Dolutegravir in Pregnancy: An overview

Landon Myer
26 October 2018
Overview

Thinking about ARVs in pregnancy
  • Risks vs benefits
  • Limited data on ARV safety in pregnancy
  • Timing of in utero exposures

Dolutegravir: risks and benefits
  • Maternal health
  • Pregnancy outcomes
  • Neural tube defects: state of evidence

Balancing evidence
Drug Therapy

Balancing act

Benefits

Risks
Drug Therapy in Pregnancy

Balancing act

Benefit of Maternal Treatment

Risk of Adverse Fetal Effects
Drug Therapy in Pregnancy

Balancing act

Benefit of Maternal Treatment

Risk of Adverse Fetal Effects

Unfortunately data on risks are (usually) very limited
Antiretroviral Drugs Approved by FDA, 1987-2018

**NNRTIs (6)**
- Doravirine
- Bictegravir (in FDC)
- Ibalizumab

**Protease Inhibitors (9)**
- Lopinavir + Ritonavir
- Saquinavir
- Ritonavir
- Amprenavir
- Nelfinavir
- Indinavir
- Nelfinavir
- Tenofovir disoproxil fumarate
- Enfuvirtide (T-20)

**Entry Inhibitor (1)**
- Maraviroc

**Integrase Inhibitors (4)**
- Darunavir
- Etravirine
- Elvitegravir (in FDC)
- Tenofovir alafenamide (in FDC)

**Fusion Inhibitor (1)**
- Maraviroc

**Post-attachment inhibitor (1)**
- Varenicline

**NRTIs (8)**
- Zidovudine
- Didanosine
- Stavudine
- Lamivudine
- Zalcitabine
- Delavirdine
- Nevirapine
- Abacavir

**21 fixed-dose combinations approved 1997-2018**
Limited Data on Pregnancy for Approved Antiretroviral Drugs

- Of the 32 ARVs approved in adults, only one (AZT) has indication in pregnancy by FDA (for prevention of perinatal transmission)
- Generally, drug label language is “use in pregnancy only if potential benefit exceeds potential risk” and prohibits use during breastfeeding
- Of the 32 drugs:
  - N=26 had significant delay between FDA approval and data in pregnancy (mean 5 years)
  - N=5, including newest drugs, have no pregnancy data
Studying rare adverse events is difficult

To rule-out a 3-fold increase in a relatively rare event like Neural Tube Defects (NTD, incidence 0.1%), need >2000 exposures ....>4000 to rule out a 2-fold increase

Timing of *In Utero* ARV Exposure and Fetal Risk
Timing of *In Utero* ARV Exposure and Fetal Risk

First 2.5 Weeks Post-Fertilization:

Pre-Organogenic Period

generally not sensitive to teratogens
Timing of *In Utero* ARV Exposure and Fetal Risk

**Embryogenesis:** Active Organogenesis

*Weeks 3 to 12 Post Fertilization*

Most sensitive period to teratogens

**Examples:**
- Neural Tube Closure by Day 28 (e.g. myelomeningocele)
- Oral Structure Formation by Day 36 (e.g. cleft palate)
Timing of *In Utero* ARV Exposure and Fetal Risk

After 8-12 Weeks Post-Fertilization

**Fetal Development Period**

- Fetal growth; teeth; external genitalia; continued brain development

**Examples:**
- Alcohol after 24 weeks & fetal-alcohol syndrome
- Smoking after 20 weeks and IUGR
Dolutegravir: benefits in pregnancy (and for maternal health)
### ARV Drug Optimization: Key Principles

- Reduce toxicity
- Improve palatability/pill burden
- Increase resistance barrier
- Reduce drug interactions
- Safe use across different age groups and populations
- Reduce cost
## Dolutegravir: Why Make the Switch?

<table>
<thead>
<tr>
<th>ARV Drug Optimization: Key Principles</th>
<th>Dolutegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Reduce toxicity</td>
<td>✓ Significant less toxicity vs EFV</td>
</tr>
<tr>
<td>✓ Improve palatability/pill burden</td>
<td>✓ Single tablet regimen, small size</td>
</tr>
<tr>
<td>✓ Increase resistance barrier</td>
<td>✓ Very high barrier to resistance</td>
</tr>
<tr>
<td>✓ Reduce drug interactions</td>
<td>✓ DDI with rifampin</td>
</tr>
<tr>
<td>✓ Safe use across different age groups and populations</td>
<td>✓ ???????????</td>
</tr>
<tr>
<td>✓ Reduce cost</td>
<td>✓ STR TDF-3TC-DTG $75 USD ppy</td>
</tr>
</tbody>
</table>
Safety and Efficacy of DTG and EFV600 in 1st line ART
(summary 2018 WHO Systematic Review)

<table>
<thead>
<tr>
<th>Major outcomes</th>
<th>DTG vs EFV&lt;sub&gt;600&lt;/sub&gt;</th>
<th>QUALITY OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral suppression (96 weeks)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>DTG better</td>
<td>moderate</td>
</tr>
<tr>
<td>Treatment discontinuation&lt;sup&gt;2&lt;/sup&gt;</td>
<td>DTG better</td>
<td>high</td>
</tr>
<tr>
<td>CD4 recovery (96 weeks)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>DTG better</td>
<td>moderate</td>
</tr>
<tr>
<td>Mortality</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>AIDS progression</td>
<td>comparable</td>
<td>low</td>
</tr>
<tr>
<td>SAE</td>
<td>comparable</td>
<td>low</td>
</tr>
</tbody>
</table>

Reference: Steve Kanters, For WHO ARV GDG, 16-18 May 2018

WHO, 2018

*SINGLE TRIAL is only randomized comparison DTG and EFV (Walmsky JAIDS 2015)*

1 Difference viral suppression btn DTG and EFV driven by lower rate of discontinuation for adverse events. True viral failure (>2 VL >50) similar in the 2 groups (9% DTG & 8% EFV).

2 Treatment discontinuation 4% with DTG, 14% with EFV.

3 CD4 +378 with DTG, +332 with EFV at week 144.
Comparative Effectiveness of 1st Line ART in Adults, Brazil – Superior Effectiveness of DTG

Meireles MV et al. IAS, Amsterdam, July 2018 Abs. TUAB0101

<table>
<thead>
<tr>
<th>ART Regimen</th>
<th>% use VS &lt;50 (%)</th>
<th>aOR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TC+TDF+DTG</td>
<td>7.2</td>
<td>85.2</td>
<td>1.42 (1.32-1.52)</td>
</tr>
<tr>
<td>3TC+TDF+EFV</td>
<td>74.0</td>
<td>78.0</td>
<td>1.0</td>
</tr>
<tr>
<td>3TC+AZT+LPV/r</td>
<td>4.9</td>
<td>67.2</td>
<td>0.59 (0.55-0.63)</td>
</tr>
<tr>
<td>3TC+TDF+ATV/r</td>
<td>4.6</td>
<td>71.3</td>
<td>0.67 (0.63-0.72)</td>
</tr>
<tr>
<td>3TC+AZT+EFV</td>
<td>3.5</td>
<td>72.9</td>
<td>0.94 (0.87-1.02)</td>
</tr>
<tr>
<td>3TC+TDF+LPV/r</td>
<td>2.0</td>
<td>63.7</td>
<td>0.54 (0.49-0.60)</td>
</tr>
<tr>
<td>Others</td>
<td>3.7</td>
<td>67.9</td>
<td>0.67 (0.62-0.73)</td>
</tr>
</tbody>
</table>

*Controlled for age, sex, adherence and baseline CD4 and VL

DTG: 42% increase in VS vs EFV
What do we know about the benefits of DTG in pregnancy?

DTG ART *Started in Late Pregnancy* is Associated with More Rapid VL Decline than EFV

*Orrell C et al. IAS, Amsterdam July 2018, Abs. THAB0307LB*

**Ongoing trials:**
- **VESTED trial / IMPAACT 2010:** Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and their Infants (results 2019-2010)
- **DolPHIN-2:** Dolutegravir in Pregnant HIV Mothers and their Neonates (results early 2019)
Dolutegravir: risks in pregnancy
Risks of ARVs in pregnancy: what are we looking for?

- **Congenital anomalies/birth defects** including neural tube defects (NTD)
- Fetal loss, stillbirth, neonatal and infant deaths
- Compromised birth outcomes: preterm birth (PT), small for gestational age (SGA), low birth weight (LBW)
- *Early complications*: mitochondrial disorders, hematologic abnormalities, metabolic complications, abnormal neurodevelopment and growth patterns, infectious complications
- *Late complications*: organ dysfunction, neurocognition, malignancies
When Started During Pregnancy, No Difference Pregnancy Outcomes EFV vs DTG-Based ART

No difference in Major Birth Defects with First Trimester Exposure
EFV: 1/395 (0.3%)  
DTG: 0/280 (0%)  
(no NTD with either drug)
Preconception DTG –
Brief Summary on Neural Tube Development & Defects

Neural Tube Closure Normally Occurs by 28 Days Post-Conception

- Fusion of the neural tube may have several origins of fusion
- Fusion proceeds in both cephalad and caudal directions, forming anterior and posterior neuropores

Cranial neuropore closes on **25th day after conception**; caudal neuropore normally closes ~ **2 days later**

Different phenotypes of neural tube defects

- Phenotype depends on location & level of the defect, whether crosses CNS segmental boundaries
Botswana Tsepamo Study – Birth Surveillance

- Designed to evaluate the *risk of neural tube defects (NTD) with preconception EFV exposure*

- Prospective birth outcomes surveillance for major surface birth defects, 8 large maternity wards, population-based (45% of Botswana births)
  - Trained hospital-based midwifes surface exam
  - Research assistant consent mother for photo
  - Medical geneticist reviews blinded to exposure

- Good denominator with control groups and ability to distinguish between ARV regimens
  - HIV-uninfected
  - HIV-infected ART preconception or started in pregnancy

Zash IAS, Amsterdam July 2018 Late Breaker
Tsepmo Study: NTD Prevalence by Exposure

<table>
<thead>
<tr>
<th>NTDs/Exposure</th>
<th>4/426</th>
<th>14/11,300</th>
<th>3/5,787</th>
<th>0/2.812</th>
<th>61/66,057</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with NTD (95% CI)</td>
<td>0.94% (0.37%, 2.4%)</td>
<td>0.12% (0.07%, 0.21%)</td>
<td>0.05% (0.02%, 0.15%)</td>
<td>0.00% (0.00%, 0.13%)</td>
<td>0.09% (0.07%, 0.12%)</td>
</tr>
<tr>
<td>Prevalence Difference (95% CI)</td>
<td>ref</td>
<td>-0.82% (-0.24%, -2.3%)</td>
<td>-0.89% (-0.31%, -2.3%)</td>
<td>-0.94% (-0.35%, -2.4%)</td>
<td>-0.85% (-0.27%, -2.3%)</td>
</tr>
</tbody>
</table>
Tsepamo Study: Update since 1 May 2018

- From 1 May-15 July, there were **2 more NTDs**; 1 in an infant exposed to **DTG started during pregnancy** (8 weeks GA) and 1 birth to an **HIV-uninfected** woman:
  - NTDs in DTG started during pregnancy: 1/3104 (0.03%, 95% CI 0.01%, 0.18%)

**Updated prevalence of DTG exposure at conception is 4/596 (0.67%, 95% CI 0.26%, 1.7%)**

- 95% CI still does not overlap with any other exposure group
With expanded surveillance to 18 sites, estimate ~ 1226 births with exposure to DTG from conception by end of March 2019

<table>
<thead>
<tr>
<th>Number of total NTDs</th>
<th>Prevalence</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 in 1226</td>
<td>0.33%</td>
<td>0.13%, 0.84%</td>
</tr>
<tr>
<td>5 in 1226</td>
<td>0.41%</td>
<td>0.18%, 0.95%</td>
</tr>
<tr>
<td>6 in 1226</td>
<td>0.49%</td>
<td>0.22%, 1.1%</td>
</tr>
<tr>
<td>7 in 1226</td>
<td>0.57%</td>
<td>0.28%, 1.2%</td>
</tr>
<tr>
<td>8 in 1226</td>
<td>0.65%</td>
<td>0.33%, 1.3%</td>
</tr>
<tr>
<td>9 in 1226</td>
<td>0.73%</td>
<td>0.38%, 1.4%</td>
</tr>
<tr>
<td>10 in 1226</td>
<td>0.82%</td>
<td>0.45%, 1.5%</td>
</tr>
</tbody>
</table>
Data on pregnancies among women on DTG from Brazil

• From Jan 2017 - Mar 2018, >100,000 persons started DTG; 28% are women; pregnant women not eligible for DTG

• To date, 363 women have become pregnant on DTG. It is recommended when pregnancy is recognized to switch to EFV-based regimen
  • 275 still pregnant (75%)
  • 78 live birth (22%)
  • 2 stillbirth (<1%)
  • 8 terminations (2%)

• No birth defects have been reported in live births

Not clear if there are data on defects with stillbirth and elective terminations
Antiretroviral Pregnancy Registry (APR): outcomes with birth defects by trimester of earliest exposure to INSTI (as of 01-2018)

<table>
<thead>
<tr>
<th>Earliest Trimester of Exposure</th>
<th>Preconception</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Trimester</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt;/3&lt;sup&gt;rd&lt;/sup&gt; Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to any ART</td>
<td>215/7785 (2.8%)</td>
<td>40/1551 (2.6%)</td>
<td>259/9322 (2.8%)</td>
</tr>
<tr>
<td>Exposure to INSTI</td>
<td>13/507 (2.6%)</td>
<td>4/111 (3.6%)</td>
<td>14/403 (3.5%)</td>
</tr>
<tr>
<td>DTG *</td>
<td>3/121 (2.5%)</td>
<td>2/40 (5.0%)</td>
<td>2/94 (2.1%)</td>
</tr>
<tr>
<td>EVG</td>
<td>5/155 (3.2%)</td>
<td>0/25</td>
<td>0/52</td>
</tr>
<tr>
<td>RAL</td>
<td>5/231 (2.2%)</td>
<td>4/60 (6.6%)</td>
<td>12/278 (4.3%)</td>
</tr>
</tbody>
</table>

*Includes 0 NTD with INSTI exposure

*Includes 0 NTD with INSTI exposure
Balancing risks vs benefits
Drug Therapy in Pregnancy

Balancing act

Benefit of Maternal Treatment

Risk of Adverse Fetal Effects
Drug Therapy in Pregnancy

Balancing act

Benefit of Maternal Treatment

- DTG: Rapid VL decline
- Better tolerated
- Effective in the face of NNRTI resistance
- High barrier to resistance

Risk of Adverse Fetal Effects

- DTG: Potential signal for neural tube defect with preconception exposure (? ~0.6%)
Drug Therapy in Pregnancy

Balancing act

Benefit of Maternal Treatment

- Rapid VL decline
- Better tolerated
- Effective in the face of NNRTI resistance
- High barrier to resistance

Risk of Adverse Fetal Effects

- Potential signal for neural tube defect with preconception exposure (0.67%)

How do we balance risks vs benefits?
How do we balance risks vs benefits?
How do we balance risks vs benefits?

STOP
one step back from the kerb

LOOK
for traffic to your right, left and right again

LISTEN
for the sounds of approaching traffic

THINK
whether it is safe to cross
How do we balance risks vs benefits?

**Pause** – don’t rush into major decisions if there is concern

**Search** systematically for all available information – what else is out there?

**Solicit inputs** from diverse stakeholders – especially patients (women living with HIV/AIDS) and civil society

**Consider implications** of decisions holistically – mathematical modelling benefits and costs of different decisions
Thank you!!!

Lynne Mofenson
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Thokozile Malaba
Martina Penazzato
Tamsin Phillips