IMPAACT 2010:
Phase III Study of Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing ART Regimens in HIV-1-Infected Pregnant Women and their Infants
Protocol Team

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Study 2010 Design

• Randomized 1:1:1 open label 3-arm treatment trial in HIV-infected pregnant women (183/arm, 549 total)
  – DTG/TAF/FTC
  – DTG/TDF/FTC
  – EFV/TDF/XTC
• Women start ART at 14-28 weeks gestation
• Mothers and their children followed through 50 weeks postpartum
Arm 1: Maternal DTG/FTC/TAF During Pregnancy and Postpartum
- Maternal follow-up for approximately 12-26 weeks prior to delivery
- Maternal and infant follow-up for 50 weeks after delivery (infant receives local standard prophylaxis)

Arm 2: Maternal DTG/FTC/TDF During Pregnancy and Postpartum
- Maternal follow-up for approximately 12-26 weeks prior to delivery
- Maternal and infant follow-up for 50 weeks after delivery (infant receives local standard prophylaxis)

Arm 3: Maternal EFV/(FTC or 3TC)/TDF During Pregnancy and Postpartum
- Maternal follow-up for approximately 12-26 weeks prior to delivery
- Maternal and infant follow-up for 50 weeks after delivery (infant receives local standard prophylaxis)

Enrollment at 14-28 weeks gestation
Delivery

12-26 weeks
6 14 26 38 50
Completion of follow-up at 50 weeks postpartum

Weeks on Study
Study 2010 Design, Continued

• Will be preceded by lead-in phase in which up to 25 women will undergo TAF pregnancy PK testing (through co-enrolment in P1026s)

• Study sites: planning communications with the sites shortly
Primary Objectives

• To determine whether a DTG-containing regimen (DTG arms combined) is superior to EFV/(3TC or FTC)/TDF with regard to virologic efficacy (HIV-1 RNA <200 copies/mL) at delivery

• To determine whether rates of the following safety outcomes differ for any pairwise regimen comparison (between the 3 regimens):
  • Adverse pregnancy outcomes (composite endpoint of spontaneous abortion, fetal death, preterm delivery, or small for gestational age)
  • Maternal grade 3 or higher adverse events through 50 weeks postpartum
  • Infant grade 3 or higher adverse events through 50 weeks postpartum
Secondary & Exploratory Objectives

- Non-inferiority of DTG-containing regimens compared with EFV/(3TC or FTC)/TDF with regard to virologic suppression (<200 cp/mL) at delivery
- Additional comparisons of rates of virologic suppression
  - To <200 cp/mL at 50 weeks postpartum
  - To <50cp/mL at delivery
  - By FDA snapshot algorithm
- Composite adverse pregnancy outcome including congenital anomalies
- Bone: DXA (subset of infants at 26 wks, mothers at 50 wks postpartum)
- Renal toxicity (mothers and infants)
- MTCT, ARV drug resistance (in HIV+ infants, mothers with VF)

- Exploratory objectives:
  - Mother-infant ARV transfer at birth and from breast milk
  - Adherence
  - Postpartum depression
  - Outcomes of new pregnancies occurring on-study
  - Hormonal, inflammatory markers of adverse pregnancy (and maternal health) outcomes
Key Inclusion / Exclusion Criteria

• **Inclusion:**
  – HIV-infected pregnant women with evidence of viable singleton pregnancy
  – Not on ART at entry
    • Prior ARVs during pregnancy, breastfeeding permitted (must have stopped these at least 6 months prior to entry)
    • Up to 10 days of ART during current pregnancy permitted

• **Exclusion:**
  – Taking medication to treat psychiatric illness, active TB, or HCV
  – H/O suicidal ideation or known significant adverse reaction to any of study ARVs
  – Known/suspected major congenital anomaly

*Note: fetal ultrasound required during screening or within 14 days of entry, but not required prior to entry*
### Maternal Antepartum Schedule of Evaluations

<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Screen</th>
<th>Entry</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
<th>Q4 Weeks¹</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit Window</td>
<td>up to -10 d</td>
<td>Day 0</td>
<td>±2 wks</td>
<td>±2 wks</td>
<td>±2 wks</td>
<td>±2 wks</td>
<td>Switch²</td>
</tr>
</tbody>
</table>

#### MATERNAL EVALUATIONS

| Informed consent⁴ | X |
| Maternal medical history | X X X X X X X X X |
| ARV adherence questionnaire | X X X X X X |
| Physical examination | X X X X X X X X X |

#### Fetal ultrasound
- during screening or within 14 days after entry

#### Confirmatory pregnancy testing⁵
- 0-1 mL

#### Confirmatory HIV testing
- 0-6 mL

#### Hepatitis B surface antigen
- 3 mL

#### AST, ALT, creatinine, CrCl
- 4 mL

#### Complete blood count
- 3 mL

#### CD4+ cell count
- 3 mL

#### HIV-1 RNA (store residual plasma)
- 6 mL

#### Perform Only For Phase III Study

| Stored plasma | 6 mL |
| Stored plasma and cell pellets | 10 mL |
| Stored urine | 15 mL |

#### Total blood volume: Lead-In
- 7-13 mL
- 12 mL
- 10 mL
- 6 mL
- 10 mL
- 0-10 mL

#### Total blood volume: Phase III
- 13-20 mL
- 22 mL
- 10 mL
- 16 mL
- 10 mL
- 0-10 mL
<table>
<thead>
<tr>
<th>Study Visit</th>
<th>Delivery</th>
<th>Weeks Postpartum</th>
<th>Post</th>
<th>Confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>up to 14 d</td>
<td>6</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>New Day 0</td>
<td>±2 wks</td>
<td>±6 wks</td>
<td>±6 wks</td>
</tr>
<tr>
<td>Visit Window</td>
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</tbody>
</table>

### MATERNAL EVALUATIONS

<table>
<thead>
<tr>
<th></th>
<th>Delivery</th>
<th>Weeks Postpartum</th>
<th>Post</th>
<th>Confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARV adherence questionnaire</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
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<td></td>
<td></td>
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<tr>
<td>AST, ALT, creatinine, CrCl</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Complete blood count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4+ cell count</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV-1 RNA (store residual plasma)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Perform Only For Phase III Study

<table>
<thead>
<tr>
<th></th>
<th>Delivery</th>
<th>Weeks Postpartum</th>
<th>Post</th>
<th>Confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stored plasma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored plasma and cell pellets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored breast milk</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Stored urine</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Stored hair</td>
<td></td>
<td></td>
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<tr>
<td>DXA scan (at selected sites)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression assessment (EPDS)</td>
<td></td>
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</tr>
</tbody>
</table>

### Total blood volume

<table>
<thead>
<tr>
<th></th>
<th>Delivery</th>
<th>Weeks Postpartum</th>
<th>Post</th>
<th>Confirmation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blood volume: Lead-In</td>
<td>10 mL</td>
<td>0 mL</td>
<td>10 mL</td>
<td>16 mL</td>
</tr>
<tr>
<td>Total blood volume: Phase III</td>
<td>26 mL</td>
<td>6 mL</td>
<td>10 mL</td>
<td>16 mL</td>
</tr>
</tbody>
</table>
## Infant Schedule of Evaluations

<table>
<thead>
<tr>
<th>INFANT EVALUATIONS</th>
<th>Delivery</th>
<th>Weeks of Age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>up to 14 d</td>
</tr>
<tr>
<td>Study Visit</td>
<td></td>
<td>±2 wks</td>
</tr>
<tr>
<td>Infant medical and feeding history</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Physical examination</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>HIV NAT (store residual plasma)</td>
<td>3 mL</td>
<td>4 mL</td>
</tr>
<tr>
<td>ALT and creatinine</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>Complete blood count</td>
<td>1 mL</td>
<td></td>
</tr>
<tr>
<td>Perform Only For Phase III Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stored hair</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>DXA scan (at selected sites)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total blood volume</td>
<td>5 mL</td>
<td>4 mL</td>
</tr>
</tbody>
</table>

Legend:
- X: Required
- Blank: Not required

**Note:** BF stands for breast feeding.
Timelines

- Protocol resubmitted on 8 June 2016 to MPRG
- Plan to submit to CSRC this month
- Aiming for final protocol by August 2016
- Anticipate that initial sites would start in first quarter of 2017
- Completion of TAF pregnancy PK lead-in phase 6-12 months
  - Will depend on # of women enrolling in unboosted TAF arm of P1026s prior to 2010; pace (and timing in gestation) of co-enrolment
- Completion of accrual to 2010 anticipated to take 8 months
- Potential challenges with timelines:
  - Completing CTA with Gilead for FTC/TAF (and FTC/TDF)
  - Finalizing purchase or donation of generic EFV/(3TC or FTC)/TDF
Many thanks to Elaine Abrams, Sharon Nachman, James McIntyre, and David Shapiro for guidance and support – and to protocol team