.00
-2.00
-1.00
0.00
1.00
2.00
3.00

TDF ART
Non-TDF ART

Siberry 2012
US
(12 mo)

Ransom 2013
US
(6 mo)

Pintye 2015
Africa
(9 mo)

Liotta 2016
Africa
(12 mo)
Length and Head Circumference for Age Z-Score at Age 9-12 Months, HIV ART Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Age</th>
<th>LAZ Z-score</th>
<th>HCAZ Z-score</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siberry 2012</td>
<td>US</td>
<td>(12 mo)</td>
<td>-0.17</td>
<td>-0.03</td>
<td>0.04</td>
</tr>
<tr>
<td>Pintye 2015</td>
<td>Africa</td>
<td>(9 mo)</td>
<td>-1.00</td>
<td>-0.30</td>
<td>0.02</td>
</tr>
<tr>
<td>Liotta 2016</td>
<td>Africa</td>
<td>(12 mo)</td>
<td>-1.30</td>
<td>-1.78</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
### Other Studies Evaluating Growth – HIV, HBV, PrEP

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Place</th>
<th>Comments comparing TDF (N=219) vs No TDF (N=3385)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigano-HIV</td>
<td>2011</td>
<td>Italy</td>
<td>No diff median/proportion &lt;10%ile for wt, ht, HC at birth btn TDF (N=33) vs non-TDF (N=35) ART</td>
</tr>
<tr>
<td>Gibb-HIV</td>
<td>2012</td>
<td>Africa</td>
<td>No diff after birth in WAZ or HAZ btn TDF (N=251) vs non-TDF ART (N=115) to age &gt;2 yr</td>
</tr>
<tr>
<td>Siberry-HIV</td>
<td>2012</td>
<td>US</td>
<td>No diff in &lt;-1.5 SD Z-score for wt, ht and HC at age 1 yr btn TDF (N=426) vs non-TDF (N=1580) ART</td>
</tr>
<tr>
<td>Ransom-HIV</td>
<td>2013</td>
<td>US</td>
<td>No diff WAZ at birth or 6 mo or &lt;5%ile btn TDF (N=630) and non-TDF (1395) ART by trimester or duration TDF exposure</td>
</tr>
<tr>
<td>Himes-HIV</td>
<td>2015</td>
<td>US</td>
<td>WAZ, LAZ were not associated with levels of TFV in infant meconium (all TDF-exposed N=53)</td>
</tr>
<tr>
<td>Le Roux-HIV</td>
<td>2016</td>
<td>Africa</td>
<td>LAZ did not vary by duration of maternal TDF ART (N=464) &lt;12 wk, 12-22 wk or &gt;22 wk</td>
</tr>
<tr>
<td>Denneman-HIV</td>
<td>2016</td>
<td>Netherlands</td>
<td>Sig lower birth WAZ and 6 mo WAZ, HAZ with TDF (N=9) ART vs non-TDF (N=65) ART; no diff severe (&gt; -2 SD) growth impairment</td>
</tr>
<tr>
<td>Greenup-HBV</td>
<td>2014</td>
<td>Australia</td>
<td>No diff in birth wt, ht, HC, TDF (N=58) vs 3TC (53) vs no drug (N=20)</td>
</tr>
<tr>
<td>Chen-HBV</td>
<td>2015</td>
<td>Taiwan</td>
<td>No diff wt or ht at birth or 6 mo btn TDF (N=65) vs no drug (N=56)</td>
</tr>
<tr>
<td>Pan-HBV</td>
<td>2016</td>
<td>China</td>
<td>No diff GA, wt or ht at birth or 28 wk, TDF (N=95) vs no drug (N=88)</td>
</tr>
<tr>
<td>Mugo-PrEP</td>
<td>2014</td>
<td>Africa</td>
<td>No diff in infant wt, ht, HC btn TDF (N=81), TDF/FTC (N=47) and placebo (N=66)</td>
</tr>
</tbody>
</table>
### Bone and Bone Markers – HIV, PrEP

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Place</th>
<th>Findings (TDF no comparison grp [N=749]; TDF [N=460] vs No TDF [N=359])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigano</td>
<td>2011</td>
<td>Italy</td>
<td>Bone ultrasound z-score (0.6 TDF, 0.8 non TDF, p=0.40) &amp; Ca, P not diff</td>
</tr>
<tr>
<td>TDF 33 Non-TDF 35</td>
<td></td>
<td></td>
<td>Urine Ca/Cr ratio: ↑ with TDF (0.08 TDF, 0.05 non-TDF, p=0.039)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PTH ↓ with TDF (9.9 TDF vs 12.3 non-TDF, p=0.023; but wnl)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bone markers BAP (formation) and CTX (resorption) not diff</td>
</tr>
<tr>
<td>Gibb</td>
<td>2012</td>
<td>Africa</td>
<td>Ca Gr 1 or 2 not diff: TDF 8% vs non-TDF 6% (p=0.60)</td>
</tr>
<tr>
<td>TDF 111 Non-TDF 62</td>
<td></td>
<td></td>
<td>Ph Gr 1 not diff: TDF 1% vs non-TDF 5% (p=0.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alk Phos Gr 1-3 not diff: TDF 20% vs non-TDF 20% (p=0.85); No bone fx</td>
</tr>
<tr>
<td>Siberry</td>
<td>2015</td>
<td>US</td>
<td>BMC with head adjusted diff 5.3 gm ↓ with TDF than non-TDF (p=0.013)</td>
</tr>
<tr>
<td>TDF 74 Non-TDF 69</td>
<td></td>
<td></td>
<td>BMC without head not diff (p=0.15)</td>
</tr>
<tr>
<td>Floridia</td>
<td>2016</td>
<td>Africa</td>
<td>BAP and CTX not sig diff from non-TDF at 12 mo. BAP/CTX not correlated</td>
</tr>
<tr>
<td>TDF 136 Non-TDF 40</td>
<td></td>
<td></td>
<td>with growth. Duration AP ART correlated with wt/ht at 6/12 mo.</td>
</tr>
<tr>
<td>Siberry</td>
<td>2016</td>
<td>Africa</td>
<td>Differ in whole body BMC ↓ with triple ART (TDF or AZT-based) (p&lt;0.001)</td>
</tr>
<tr>
<td>TDF 114 Non-TDF 127</td>
<td></td>
<td></td>
<td>compared to AZT/sdNVP but not between the 2 ART regimens (p=0.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lumbar spine BMC not sig differ btn regimens</td>
</tr>
<tr>
<td>Jao</td>
<td>2016</td>
<td>Africa</td>
<td>Fetal femur &amp; humerus length z-score did not vary by duration</td>
</tr>
<tr>
<td>TDF: 646</td>
<td></td>
<td></td>
<td>maternal TDF ART (N=646) &lt;10 wk (188), 10-24 wk (326), &gt;25 wk (132)</td>
</tr>
<tr>
<td>Floridia</td>
<td>2016</td>
<td>Africa</td>
<td>Serum C and P abnormalities rare (1.4-9.2%), mild (grade 1) and transient</td>
</tr>
<tr>
<td>TDF 136</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mugo (PrEP)</td>
<td>2014</td>
<td>Africa</td>
<td>No differ btn TDF, TDF/FTC, or placebo in infant creatinine at 1 and 3 mo</td>
</tr>
<tr>
<td>TDF 81, TDF/FTC 47, PL 66</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Fetal Long Bone Humerus and Femur Growth Does Not Differ by Duration of IU TDF Exposure


- 646 women/fetal dyads: 132 with >25 wk, 326 with 10-24 wk, and 188 with <10 wk TDF exposure; underwent 2 or more (N=1376) fetal ultrasounds to measure long bone growth.
Mean WB-BMC Significantly Lower in Both Triple ART Arms Compared to AZT/sdNVP
But NOT Different between TDF and non TDF ART

\[ p < 0.001 \text{ (est mean diff 7.97 g)} \]

\[ p < 0.001 \text{ Est mean diff 9.73} \]

\[ p = 0.41 \text{ Est mean diff 1.76} \]

Siberry GK et al. CROI 2016, Abs.36
Maternal Adverse Events
PROMISE (Antepartum): Antepartum Maternal Adverse Events/Mortality, HIV ART


Any >= Grade 2 AE

- TDF ART: 16%
- AZT ART: 16%
- AZT/sdNVP: 15%

Any >= Grade 2 Chemistry

- TDF ART: 3%
- AZT ART: 5%
- AZT/sdNVP: 1%

Maternal mortality

- TDF ART: 0%
- AZT ART: 0%
- AZT/sdNVP: 0%

P-values:
- Any >= Grade 2 AE: P=NS
- Any >= Grade 2 Chemistry: P<0.001
- Maternal mortality: P=0.03
PROMISE (Postpartum): Postpartum Maternal Adverse Events/Mortality, HIV ART

Taha T et al. AIDS Conference 2016 Durban, South Africa Abs. LBPE013

<table>
<thead>
<tr>
<th>Event</th>
<th>TDF ART</th>
<th>No ART</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>14.8%</td>
<td>14.6%</td>
<td>0.99</td>
</tr>
<tr>
<td>Severe composite</td>
<td>5.1%</td>
<td>5.6%</td>
<td>0.61</td>
</tr>
<tr>
<td>Death</td>
<td>0.16% (2 deaths)</td>
<td>0.08% (1 death)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Grade 3/4 sign/sx or Grade 2-4 lab AE or Death

N = 1220

N = 1211
Maternal Mortality, HIV-Uninfected Women

HBV Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>TDF</th>
<th>3TC</th>
<th>No drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenup 2014</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Chen 2015</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Pan 2016</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

N= 58 52 20 62 56 97 100
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Place</th>
<th>Comments comparing TDF (N=219) vs No TDF (N=3385)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenup-HBV</td>
<td>2014</td>
<td>Australia</td>
<td>“No nephrotoxicity” any arm TDF (N=58), 3TC (N=53), no drug (N=20)</td>
</tr>
<tr>
<td>Chen- HBV</td>
<td>2015</td>
<td>Taiwan</td>
<td>No difference creatinine at delivery: TDF (N=62) mean 0.50 vs no drug (N=56) mean 0.51</td>
</tr>
<tr>
<td>Hu-HBV</td>
<td>2015</td>
<td>China</td>
<td>“No significant change creatinine or phosphorus”(TDF N=17)</td>
</tr>
<tr>
<td>Kochaksarai-HBV</td>
<td>2016</td>
<td>Canada</td>
<td>TDF (N=23): Creatinine increased from baseline 48.5 Umol/L to delivery 53 Umol/L (p=0.02), with slight decline GFR from baseline 146 to delivery 120.5 (p=0.04). No hypophosphatemia or Fanconi syndrome.</td>
</tr>
<tr>
<td>Pan-HBV</td>
<td>2016</td>
<td>China</td>
<td>• No difference Grade 3 or 4 adverse event: 0 TDF (N=97) vs 1% no drug (N=100)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Higher frequency Grade 1 or 2 creatinine kinase 7% TDF vs 0% no drug (asymptomatic)</td>
</tr>
</tbody>
</table>
BMD in Breastfeeding HIV+ Women but No Difference in ↓ Between AZT/sdNVP or TDF-ART

Onyango-Makumbi C et al. CROI 2014, Boston, MA Abs.850

- ↓ in Spine/ Hip DXA T-score in BF women between 2 wk and 9 mo PP (normal in BF women).

- No significant difference in T score between AZT/sdNPV Option A and TDF-based Option B.
BMD in Breastfeeding HIV+ Women in PP PROMISE Receiving TDF-ART vs no ART (Infant NVP) PMTCT

Stranix-Chibanda L for PROMISE P1084s. 8th Pediatric Workshop, 2016, Durban S Africa Abs. 0.20

- Compared to no ART, significant decrease in Spine (-3.2%) and Hip (-2.3%) DXA T-score in BF HIV+ women on TDF ART between 1 wk and 74 wks PP.

**Lumbar Spine BMD**

- Mean difference of -3.16% (-4.44, -1.84)
- (p-value <0.001)

**Hip BMD**

- Mean difference of -2.33% (-3.23, -1.42)
- (p-value <0.001)

Maternal Triple ART

- N=167
- Mean % change: -2.06 (-2.9, -1.23)
- (95% Confidence Interval)

No maternal ART

- N=170
- Mean % change: +1.09 (0.11, 2.07)
- (95% Confidence Interval)
### Case Reports: No Similarities in Anomalies
No Conclusions Can be Drawn

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sabbatini</td>
<td>2007</td>
<td>2 cases of congenital pyelectasis (detected by ultrasound, not present in 1 at 8 mos; confirmed in 1 at 1mo)</td>
</tr>
<tr>
<td>Kinai</td>
<td>2012</td>
<td>Fetal growth “significantly blunted” after switch to TDF (ABC/LPVR/TDF) at GA 35 wk (had been on ABC/LPV/r/RAL 1st 33 wk); delivered at 38 wk; infant BW, BL &lt;-2SD; birth Ca 7.4 (LLN 8.6); birth alk P 560 (ULN 316); urine beta-2 microglobulin 1780 ug/L; plasma TDF 24 hr after delivery 102 ng/L</td>
</tr>
<tr>
<td>Jibril</td>
<td>2013</td>
<td>2 cases spina bifida on TDF/FTC/NVP prior to conception</td>
</tr>
<tr>
<td>Fasunla</td>
<td>2014</td>
<td>2 cases cleft palate in infants exposed to TDF/3TC/EFV at conception to 2-3 mo GA (1 additional case in infant exposed to AZT/3TC/NVP)</td>
</tr>
</tbody>
</table>
### ClinicalTrials.Gov Listing of Trials of TDF in Pregnancy Enrolling or in Follow-Up

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Population</th>
<th>Dates initiation</th>
<th>Planned N</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT 02039362</td>
<td>HBV-TDF (Observational)</td>
<td>GA 28 wk-12 wk PP</td>
<td>25 TDF</td>
<td>07/2016</td>
</tr>
<tr>
<td>NCT02510963</td>
<td>HBV-TDF (compare duration)</td>
<td>GA 24, 28 or 32 wk</td>
<td>300 TDF (100 per group)</td>
<td>06/2017</td>
</tr>
<tr>
<td>NCT01745822</td>
<td>HBV-TDF (RCT)</td>
<td>GA 28 wk</td>
<td>164 TDF 164 no drug</td>
<td>12/2016</td>
</tr>
<tr>
<td>NCT02301650</td>
<td>Infants exposed to TDF, 3TC or telbivudine</td>
<td>1 yr developmental FU of children aged 1-3 yr born to HBV+ mothers who received drug or no drug during pregnancy</td>
<td>100 TDF 100 3TC 100 TBV 100 no drug</td>
<td>12/2017</td>
</tr>
<tr>
<td>NCT01125696</td>
<td>HIV-TDF ART (Observational)</td>
<td>GA 14 wk</td>
<td>80 TDF-3TC-LPV/r</td>
<td>05/2015 (no results listed)</td>
</tr>
</tbody>
</table>
Conclusions

- There is significant exposure \textit{in utero} as TDF in amniotic fluid and cord blood.
- While the safety data are reassuring, most are not from the population of interest – HIV-uninfected women.
- Most studies are from HIV+ women on ART, who already have higher adverse pregnancy outcomes than HIV- women, which may be exacerbated by 3 drug ART (as lower rates seen in women receiving AZT/sdNVP).
- In HIV+ women, TDF ART appears generally similar to other ART regimens in HIV+ women in terms of maternal outcomes, pregnancy and infant growth outcomes, and there is limited exposure during breastfeeding.
Conclusions

- Potential for ↓ in maternal BMD while on TDF but only evaluated in HIV+ women; has been seen with PrEP but stabilizes over time and reverses when stopped.

- Studies in HIV-uninfected women are much fewer, most have adverse event rates significantly lower than in the HIV+ population, with no obvious differences between TDF or TDF/FTC and control.

- PrEP benefits in women at high risk of HIV acquisition appear to outweigh any risks observed to date.

- As PrEP in women of childbearing age is implemented, it will be important to continue surveillance of maternal, pregnancy and infant outcomes to confirm the safety that reviews to date suggest.
Thanks For Your Attention!