HIV/AIDS in Pregnancy: A 40-Year Journey and Look to the Future

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Conflict of Interest Statement

- Dr. Delke has no conflict of interest related to the content of this presentation.
Learning Objectives:
1. Review the demographics of HIV infection in the US.
2. Identification of women with HIV infection:
   - Confidentiality
   - Preconception
   - During pregnancy
   - Labor/delivery and/or postpartum
3. Management:
   - Preconception – special considerations
   - Antepartum care
   - Intrapartum care
   - Postpartum care and follow-up including breastfeeding
4. Primary prevention
5. Summary

Past: Where we’ve been
Present: Where we’re now
Future: Goals and Challenges

Rounding on AIDS Ward, NIH Clinical Center, Early 1980s

Median survival of AIDS patients: ~6-8 months
New HIV Diagnoses Among Women by Transmission Category in the US and Dependent Areas, 2018

- Heterosexual Contact: 85% (6,130)
- Injection Drug Use: 16% (1,049)
- Other*: 1% (41)
HIV Prevention and Care Outcomes

When compared to people overall with HIV, women have about the same viral suppression rates. But more work is needed to increase these rates. In 2018, for every 100 women with HIV:

- 66 received some HIV care
- 51 were retained in care
- 53 were virally suppressed

For comparison, for every 100 people overall with HIV,
- 64 received some HIV care
- 49 were retained in care
- 53 were virally suppressed

 Rank of HIV Diagnosis Rates (All Ages) by State¹

Diagnosed in 2018, United States

<table>
<thead>
<tr>
<th>State</th>
<th>Rate per 100,000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>District of Columbia</td>
<td>29.6</td>
</tr>
<tr>
<td>FLORIDA</td>
<td>24.3</td>
</tr>
<tr>
<td>Nevada</td>
<td>22.1</td>
</tr>
<tr>
<td>Mississippi</td>
<td>16.8</td>
</tr>
<tr>
<td>South Carolina</td>
<td>16.0</td>
</tr>
<tr>
<td>US</td>
<td>14.1</td>
</tr>
</tbody>
</table>

Perinatally Acquired HIV Diagnoses, Born in Florida, 1979–2019

Year of Birth | Number of Diagnoses | Percent change from previous year
--- | --- | ---
1992–1994 | Introduction of cART\(^1\) | 
2015 | 9 | N/A
2016 | 8 | -11%
2017 | 9 | 13%
2018 | 9 | N/A
2019 | 0 | -100%

\(^1\)Combination antiretroviral therapy (cART) is an HIV treatment that suppresses viral load and reduces HIV transmission.

Perinatal HIV Exposures, Born in Florida, 2019

- Pediatric HIV (not AIDS) (N=0)
- Pediatric AIDS (N=0)
Timing of Perinatal HIV Transmission

1/3 Antepartum (in utero)

2/3 Peripartum

1 2 3 Birth

Breast feeding 15%-20% risk

Pediatric AIDS Clinical Trials Group (PACTG)
PACTG 076

A phase III randomized placebo-controlled trial of ZDV for preventing maternal-fetal HIV transmission.

Treatment Regimen
- Antepartum: 100 mg ZDV po 5x day, started at 14–34 weeks gestation
- Intrapartum: During labor, 1-hour initial dose 2 mg/kg IV followed by continuous infusion of 1 mg/kg until delivery
- Postpartum/Infant: 2 mg/kg po q 6 hr for 6 weeks, start 8–12 hours after birth


Antiretroviral Therapy in Pregnancy: Protective Benefits to the Infant

Mechanisms of protection:
- Reduce maternal plasma viral load by using combination antiretroviral therapy (cART)
- Reduce infant in utero exposure
- Reduce genital viral load
  - Reduce infant viral exposure in birth canal
- Drugs crossing the placenta provide infant pre- and post-exposure prophylaxis
Perinatal HIV Transmission

- Breast-feeding populations
  - Overall risk 20-45%
  - Among transmissions –
    - In utero: 15-25%
    - Intra-partum: 35-45%
    - Breast-feeding: up to 40%

- Non-breast-feeding populations
  - Overall risk 15-30%
  - Among transmissions –
    - In utero: 25-40%
    - Intra-partum: 60-75%

Factors Influencing Perinatal HIV Transmission

- Maternal Factors
  - Viral load
    - Newly infected?
      - Very high VL!!!
  - HIV-1 RNA Levels
  - CD4 lymphocyte count
  - Other infections
    - Hepatitis C
    - CMV
    - Genital ulcer
  - Maternal IDU

- Obstetrical Factors
  - Length of ruptured membranes
  - Intra-amniotic infection
  - Vaginal delivery
  - Invasive procedures

- Infant Factors
  - Prematurity

Relative Proportion of HIV-1 Transmission from an Untreated Mother to Her Infant, According to Gestational Period and Mode of Infant Feeding.

Luzuriaga K, Mofenson, LM.
How Important is Maternal Viral Load?

- Maternal HIV-1 RNA Level is strongly correlated with risk of transmission
- HIV-1 RNA level near the time of delivery is an important predictor of transmission even among ARV-treated women
- The threshold, below which transmission does not occur, has not been determined!
- Transmission risks vs. start of ART (independent of viral load)
  - Prior to start of pregnancy: 0.2%
  - 1st trimester: 0.4%
  - 2nd trimester: 0.9%
  - 3rd trimester: 2.02%


Childbearing Women and HIV Infection

- Approximately one in four people living with HIV infection in the United States is a woman
  - Most new HIV infections in women are from heterosexual contact (84%)
  - An estimated 88% of women who are living with HIV knew their diagnosis but only 51% have achieved viral suppression.
- 6,000 to 7,000 women with HIV infection deliver annually
  - Fewer than 200 infants with HIV infection are born in the US each year
  - 40% of infants with HIV infection are born to mothers with unknown HIV status

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network
More pregnant women with HIV infection are receiving ART and entering pregnancy on ART.

“"The good physician treats the disease; the great physician treats the patient who has the disease""

Sir William Osler, MD

Patient-Provider Partnership
Time to HIV detection for various generations of diagnostic tests, relative to times of symptom onset and detection of p24 antigen and HIV RNA.


HIV Diagnostic Testing

- Step 1: 4th generation HIV-1/2 Ag/Ab combo immunoassay (preferred)
- Step 2: HIV-1/HIV-2 antibody differentiation immunoassay
- Step 3: HIV-1 RNA assay

Rapid testing at delivery for women with no PNC or HIV test

- High risk of perinatal HIV transmission in women without prenatal care or prior HIV test
- Rapid testing in labor makes it possible to begin ART prophylaxis and refer mother and neonate for care
- Begin ART prophylaxis ASAP after a positive rapid test (before confirmatory test results are available)

CDC (USPHS) Recommendations for HIV Testing of Pregnant Women

- Prenatal: routine HIV screening for all pregnant women using the "opt out" approach
- Third trimester: repeat screening in areas with elevated HIV infection rates or in high risk situations
- Labor and delivery: Routine rapid testing for women whose HIV status is unknown
- Postnatal: Rapid testing for all infants whose mother's status is unknown

Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-care Settings, CDC MMWR 55(RR14) September 22, 2006

Case 1: Pregnancy Saved My Life
### Preconception Counseling

- Identify risk factors for adverse maternal or perinatal outcomes
- Treat or stabilize where needs are identified
- Discuss HIV in pregnancy
- Perinatal HIV prevention
- General pregnancy considerations
- Contraception (ART effects on hormonal contraception)

### Preconception Counseling

- For those who are actively trying to conceive – We suggest one of the following preferred regimens for individuals actively trying to conceive:
  - Dolutegravir or raltegravir
  - Plus one of the following: Tenofovir disoproxil fumarate-emtricitabine (TDF-FTC), d4T-lamivudine, or TDF-3TC

### Women and HIV: Snapshot

- 19% (7401) of new HIV infections in 2017:
  - 21% decrease since 2008
- 8102 new AIDS diagnoses among women: 25% of diagnoses that year (a decline)
- One quarter of deaths in 2010
- Heterosexual sex most common risk factor (84% of new infections in 2010)
Women and HIV: Snapshot (2)

- Black women highly affected: New infections, living with HIV, and HIV-related deaths in US
- In 2016: 61% of new HIV infections in women occurred in Black women (only 13% of female population)
- HIV incidence higher in Blacks and Latinas than for white women (28x, 4x, respectively)
- HIV is 7th leading cause of death in black women

HIV in Pregnancy

- Preventing HIV infection in women is the best way to prevent perinatal HIV transmission
- Offer HIV testing to ALL pregnant women
- Treatment is available to nearly eliminate perinatal HIV transmission
- With good medical care and combination antiretroviral therapy (cART), mothers/parents with HIV infection can live long, relatively healthy lives

Antepartum Management

HIV History Details
- Infection duration (route of transmission)
- HIV related illnesses
- ART use (medication used, adherence/adverse events)
- CD4 counts and VL (relation to ART history)
  - Was AIDS ever diagnosed?
  - Ever on opportunistic infection (OI) prophylaxis?

Obstetric outcomes affected by HIV dx.
### Antepartum Management (2)

- Testing for STI, hepatitis A, B, and C virus infections; CMV, toxo 
- Metabolic panel with aminotransferase 
- HIV-1 RNA levels 
- CD4 cell counts (with CBC with diff) 
- ARV resistance studies (HIV genotype); human leukocyte antigen (HLA) B*5801 
- Team approach: ID provider with HIV medicine focus 
- Ryan White CARE network

### HIV Serodiscordant Couples

- Females with HIV infection: 
  - U=U (undetectable=untransmissible): 2-3 days unprotected intercourse around ovulation 
  - IUI in office; IUI at home 
- Females uninfected with HIV: 
  - Have partner achieve viral suppression 
  - Sperm preparation techniques +/- assisted reproduction 
  - PrEP 
  - Plan for periodic HIV screening

### Specific drug recommendations: ARV-naïve pregnant women

- **INTEGRASE INHIBITORS**
  
  **Dolutegravir is preferred**
  
  - Rapid viral load reduction; preferred for women presenting late in pregnancy, with high viral load, or with acute HIV 
  - Useful when drug interactions with protease inhibitor regimens are a concern 
  - Well-tolerated 
  - Once-daily administration 
  - Available as a fixed-dose combination with abacavir and lamivudine 
  - Small risk of neural tube defects when used at the time of conception; 
  - No excess risk with initiation during pregnancy
Specific drug recommendations: ARV-naive pregnant women

Case 2. Starting immediate ART

- NRTIs:
  - Abacavir/Lamivudine: HLA-B*5701 allele testing to avoid hypersensitivity to abacavir
  - Tenofovir (TDF) with emtricitabine or lamivudine
- NNRTIs: None preferred
- Protease inhibitors:
  - Atazanavir/ritonavir
  - Darunavir/ritonavir
  - Alternative: lopinavir/ritonavir (BID)
Standards for ART in Pregnancy

- Combination antiretroviral therapy (cART) starts as soon as possible after diagnosis
  - Women should
    - Continue their combination antiretroviral therapy (cART) regimen during pregnancy, provided it is well-tolerated and effective in suppressing viral replication
    - Continue taking their antepartum cART on schedule as much as possible during labor and before scheduled cesarean delivery
  
- Add IV AZT during labor?

- Infant receives 4-6 weeks of oral AZT

- Women should continue on cART after delivery
  - cART is currently recommended for all individuals with HIV infection to reduce the risk of disease progression and to prevent HIV sexual transmission

Intrapartum management and infant prophylaxis for pregnant women with HIV in resource-rich settings

<table>
<thead>
<tr>
<th>Risk for HIV transmission</th>
<th>Low risk</th>
<th>High risk</th>
<th>High risk</th>
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<tr>
<td>Other Intrapartum Interventions</td>
<td>Avoid fetal scalp electrodes</td>
<td>Avoid artificial rupture of membranes</td>
<td>Avoid operative delivery with forceps or vacuum extractor</td>
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Avoid artificial rupture of membranes (if not undergoing cesarean) | Avoid operative delivery with forceps or vacuum extractor (if not undergoing cesarean) | Avoid fetal scalp electrodes

Uptodate.com (2021)
Intrapartum management and Infant prophylaxis for pregnant women with HIV in resource-rich settings

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</thead>
<tbody>
<tr>
<td>Infant antiretroviral prophylaxis</td>
<td>4 weeks of zidovudine</td>
<td>Presumptive HIV therapy</td>
<td>Presumptive HIV therapy</td>
<td>Presumptive HIV therapy</td>
</tr>
</tbody>
</table>

Pharmacokinetic Concerns for Antiretrovirals

- Pharmacokinetic considerations
  - Physiologic changes affect drug absorption, distribution, elimination, etc.
  - Prolonged GI transit time
  - Placental transport/compartmentalization
- PKs of NRTI and NNRTIs: non-preg=preg
- PKs of PI and integrase inhibitors: variable

Teratogenicity

- Antiretroviral Pregnancy Registry
  - [http://APRegistry.com](http://APRegistry.com)
- Inform mothers that drugs are prescribed based upon available safety data from animal toxicity data, registry data, and clinical trials
- Based on multiple studies showing no difference in birth defect rates for 1st trimester exposure vs later ARV exposures, ARV during pregnancy does not increase the risk of birth defects.
Special Considerations for Postpartum Hemorrhage

- In women who are receiving a cytochrome P450 3A4 enzyme inhibitor such as protease inhibitors (Atazanavir, Lopinavir, Darunavir, fosamprenavir, Indinavir, etc.), methergine should be used only if no alternative treatments for postpartum hemorrhage (PPH) are available and the need for pharmacologic treatment outweighs the risks.
  - If used, methergine should be administered in the lowest effect dose for the shortest possible duration. Misoprostol and carboprost (hemabate) should be first line agents for PPH.
- In women who are receiving a CYP3A4 enzyme inducer such as nevirapine, efavirenz, or etravirine, additional uterotonic agents may be needed due to potential for decreased methergine levels and inadequate treatment effect.

Patients may request to breastfeed

- 2010 WHO recommended maternal ARV therapy throughout pregnancy and breastfeeding or maternal ARV therapy during pregnancy and infant ARV prophylaxis during exclusive breastfeeding (6 – 24 months) until 1 week after complete weaning.
  - Risk of transmission 1.1%-1.7%
  - Without therapy, transmission is 1.6% if CD4 >350 or 17% if CD4 <200

Elizabeth Glaser Pediatric AIDS Foundation

- Elizabeth Glaser contracted HIV in a blood transfusion in 1981 while giving birth to her daughter, Ariel.
  - She and her husband, Paul, later learned that Elizabeth had unknowingly passed the virus on to Ariel through breast milk, and
  - That their son, Jake, had contracted the virus in utero.
When a woman with HIV infection wants to breast feed

- Avoidance of breastfeeding has been the DHHS recommendation for three decades

Harm Reduction Counseling

- Validate her desire to breastfeed
  - Encourage discussion about her feelings and thoughts well before delivery
- Seek to understand her motivation
  - Is it social or cultural?
    - Stigma, cultural pressure, and/or awareness of benefits of breastfeeding
    - Knowing the motives can guide counseling

Potential Interventions

- Explore alternatives
  - Formula feeding (0% risk of transmission)
  - Banked breast milk
    - Milk banks pasteurize donated human milk and test donor for HIV
Potential Interventions

Offer harm reduction
• After emphasizing formula as optimal, offer exclusive breastfeeding with maternal and/or infant ARV therapy
• Risk of transmission 0.3-0.8%
• Flash heating of breast milk inactivates the infectivity of HIV in vitro without losing nutritional value
• Lactational surrogate
  • Needs to be HIV negative
  • Rule out HIV in infant

Remaining U.S. Groups at Risk for Perinatal HIV Transmission

• Late presenters without prenatal care
• Women seen in antenatal care but not offered voluntary counseling/testing due to perceived low risk
• HIV-infected pregnant women who were prescribed but did not take antiretrovirals

HIV Treatment Can Prevent Transmission

<table>
<thead>
<tr>
<th>% of People with HIV</th>
<th>Status of Care</th>
<th>Accounted for % of New Transmissions*</th>
</tr>
</thead>
<tbody>
<tr>
<td>15%</td>
<td>didn’t know they had HIV</td>
<td>38%</td>
</tr>
<tr>
<td>23%</td>
<td>knew they had HIV but weren’t in care</td>
<td>43%</td>
</tr>
<tr>
<td>11%</td>
<td>in care but not virally suppressed</td>
<td>20%</td>
</tr>
<tr>
<td>51%</td>
<td>taking HIV medicine and virally suppressed</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Values do not equal 100% because of rounding
Data-Informed Approaches To Reach Men and Boys

- Reach more boys and men with HIV testing services
  - Index case testing
  - Male testing, family testing days
  - Voluntary Assisted PN
  - VMMC and linkage to other services
  - Self-testing

- Create Male Friendly Services
  - Extended hours
  - Male friendly clinics and support (e.g., male clinicians, male only hours on weekends)
  - Health friendly health services

- Improve access through community engagement programs
  - Targeted community testing and care footprints & awareness testing, workplace programs, DMOC
  - Community wellness program (integrated package including mobile testing)

- Comprehensive programming to change attitudes and behavior
  - Programming for sexual violence prevention, such as Families Matter
  - Targeted gender/age risk reduction and risk-based testing

Summary

- Incidence of HIV is trending down for women for first time in a decade
- Lowering viral load to undetectable remains a cornerstone of protecting maternal health and preventing perinatal HIV transmission
- DHHS guidelines currently call for avoidance of breastfeeding, but there will likely be an increase in women with interest in BF
- Despite clear guidelines for screening all pregnant women, there are still missed opportunities for prevention of perinatal HIV transmission, making perinatal HIV transmission unlikely to be a never event!

Resources

- THE 2021 POSITIVELY AWARE HIV DRUG CHART