Preventing Vertical transmission: pharmacotherapy considerations for pregnant women

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- This slide set has been peer-reviewed to ensure that there are no conflicts of interest represented in the presentation.
Objectives

1. Describe the current guideline recommendations for management of ARV therapy during pregnancy and at birth

2. Discuss literature regarding efficacy and safety of ARV interventions to reduce perinatal HIV transmission

3. Describe clinical management of pregnant patients ARV therapy to reduce perinatal HIV transmission
INTRODUCTION
Epidemiology

- At the end of 2013, ~1.2 million persons 13+ were living with HIV infection in the US
  - including ~161,200 (13%) persons whose infections had not been diagnosed
- In 2015: There were 39,513 new HIV diagnoses in the United States
  - 31,991 adult and adolescent males (13+)
  - 7,402 adult and adolescent females
  - 120 children < 13 years

Modes of transmission

- Blood
- Semen
- Vaginal and cervical secretions
- Breast milk
- Outside of the body, HIV is very fragile and dies very quickly
  - Feces, nasal secretions, saliva, sputum, sweat, tears, urine, and vomitus are not considered infectious unless they are visibly bloody
There were 86 children diagnosed with HIV from the perinatal route in the US in 2015

<table>
<thead>
<tr>
<th>Race</th>
<th>American Indian/Alaskan</th>
<th>Asian</th>
<th>Black/African American</th>
<th>Hispanic/Latino</th>
<th>White</th>
<th>Multiple Races</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of perinatal infections</td>
<td>2</td>
<td>4</td>
<td>54</td>
<td>10</td>
<td>11</td>
<td>5</td>
</tr>
</tbody>
</table>
Vertical transmission

- Mother-to-child transmission of HIV (MTCT) is the transmission of HIV from an infected mother to her baby during pregnancy, labor/delivery and breastfeeding
- Also known as “vertical transmission” or “perinatal transmission”
- Most children with HIV acquired the virus through MTCT
Brief historical milestones MTCT

- In 1994 the USPHS recommend the use of zidovudine to reduce perinatal transmission (after “076” trial results)
- In 1997, combination ARV and elective C-section* recommended
  *Although no longer required if virally suppressed
- In 1999, opt-OUT HIV testing for pregnant women
Approx 187,157 HIV-infected women gave birth
Approx 21,003 infants were prenatally infected
  - Peaked in 1991, declined steadily after 1993
In the United States, there are approximately 8500 women living with HIV who give birth annually
Rate of HIV infection among children is declining in the US

Table 7a. Diagnoses of HIV infection among children aged <13 years, by race/ethnicity, 2010–2015—United States

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Rate</td>
<td>No.</td>
<td>Rate</td>
<td>No.</td>
<td>Rate</td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.2</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>0.1</td>
<td>9</td>
<td>0.4</td>
<td>12</td>
<td>0.5</td>
</tr>
<tr>
<td>Black/African American</td>
<td>149</td>
<td>2.0</td>
<td>119</td>
<td>1.6</td>
<td>168</td>
<td>2.3</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>37</td>
<td>0.3</td>
<td>23</td>
<td>0.2</td>
<td>17</td>
<td>0.1</td>
</tr>
<tr>
<td>Native Hawaiian/Other Pacific Islander</td>
<td>1</td>
<td>1.0</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>White</td>
<td>32</td>
<td>0.1</td>
<td>36</td>
<td>0.1</td>
<td>33</td>
<td>0.1</td>
</tr>
<tr>
<td>Multiple races</td>
<td>15</td>
<td>0.7</td>
<td>13</td>
<td>0.6</td>
<td>11</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>236</strong></td>
<td><strong>0.4</strong></td>
<td><strong>201</strong></td>
<td><strong>0.4</strong></td>
<td><strong>242</strong></td>
<td><strong>0.5</strong></td>
</tr>
</tbody>
</table>

*Note:* Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis. Data for the year 2015 are preliminary (subject to change) because they are based on only a 6-month reporting delay. Data for the year 2015 should not be used when assessing trends. Numbers less than 12, and rates and trends based on these numbers, should be interpreted with caution.

* Rates are per 100,000 population.

* Hispanics/Latinos can be of any race.*
How does transmission occur?

- For an HIV-positive woman not taking HIV medications, chance of passing the virus to her child:
  - Range of 15 to 45% during pregnancy, labor and delivery
  - Breastfeeding carries an additional 35 to 40% chance of transmission
Current strategies in the US

- Treatment with ART to control the virus and make it undetectable (Pregnancy)
- Cesarean delivery (Labor and delivery)
- Avoidance of breastfeeding (Breastfeeding)
CURRENT GUIDELINE RECOMMENDATIONS FOR MANAGEMENT OF ARV THERAPY DURING PREGNANCY AND AT BIRTH
# Guideline recommendations ABCs

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Quality of Evidence for Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Strong recommendation for the statement</td>
<td>I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints</td>
</tr>
<tr>
<td>B: Moderate recommendation for the statement</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 recommendation for the statement</td>
<td>III: Expert opinion</td>
</tr>
</tbody>
</table>
Preconception counseling and care for HIV-Infected women of childbearing age

- Discuss childbearing on an ongoing basis (if age approp)
- Provide info about contraceptive methods (AI)
- All HIV-infected women contemplating pregnancy should be receiving antiretroviral therapy
  - viral load below the limit of detection prior to conception (AII)
PrEP for serodiscordant partner?

- Administration PrEP for 30 days before and 30 days after conception for HIV-uninfected partners may offer additional protection (BII)
  - It is not known whether PrEP confers additional benefit when the partner is virally suppressed
General principles regarding use of ARV drugs during pregnancy

- All pregnant HIV-infected women should receive ART ASAP (AI)
- Maternal antepartum and intrapartum (ARV) treatment/prophylaxis is needed as well as infant ARV prophylaxis (AI)
- Adherence to ARV should be emphasized (AII)
Antiretroviral pregnancy registry

- All cases of antiretroviral (ARV) drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see http://www.APRegistry.com) (AIII).

- Based on the preponderance of studies indicating no difference in rates of birth defects for first-trimester compared with later ARV exposures, women can be counseled that antiretroviral therapy during pregnancy generally does not increase the risk of birth defects. (BIII).
Patients on ART prior to pregnancy

- If virally suppressed, continue regimen
  - **UNLESS** it contains didanosine, stavudine, or treatment-dose ritonavir
    - These regimens should initiate a change in therapy
  - Although FDA recommends efavirenz to be avoided, studies in humans have not reproduced the neuro-tube defects seen in animal studies
In the case of lack of viral suppression

- Suppression of HIV RNA to undetectable levels should be achieved as rapidly as possible
- If an ultrasensitive HIV RNA assay indicates failure of viral suppression (after an adequate period of treatment):
  - Assess adherence and resistance
  - Consult an HIV treatment expert and consider possible antiretroviral regimen modification
- Scheduled cesarean delivery is recommended for women who have HIV RNA levels >1,000 copies/mL near the time of delivery (AII)
Antiretroviral (ARV) drug regimen for a pregnant woman

- Multiple factors must be considered when choosing regimen including:
  - Potential teratogenic effects and other short-and long-term adverse effects on fetuses or newborns including preterm birth, mutagenicicty, and carcinogenicity.
  - Experience with use in pregnancy
  - Drug-drug interactions
  - Genotypic resistance testing and prior ART use
  - PK changes in pregnancy
  - Potential maternal adverse effects
  - Comorbidities
  - Convenience

Considerations when designing a regimen

- Transplacental passage of ARV drugs is an important mechanism of infant pre-exposure prophylaxis.
  - At least one NRTI agent with high placental transfer should be included as a component of the ART regimen.
    - TDF, 3TC, FTC, ABC (all preferred with high placental transfer)
    - Zidovudine (AZT) has high placental transfer.
Preferred regimens

- 2 NRTI Backbone Plus
  - Raltegravir
  - Or
  - Darunavir/r (must be BID due to PK changes)
    - Or
  - Atazanavir/r
Preferred NRTIs

- Abacavir, Emtricitabine, Lamivudine and Tenofovir disoproxil fumarate
  - No changes to dosing recommended

- Tenofovir Alafenamide has no PK studies in pregnancy and thus dosing recommendations do not exist
Atazanavir

- Must be boosted 300 mg dose, ritonavir is preferred (cobicistat does not have data in pregnancy)
- Not recommended in tx-experienced taking TDF and H2 blockers
- Dosing may need to be increased in 2nd/3rd trimester if patient is ARV-experienced and taking either TDF or H2
Darunavir

- Must be boosted with ritonavir (cobicistat does not have data in pregnancy)
- Twice daily dosing with 600 mg DRV plus 100 mg RTV
  - The higher dose of 800 mg qd or bid is not recommended
Raltegravir

- Dosing does not change throughout pregnancy
  - 400 mg bid without regard to food
Antiretroviral drug resistance and resistance testing in pregnancy

- Drug-resistance studies before starting or modifying ARV in all ARV-naive pregnant women with HIV RNA >500 to 1,000 copies/mL
  - unless they have already been tested for ARV resistance
- ART should be initiated in pregnant women prior to receiving results of ARV-resistance studies. (Don’t wait!)
- Zidovudine resistance does not affect the indications for use of intrapartum zidovudine (BIII)
- Consultation with a pediatric HIV specialist is needed if virus is resistant

Monitoring of the HIV/CD4 counts during pregnancy

- Plasma HIV RNA levels should be monitored:
  - initial visit
  - 2 to 4 weeks after initiating (or changing) ART
  - monthly until RNA levels are undetectable
  - at least every 3 months during pregnancy
  - approx 34 to 36 weeks’ gestation

- CD4 count should be monitored
  - at the initial antenatal visit (AI)
  - every 3 to 6 months during pregnancy
    - can be performed every 6 months in patients on combination antiretroviral therapy (ART) with consistently suppressed viral load who have CD4 counts well above the threshold for opportunistic infection risk (CIII)
Intrapartum Antiretroviral Therapy/Prophylaxis

- Women should continue (ART) drug regimen on schedule as much as possible during labor and before scheduled cesarean delivery (AIII)
- Zidovudine (IV) should be administered to HIV-infected women
  - W/ HIV RNA >1,000 copies/mL (or unknown HIV RNA) near delivery (AI)
  - Scheduled cesarean delivery at 38 wks’ gestation is recommended for women who have HIV RNA >1,000 copies/mL near delivery (AI)
- Women who present in labor with unknown HIV status should undergo expedited antigen/antibody HIV testing (AII)

Zidovudine intrapartum

- Not required for women on ART with HIV RNA <1000 copies/mL in late pregnancy and/or near delivery
  - As long as no concern about adherence
- IV zidovudine administration should begin 3 hrs before the scheduled operative delivery
  - Loading dose: 2 mg/kg followed by a continuous IV infusion of 1 mg/kg/hour until delivery

Postpartum Care

- ART should be continued
- Immediate postpartum period poses unique challenges to adherence, arrangements for new or continued supportive services should be made before hospital discharge (AII)
- Contraceptive counseling is a critical aspect of postpartum care (AIII)
- Breastfeeding is not recommended for HIV-infected women in the United States (AII)
Infant Antiretroviral Prophylaxis

- All HIV-exposed infants should receive ART pref. w/in 6 to 12 hrs of delivery (AII)

- A 4-wk neonatal zidovudine prophylaxis regimen can be used for full-term infants
  - 6-wk course as part of a combo infant prophylaxis (if mother has not sustained viral suppression or maternal adherence concerns)

- Combination infant prophylaxis regimen is recommended in infants at higher risk:
  - Have not received antepartum or intrapartum ARV drugs (AI)
  - Have received only intrapartum ARV drugs (AI)
  - Have received antepartum ARV drugs but lack viral suppression near delivery (BIII)

- Use of ARV drugs other than zidovudine and nevirapine cannot be recommended in premature infants as prophylaxis bc of lack of dosing and safety data (BIII)
DISCUSS LITERATURE REGARDING EFFICACY AND SAFETY OF ARV INTERVENTIONS TO REDUCE PERINATAL HIV TRANSMISSION
Efficacy of ART in preventing MTCT

- With the implementation of the universal prenatal recommendations the rate of perinatal transmission of HIV has declined to 2% or less in the US and Europe.
- Combination ART can reduce MTCT to < 1%.
Transmission from women on ART for at least the last 14 days of pregnancy was 0.8% (40/4864, 95% CI: 0.6–1.1%), regardless of type of therapy or mode of delivery.

- Included monotherapy (AZT) and HAART combos

- The overall transmission rate was 1.2%
Earlier initiation of ART and further decline in mother-to-child HIV transmission rates, 2000–2011

- Population-based surveillance data on diagnosed HIV-positive women and their infants in UK and Ireland
- 12,486 infants, with 11,515 infants HIV status available
- MTCT declined:
  - 2.1% (17/816) in 2000–2001
  - 0.46% (9/1975) in 2010–2011
- More people in the 2010-2011 years were receiving combination ART (96% vs. 82%)
### Viral load nearest to delivery and risk

<table>
<thead>
<tr>
<th>HIV RNA Viral Load (n=4783)</th>
<th>Total (N)</th>
<th>Infected (n)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>3859</td>
<td>2</td>
<td>0.05</td>
</tr>
<tr>
<td>50-399</td>
<td>655</td>
<td>7</td>
<td>1.1</td>
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<tr>
<td>400-999</td>
<td>104</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td>1000-9999</td>
<td>100</td>
<td>3</td>
<td>3.0</td>
</tr>
<tr>
<td>&gt;10,000</td>
<td>65</td>
<td>6</td>
<td>9.2</td>
</tr>
</tbody>
</table>
N= 22

Approaching delivery, 86% of the pts had an undetectable viral load (<50 copies/mL)

3rd trimester AUC was on average lower but not consistently decreased

All infants tested HIV negative

No congenital abnormalities

Three infants (14%) were small for gestational age
Risk for Preterm Delivery

- Conflicting data exists related to this risk
- A large meta-analysis of 11,224 women in 14 European and American studies did not demonstrate an increased rate of PTD among women using ART during pregnancy.

Which is the optimal postnatal-infant prophylaxis (PnP) for “High Risk” infants?

- Recent systematic review
- Multi-drug regimens significantly reduce transmission rates vs. single-drug regimens
  - No significant difference between 2 vs 3 drug regimens
- Two large studies (PHPT-5 and HPTN-040) provide the evidence that multi-drug regimens have superior protection
Summary

- ‘Getting to Zero’ is possible with interventions and HIV status awareness
- Viral suppression is a major factor in preventing MTCT
- ART selection will be similar to non-pregnant (few exceptions)
- ART is safe and effective to prevent MTCT
References


