Antiretroviral Therapy (ART) at Conception and Pregnancy in Women With HIV

Jodie Dionne-Odom, MD
Assistant Professor of Medicine
University of Alabama at Birmingham
Birmingham, Alabama

Learning Objectives

After attending this presentation, learners will be able to:

- Identify 2 web-based resources for perinatal HIV information
- Initiate data-driven ART therapy in a pregnant woman in clinic
- List 2 risks and benefits of ART in pregnancy

Outline

- Case Presentation
- Benefits of ART in Pregnancy
- Risks of ART in Pregnancy
- Optimizing Management
- Perinatal HIV Resources
- Key Research Questions
Case Presentation

- 35 year old woman G4P3 with HIV is 33 2/7 weeks pregnant
- Arrived in the US from Guatemala 8 days ago.
- Presents to HIV clinic to establish care. Feels well.

HIV History:
- Diagnosed in 2017 when she had stillbirth at 34 weeks gestation.
- Initial antenatal care HIV screening test had been negative.
- Her male partner is HIV-positive.
- Started on ART in 2017 with efv/tdf/ftc. Adherent until 8 days ago.

Obstetrical and Social History

- Two prior uncomplicated vaginal deliveries. Healthy children 15,11.
- Started prenatal vitamins at 4 weeks GA with current pregnancy.
- Diagnosed with anemia (HCT 29), taking supplemental FeSO4.

Social History
- Born and raised in semi-rural town in Guatemala.
- Worked in a local store, selling clothes.
- Living in US with family.
- Denies tobacco/alcohol use/drug use.

Exam, Medications, Labs

- T 98.5  BP 113/72  HR 94  RR 18
- BMI 26
- Fetal heart tones present.
- Gravid uterus. Exam normal.
- ROS – negative

Medications:
- Efavirenz/tenofovir/emtricitabine
- FeSO4

- CD4 658 (47%)
- HIV viral load pending
Clinical Management

ARS Question 1

• How to manage her ART?

A. Hold ART pending labs
B. Continue efv/tdf/ftc
C. Switch to bic/taf/ftc
D. Switch to atv/cobi and tdf/ftc
E. Call the HIV perinatal hotline

HIV Prevalence in US Women
An estimated 5000 women with HIV give birth each year in the US.

- Perinatal HIV cases decreased 41% between 2012 and 2016.
- 73 pediatric cases diagnosed in 2017.

Benefits of ART in Pregnancy
When to Initiate Therapy?

No Perinatal HIV-1 Transmission From Women With Effective Antiretroviral Therapy Starting Before Conception

- 8075 mother-infant pairs
- Followed prospectively in France 2000-2011.
- Cohort analyzed according to maternal viral load at delivery and timing of ART initiation.
- 5608/8075 vertical transmissions (0.7%).
- Zero MTCT among 2651 women with VL <50 before conception

Risks of ART in Pregnancy

Adverse Pregnancy Outcomes

- Congenital Malformation
- Stillbirth
- Low Birth Weight (<2500 grams)
- Preterm Delivery (<37 weeks)
Pediatric HIV/AIDS US Prospective Cohort Study Surveillance

- 2580 HIV exposed uninfected (HEU) children enrolled in 2007-2012
- **Outcome:** Anomaly based on physician review of exam <12 months.
  - Adjusted for demographics, CD4, BMI, drug use, other meds.
  - Prevalence 6.8% (mostly musculoskeletal and cardiovascular)

<table>
<thead>
<tr>
<th>Variable</th>
<th>% Exposed</th>
<th>Control</th>
<th>Intervention</th>
<th>Standard Error</th>
<th>CI 95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No abnormal drug use</td>
<td>48.4</td>
<td>50.8</td>
<td>47.6</td>
<td>0.9</td>
<td>0.87-1.03</td>
</tr>
<tr>
<td>Mother antenatal treatment</td>
<td>53.7</td>
<td>60.9</td>
<td>56.4</td>
<td>1.4</td>
<td>1.03-1.85</td>
</tr>
<tr>
<td>Maternal vitamin intake</td>
<td>48.1</td>
<td>53.7</td>
<td>47.6</td>
<td>1.2</td>
<td>1.01-1.50</td>
</tr>
</tbody>
</table>

Prevalence 6.8% (mostly musculoskeletal and cardiovascular)

**Neural-Tube Development and Defects (NTD)**

- Neural tube begins to close 17-18 days after fertilization.
- Forms by 7 weeks gestational age (GA)
- 0.1% prevalence in general population
- Case reports of NTD association with EFV
- FDA 2005: Avoid EFV in 1st trimester.
• TSEPAMO Study
  • Botswana adopted DTG as 1st line ART in 2016
  • 1683 pregnancies DTG exposure at conception.
  • Overall 98 NTD (0.08%)

NTD: Role of Folate Supplementation

• MRC Study (Lancet 1991) led to folate supplementation as primary prevention.
  • Bread flour supplementation since 1998 in US
• NTDs are multifactorial
  • Genetic Predisposition (70%)
  • Environmental (30%)
• Folic acid prevents certain NTDs
• DTG is a non-competitive antagonist of the folate receptor at therapeutic concentrations
Summary of Birth Defects among 
First Trimester Exposures (1989-Jan 2019)
**Preterm Delivery (<37 weeks)**

- PACTG SMARTT
- 2007-2010
- n=1869 infants
- PTD 19%

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unaffected OR (95% CI)</th>
<th>Advanced OR (95% CI)</th>
<th>Developmental OR (95% CI)</th>
<th>Reference OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>1.80 (0.86-3.81)</td>
<td>1.49 (0.69-3.21)</td>
<td>1.14 (0.54-2.39)</td>
<td>1.41 (0.80-2.50)</td>
</tr>
<tr>
<td>Consumption</td>
<td>1.09 (0.22-5.30)</td>
<td>1.16 (0.31-4.48)</td>
<td>1.12 (0.42-3.10)</td>
<td>0.99 (0.40-2.43)</td>
</tr>
<tr>
<td>Maternal age</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.00 (0.31-3.26)</td>
<td>1.00 (0.31-3.26)</td>
<td>1.00 (0.31-3.26)</td>
<td>1.00 (0.31-3.26)</td>
</tr>
</tbody>
</table>

**Table 2. Associations of First Trimester Exposure to Combination Antiretroviral (ARV) Regimens Including Protease Inhibitors (PI), Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs), and 3 Reverse Transcriptase Inhibitors (RTIs) With Preterm Birth and Small for Gestational Age (<1500g)**

- n=748 women with 1st trimester ART exposure
- PTD in 155/748 (21%)

**ART Dosing and PK in Pregnancy**

- Cardiac output increase (4-6 L/m)
  - 40% increase in plasma volume
    - Increase in volume of distribution leads to lower plasma drug concentrations
  - Increased portal vein flow rate and renal glomerular filtration rate
    - Speeds drug elimination and excretion
  - Changes in hepatic enzyme activity
    - Increases in CYP1A2, CYP2D6
    - Decrease in CYP3A4, CYP2C19
  - Placental drug transporters (P-gp)
Pharmacokinetics of elvitegravir/cobicistat in Pregnancy

- N=30 pregnant women prescribed evg/c/tdf/ftc QD
- Compared to postpartum levels 0-24 hours post dose:
  - AUC 24% lower in 2nd trimester
  - AUC 59% lower in 3rd trimester

Optimizing ART Management in Pregnancy

- Support ART adherence
- Address comorbidities
  - HBV/HCV
  - Drug Use
  - Mental Health
- Assess support network
- Discuss postpartum infant care and HIV care retention

Perinatal HIV Resources

1. NIH AIDS INFO Perinatal HIV Guidelines
   aidsinfo.nih.gov
2. Perinatal HIV Consultation Service (UCSF)
   1-888-448-8765
3. Repro ID HIV Listserv
4. Your local team: OB/GYN/MFM + Pediatrics
Current US Perinatal ART Guidelines

- **NRTI:** TDF/FTC or ABC/3TC
- **Protease Inhibitors:** Atazanavir/r or Darunavir/r
- **Integrase Inhibitors:**
  - RAL or DTG after 14 weeks

**Recommended**
- PI boosted with cobicistat
- Elvitegravir/cobicistat

**Not Recommended**
- Nelfinavir or Tipranavir
- Ritonavir

Research Questions

- Safety and efficacy data on newer ART
  - Tenofovir alafenamide (TAF), Bictegravir (BIC)
- Pharmacologic studies to inform dosing
- Postpartum Retention in Care
- Breastfeeding in Women with HIV
- Long term Pediatric Outcomes (HEU)
- Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC)

Conclusions

- PMTCT is one of the great success stories of the HIV epidemic.
- Clinical trials are needed to identify ART outcomes in pregnancy.
  - Prospective ART registries are useful to look at rare outcomes.
  - Women of reproductive age warrant access to well-designed clinical trials.
- Supporting sexual health in women with HIV includes an ongoing discussion of contraception preferences, fertility desires, and the risks and benefits of various ART regimens.
- Thoughtful collaboration and communication with colleagues in Obstetrics and Gynecology/Maternal Fetal Medicine and Pediatrics is key to achieving optimal perinatal HIV outcomes.
Acknowledgements
UAB Division of Infectious Diseases
1917 HIV Clinic
Center for Women’s Reproductive Health

Jeanne Marrazzo, MD MPH
Asha V. Trin, MD PhD
James Raper, CRNP PhD
Karen Fry, CRNP
Cecilia Ikuya, MD MPH

Cameroon Health Initiative (CHI UAB)

Funding
NIH NICHD
K23 HD099865

Contact Information
jdionne@uabmc.edu

Question-and-Answer