Antiretroviral Therapy and Pregnancy in 2019: Current Recommendations and Controversies

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Learning Objectives
After attending this presentation, learners will be able to:
• Describe the current state of perinatal transmission of HIV infection
• Discuss current recommendations regarding the use of antiretroviral therapy (ART) regimens in pregnant women or those desiring pregnancy
• Describe current recommendations for preexposure prophylaxis (PrEP) in pregnancy and breastfeeding

Financial Relationships With Commercial Entities
Dr Anderson's spouse holds stock or stock options in Gilead Sciences, Inc. (Updated 11/21/19)
ARS Question #1

• A 24-year-old woman presents at 7 weeks gestational age on DTG/3TC/ABC. Her CD4 count is 430 cells/µL and HIV-RNA is <20 copies/ml. She is tolerating this regimen well. After appropriate counseling, which of the following is the most appropriate management of her ART during pregnancy?

A. Continue her current regimen
B. Stop all ARVs until 14 wks gestation and then restart current regimen
C. Change to BIC/FTC/TAF
D. Change to EVG/COBI/FTC/TDF

ARS Question #2

• A 36-year-old woman presents at 24 week gestational age with a new diagnosis of HIV. Her CD4 count is 246 cells/µL and HIV-RNA is 21,000 copies/ml. She is also found to be HBsAg+. Which would be the most appropriate regimen to start?

A. EVG/COBI/FTC/TDF
B. DTG/ABC/3TC
C. DTG + TDF/FTC
D. BIC/TAF/FTC

ARS Question #3

• A 34 year old is in her 2nd pregnancy. She delivered her first infant in Zambia 4 years ago and did not breastfeed because of her HIV diagnosis. She states that she never bonded with him and states her intention to breastfeed after this pregnancy. She is currently on TDF/FTC + ATV/r. Which of the following should you consider?

A. Tell her she cannot breastfeed her infant and threaten to call Child Protective Services
B. Counsel that BF is not recommended and offer only formula as option
C. Discuss importance of continuous viral suppression throughout pregnancy and BF
D. Recommend that breastmilk be mixed with formula to reduce risk
Change in MTCT in Resource-Rich Countries

Perinatal Cascade: 2005-2014

<table>
<thead>
<tr>
<th>Event</th>
<th>HIV Exposed/Uninfected</th>
<th>HIV-Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal HIV dx before pregnancy</td>
<td>75-82%</td>
<td>~50%</td>
</tr>
<tr>
<td>Maternal HIV dx after delivery</td>
<td>≤10%</td>
<td>21-29%</td>
</tr>
<tr>
<td>Breastfed</td>
<td>1.5%</td>
<td>10%</td>
</tr>
<tr>
<td>Intrapartum ARVs</td>
<td>80-95%</td>
<td>50-62%</td>
</tr>
<tr>
<td>Elective C-section</td>
<td>40%</td>
<td>20-40%</td>
</tr>
<tr>
<td>Neonatal ARVs</td>
<td>93-95%</td>
<td>67-92%</td>
</tr>
<tr>
<td>Prenatal ARVs</td>
<td>86-95%</td>
<td>40-52%</td>
</tr>
<tr>
<td>No/inadequate prenatal care</td>
<td>21-31%</td>
<td>46-58% (no PNC 11%)</td>
</tr>
<tr>
<td>Overall prenatal HIV testing rate</td>
<td>Has not exceeded 76% since 2005</td>
<td></td>
</tr>
</tbody>
</table>

Nesheim et al. Pediatr Infect Dis J 2019; 38:611
**Rating Scheme for Recommendations**

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
</tr>
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<tbody>
<tr>
<td>A: Strong</td>
<td>I: One or more RCTs with clinical outcomes and/or validated lab endpoints</td>
</tr>
<tr>
<td>B: Moderate</td>
<td>II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes</td>
</tr>
<tr>
<td>C: Optional</td>
<td>III: Expert opinion</td>
</tr>
</tbody>
</table>

**General Principles for the Use of ARVs in Pregnancy**

- ART is recommended for all pregnant women to prevent perinatal transmission and to optimize the health of the mother (AI)
  - Perinatal transmission is directly related to HIV viral load
    - Undetectable VL (<50 c/mL) at time of delivery associated with 0.09% transmission (UK/Ireland Townsend 2014)
  - Early initiation of ART increases viral suppression by time of delivery and further reduces risk of transmission
    - French Perinatal Cohort: with NDVL at delivery: 0% transmission with preconception ART, 0.2% with 1st trimester, 0.5% with 2nd trimester, 0.9% with 3rd trimester (Mandelbrot 2015)
- HIV drug resistance tests should be performed but ART initiation should not be delayed while waiting for results (AII)
- ARV drugs further reduce transmission risk through infant pre- and post-exposure prophylaxis

- Choice of ART regimen should be informed by current adult treatment guidelines but there are special considerations in pregnancy:
  - Risk of birth defects or other adverse pregnancy outcomes
  - Availability of pregnancy-specific pharmacokinetic data
  - Maternal factors (e.g., nausea/vomiting, comorbid conditions)
- Women who become pregnant on ART should continue their regimen during pregnancy, provided the regimen is safe, effective in suppressing viral replication and tolerated (AII)
  - Drugs not recommended due to toxicity (e.g., d4T, ddi) should be stopped and women switched to another ART regimen (AIII)
  - EVG/COBI, ATV/COBI, DRV/COBI regimens: consider switching due to PK concerns in 2nd/3rd trimester (BIII)
Lack of Viral Suppression in Pregnancy

- HIV Outpatient Study (2005-2013): 28% of women had HIV RNA >500 c/ml at end of pregnancy
- Adherence issues: systematic review/meta-analysis: 73.5% pregnant women had >80% adherence (Nachega 2012)
- Pharmacologic issues/food requirements
- Treatment interruption
- Inadequate time on ART
- ART resistance
- Perinatally infected
- Acute infection
- Associated with higher viral load and lower likelihood of diagnosis
- May represent significant proportion of residual perinatal transmission in US (Hedegaard et al 2013)
- Maintain high level of suspicion with clinical sx/sx—obtain plasma HIV-RNA
- 3rd trimester repeat screening

Integrase Strand Transfer Inhibitors (InSTIs) and Neural Tube Defects

Birth Defect Surveillance Uganda – Neural Tube Defects
Barlow-Mihigo et al. CROI 2019, Seattle Abs. 743

- 4 hospital defect surveillance: 69,766 births (6,494 to HIV+ women, 80% on TDF-3TC-EFV (no DTG used in country yet)

<table>
<thead>
<tr>
<th>HIV-</th>
<th>HIV+</th>
<th>NTD% births HIV- women</th>
<th>NTD% births HIV+ women</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTD</td>
<td>71</td>
<td>66</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.11% (0.08-0.13)</td>
<td>0.07% (0.03-0.17)</td>
</tr>
</tbody>
</table>

Tsepamo NTD prevalence:
- HIV- women: 0.09% (95% CI 0.07-0.12%)
- HIV+ EFV preconception: 0.05% (95% CI 0.02-0.15%)

Phenotypes of the 71 NTD:
- Spina Bifida: 41 (58%)
- Anencephaly: 19
- Encephalocele: 12
**Merck Review of Raltegravir-Exposed Pregnancies**

- Merck review of database on 2426 pregnancies with RAL exposure, including data from:
  - Merck safety database, including APR
  - UK/Ireland National Surveillance HIV in Pregnancy and Childbirth (NSHPC)
  - French Perinatal Cohort (includes data from abstract 774)
- Prospective: 1991 cases, with 456 periconception RAL: no NTD
- Retrospective: 435 retrospective reports (no denominator), 4 NTD cases → 1 with periconception exposure; also 1 encephalocele with periconception exposure (APR)
- NSHPC (Rasi V et al. JAIDS 2018 Nov 20) reported on 33 EVG exposures → 26 preconception → no birth defects

**Dolutegravir in Pregnancy**

- Use at conception:
  - May 2018: unplanned interim analysis of observational surveillance study of pregnant women on ART in Botswana: 4/426 (0.94%) NTD among women who conceived on DTG-based regimen (Zash et al. NEJM 2018)
  - July 2019: update – DTG exposure at conception associated with slightly higher rate of NTDs, compared to other types of ARV exposure (3/1000 deliveries vs 1/1000 deliveries) (Zash et al NEJM 2019)
- DTG started in pregnancy: (Zash. Lancet Global Health 2018;6:e804)
  - 1st trimester >4-6 wk GA: 0/280 birth defects
  - 2nd, 3rd trimester: 0/729 birth defects


- DTG is a preferred INSTI for ART-naïve women irrespective of trimester
  - For pregnant women receiving DTG and present to care in 1st trimester, counsel about risks/benefits of continuing DTG vs switch to alternative regimen. In most cases, continuation of DTG is recommended (AIII)
    - NTDs may have already occurred
    - Additional risk of NTD may be small, depending on current GA
    - Background risk of NTD (0.06% in US)
    - Changes in ART, even in 1st trimester, may increase risk of viral rebound
  - DTG +TDF/FTC is recommended with acute HIV in pregnancy
  - DTG is an alternative agent for women trying to conceive

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New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
Antiretroviral Pregnancy Registry (APR): Integrase Inhibitors (InSTI) and Neural Tube Defects (NTD)
Albano J et al. CROI 2019 Seattle, WA Abs. 747

- Evaluation of the prevalence of NTD with InSTI exposure in prospective and retrospective components of the APR (through 31 Jul 2018).
- Prospective APR - primary analysis: Clinicians register pregnant women (no identifiers) with prenatal ARV exposures before pregnancy outcome is known, report data on exposure throughout pregnancy, and provide birth outcome data.
- Retrospective APR - secondary review: Reports of exposed pregnancies after pregnancy outcome is known; no denominator.

APR reports come from North America (75%), Europe (8%), Africa (7%), South America (6%) and Asia (4%).

Through 31 Jul 2018: includes 20,044 pregnancies with 20,413 fetal outcomes including 19,005 live births.

- Through 31 Jul 2018: includes 1,193 live births with InSTI exposure at any time in pregnancy, 604 periconceptional exposure, including 174 DTL, 186 EVG, 244 RAL.
- 2 CNS defect cases were reported with InSTI exposure at any time (both DTV, one 1st trimester, one 2nd/3rd trimester).
- There were no NTD among prospective cases for any InSTI drug.

<table>
<thead>
<tr>
<th>Earliest Trimester of Exposure – Prospective Cases</th>
<th>Periconception</th>
<th>1st Trimester</th>
<th>2nd/3rd Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defects/live birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defects/live birth</td>
<td>16/604 (2.6%)</td>
<td>4/135 (3.0%)</td>
<td>17/452 (3.8%)</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>6/174 (3.4%)</td>
<td>2/55 (3.6%)</td>
<td>4/137 (2.9%)</td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>5/186 (2.7%)</td>
<td>0/27 (0%)</td>
<td>0/57 (0%)</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>5/244 (2.0%)</td>
<td>4/68 (5.9%)</td>
<td>13/290 (4.5%)</td>
</tr>
</tbody>
</table>

Can be more than one organ system for a defect.
No Neural Tube Defects
CNS: 2: 1 (lissencephaly – neural migration disorder) with preconception DTV; 1 (ventriculomegaly) with 2nd/3rd trimester DTG exposure.
Face, ear, face, neck: 2
Cleft lip/palate: 2
Respiratory: 1
Cardiac/circulatory: 11
Lower GI: 1
Renal: 4
Musculoskeletal: 8
Chromosome abnl: 2
Other organ systems: 1
Specified syndromes 1
Integrase Inhibitors (InSTIs)

- Rapid viral decay after initiation (approx. 2 log reduction in VL by wk 2-RAL in naïve pts) and good placental passage
- Acute infection-InSTI associated with shorter time to viral suppression than PI-based regimen (median 12 vs 24 wk) (Hoenigl 2016)
- Use of an InSTI-based regimen has been suggested in late pregnancy in the following circumstances:
  - Women presenting late and not on ART, especially with high VL
  - As part of new regimen for women on failing regimen—consider after review of treatment history and resistance testing
  - Women on failing regimen with high VL or incomplete suppression as 4th ARV
- Efficacy and safety of this approach have NOT been evaluated in clinical trials
- If failing regimen, intensification with addition of single agent may risk loss of future effectiveness

Randomized Trial of RAL vs EFV-Based ART
Started in Late Pregnancy: IMPAACT P1081
Mirochnick M et al.  CROI, 2019 Seattle Abs. 39LB

- Randomized trial of RAL+2NRTI vs EFV+2NRTI in 408 pregnant ART-naïve women S America, Africa, Thailand and US presenting to ANC at ≥28-36 weeks (later expanded to ≥20 weeks) gestation.
  - Primary endpoint is virologic response (VL <200) at delivery.
- EFV + 2 NRTI
- RAL + 2 NRTI
- Median Time to VL <200 copies/mL:
  - RAL: 8 days
  - EFV: 15 days

- VL decline was greater in raltegravir arm than efavirenz arm at study weeks 2, 4 and 6.
- Both regimens well-tolerated; no difference AE, stillbirth, preterm.
- 1 raltegravir and 6 efavirenz infants were infected (p=0.06).
DTG vs EFV When Starting ART in Late Pregnancy

- Randomized trial of DTG+2NRTI vs EFV+2NRTI in 268 pregnant ART-naive women presenting to antenatal clinic at ≥28-36 weeks gestation in Kampala and Cape Town.
- Primary endpoint is virologic response (VL <50) at delivery.

Analysis at delivery (ITT): 122 DTG, 115 EFV
- Median gestation age at enrollment, 31 weeks
- No difference in baseline VL (median 4.4 log), CD4 (median 445), prior obstetric history, gestation, BMI

- Open-label randomized trial of DTG+2NRTI vs EFV+2NRTI in 268 pregnant ART-naive women presenting to antenatal clinic at ≥28-36 weeks gestation in Kampala and Cape Town.

More Rapid VL Decline with Dolutegravir than Efavirenz

- Primary outcome - Time on medication before delivery, median 55 days

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Delogetavir</th>
<th>Efavirenz</th>
<th>aRR DTG vs EFV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL &lt;50</td>
<td>73.8% (90/122)</td>
<td>42.6% (49/115)</td>
<td>1.66 (1.2, 2.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VL &lt;1000</td>
<td>92.6% (113/122)</td>
<td>82.6% (95/115)</td>
<td>1.11 (1.0, 1.2)</td>
<td>0.0513</td>
</tr>
</tbody>
</table>

- Adjusted for age, country, VL (<> 100,000), CD4 (<200), GA at start ART

Pharmacokinetics in Pregnancy

- EVG/COBI: lower drug levels in 3rd trimester [P1026]; only 74% of women maintained viral suppression at delivery
- DRV/COBI: low drug levels in late pregnancy and high rates of virologic failure in late pregnancy; once daily dosing of DRV not recommended in pregnancy
- ATV/COBI: PK data not yet available, but anticipated to be similar to DRV/COBI
- LPV/r: dose adjustment recommended in 2/3 trimester
- ATV/r: consider dose adjustment in 2/3 trimester
**Initial ART Regimens for ARV-Naïve Pregnant Women (December 2019)**

**Preferred NRTI backbone:** ABC/3TC or TDF/FTC or TDF/3TC

**INSTI:** DTG/ABC/3TC or DTG + preferred 2-NRTI backbone; or BIL + preferred 2-NRTI backbone

**PI:** ATV/r + preferred 2-NRTI backbone or DRV/r + preferred 2-NRTI backbone

**Alternative NRTI backbone:** ZDV/3TC

**PI:** LPV/r + preferred 2-NRTI backbone

**NNRTI:** EFV/TDF/FTC or EFV/TDF/3TC or EFV + preferred 2-NRTI backbone; or RPV/TDF/FTC or RPV + preferred 2-NRTI backbone

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**Initial ART Regimens for ARV-Naïve Pregnant Women**

**Insufficient Data**

- BIC/TAF/FTC; DOR; IBA; TAF/FTC; RPV/TAF/FTC

**Do Not Use**

- Not recommended in pregnancy due to concerns about maternal or fetal safety or inferior efficacy:
  - ATV/COBI; DRV/COBI; DRV/COBI/FTC/TAF
  - EVG/COBI/FTC/TDF; EVG/COBI/FTC/TAF

**Not recommended in ARV-naïve pregnant women due to limited data on PK, safety and efficacy:**

- MVC; ETR; NVP (potential for adverse events, low resistance barrier); T20

**Not recommended in pregnancy:**

- ddI; d4T; FPV; FPV/r; IDV; IDV/r; NFV; RTV; SQV; SQV/r; TPV; TPV/r; DTG/RPV; ABC/3TC/ZDV

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**Table 7. Situation-specific Recommendations for Use of Antiretroviral Drugs in Pregnant Women and Nonpregnant Women Who Are Trying to Conceive**

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New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
USPHS Perinatal Guidelines: Breastfeeding

- Breastfeeding is NOT RECOMMENDED for women living with HIV in US (AII)
- However, women who have questions about breastfeeding or a desire to breastfeed should receive patient-centered, evidence-based counseling on infant feeding options (AII)
- When a woman with HIV chooses to breastfeed after counseling, a harm-reduction approach should be taken to help minimize the risk of HIV transmission to their infant.
Why is breastfeeding (BF) not recommended in US?

- Maternal ART reduces but does not fully eliminate the risk of HIV transmission via breastmilk
- Safe and affordable infant feeding alternatives and safe water are readily available
- Little safety data on most modern ART regimens during breastfeeding.
- Potential differential diffusion of ARV drugs into breast milk, so that infant may be exposed to incomplete regimen, which could increase risk of resistance if transmission occurs
- U=U: BF represents an area of uncertainty
- In PROMISE study there were 2 postnatal transmissions in BF women with undetectable HIV-RNA

Why would a woman with HIV want to breastfeed?

- Women from some areas of the US may face challenges that are similar to women in developing countries: cost limits access to formula, inadequate quantities of formula, lack of access to clean water
- May face environmental, social, familial and personal pressure to consider breastfeeding.
- Patients will often cite not wanting to disclose their HIV status to their families that may be closely interacting with them following delivery
- There may be safety concerns for interpersonal violence if HIV status is disclosed to close relatives or extended family or partners.
- Increasing number of immigrants living with HIV from countries where HIV stigma is greater and cultural expectations are to breastfeed

Non-judgmental counseling is key

- Offer joint problem solving and shared decision making
- Recommended harm-reduction measures:
  - Demonstrate maternal engagement in care during pregnancy and throughout breastfeeding.
  - Document consistent viral suppression prior to delivery and throughout breastfeeding.
  - Breastfeeding exclusively for up to 6 months postpartum, followed by breastfeeding in combination with the introduction of complementary foods.
  - Developing a plan for weaning with input from the family and providers. Rapid weaning over a few days is not recommended.
  - Neonatal prophylaxis: ZDV +/- NVP for 6 weeks
  - Promptly identify and treat maternal mastitis and infant thrush
  - Monitor the infant for HIV acquisition via breastfeeding
  - If infant transmission does occur, it is critical to immediately start fully suppressive ART regimen and perform resistance testing
PrEP in Pregnancy or Breastfeeding

- Pregnancy is associated with an increased risk of HIV acquisition
- Women whose partners have HIV infection with sustained VL suppression are at effectively no risk for sexual acquisition of HIV
- Clinicians providing preconception or pregnancy care to women whose partners have HIV may not have access to partner’s medical records documenting viral suppression
- HIV testing should be offered to partners of women receiving preconception or pregnancy care when their HIV status is unknown
- TDF/FTC used extensively in pregnancy in setting of HIV and no evidence of adverse effects; recommended by WHO for all pregnant/BF women with HIV in low resource areas
- Use of PrEP for HIV-uninfected but at risk pregnant or breastfeeding US women is recommended after appropriate counseling
- TAF/FTC not recommended at this time in pregnancy or BF

Postpartum Considerations

- Only 37–39% of postpartum women are retained in care (Rana 2010; Adams 2015)
- Systematic review and meta-analysis estimated adequate adherence (>80%) in pregnancy but only 53% postpartum (Nachega 2012)
- Viral suppression achieved by 30–61% of postpartum women (Adams 2015; Sha 2011)
- South Africa (n= n=) after viral suppression in pregnancy, VL obtained over a total of 4,850 woman-months (wm) of observation postpartum
- May consider simplification of ART regimen postpartum
- Remember potential drug-drug interactions with hormonal contraception

Summary

- Elimination of perinatal transmission is within reach, but...There remain missed opportunities to identify HIV infection in pregnant women and treat appropriately
- The strongest predictor of prevention of perinatal transmission is viral load suppression
- DTV is a preferred INSTI for ART-naïve women irrespective of trimester
- There may be a role of INSTIs in women presenting in late pregnancy to lower viral load more rapidly
- Several ARV agents have lower blood levels in 2nd/3rd trimesters with consideration to increase dose or increase frequency of VL monitoring
- The postpartum period is a time of special risk for nonadherence to ART and to care
For Further (and Ongoing) Guidance

• DHHS Clinical HIV Guidelines: aidsinfo.nih.gov: Perinatal Guidelines—these are updated regularly and recommendations may change as more data becomes available

• National Perinatal HIV Hotline/Clinician Consultation Center: (888)448-8765—for consultation 24 hr/7 days per week

Question-and-Answer Period