Management of the HIV-Exposed Infant

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Disclosures

No conflicts of interest to disclose
Objectives

• To review current national guidelines for the management of the HIV-exposed infant
• To describe the epidemiology of perinatal HIV infection in the US
• To make providers aware of research on long-term outcomes in perinatally-exposed children
Resources

- https://www.cdc.gov/hiv/
surveillance data
- https://aidsinfo.nih.gov/
guidelines
MOTHER-TO-CHILD TRANSMISSION OF HIV
Mother-to-Child Transmission (MTCT) of HIV

- Perinatal transmission
  - *in utero*
  - Intrapartum
    - Accounts for majority of MTCT
- Breast milk
- Premastication
Historical Perspective

- 1981 – AIDS first reported
- 1982 – pediatric cases reported
- 1987 – FDA approval of first drug for treatment of HIV: AZT (3’-azido-3’-deoxythymidine) = zidovudine
  - 1989 – syrup formulation
  - 1990 – IV formulation
Observational Data – Zidovudine Use During Pregnancy, Late 1980s

- AIDS Clinical Trials Group (ACTG) sites surveyed re: women taking zidovudine who became pregnant and intended to maintain pregnancy
- Data reported for 43 women from 17 sites
- Doses ranged from 300 – 1200 mg per day, 56% took for at least 2 trimesters, 29% of infants exposed during 1st trimester
- Zidovudine was well-tolerated, no associations with congenital anomalies, premature birth, fetal distress

(P)ACTG Protocol 076

- Began enrollment in April 1991
- Double-blind, placebo-controlled trial
- Pregnant women between 14 and 34 weeks gestation
- CD4 count >200 cells/mm³
- “Had no indication for antiretroviral therapy in the judgment of their health care providers”
- 59 centers in US and France (including St. Jude)
076 Regimen

- **Antepartum**: 100 mg by mouth FIVE TIMES a day
  - Standard adult dose at the time (now 300 mg twice daily)
- **Intrapartum**: 2 mg/kg IV over 1 hour, then 1 mg/kg/hour until delivery
  - Based on PK modeling of data obtained during pregnancy (ACTG 082)
- **Newborn**: 2 mg/kg by mouth every 6 hours for 6 weeks
  - Dose established in studies of zidovudine in newborns (ACTG 049)
  - Now dose for TNBs is 4 mg/kg/dose twice daily
076 Results

- Transmission rate decreased by 2/3 in zidovudine group
- Stopped at planned first interim analysis in December 1993 and all participants offered zidovudine
- Landmark study demonstrating medication could prevent mother-to-child transmission of HIV

Post-076

• 076 regimen quickly adopted in the US and other resource-abundant countries → significant declines in MTCT

• Further studies with combination antiretroviral therapy showed even greater effects (<2%)
PEDIATRIC HIV EPIDEMIOLOGY

076 trial results released (ARV prophylaxis decreases MTCT) > 95% reduction

2014 change in case definition

Aged <13 years

Aged ≥13 years
Diagnoses of HIV Infection among Children Aged <13 Years, by Age at Diagnosis, 2010–2016—United States and 6 Dependent Areas

N = 1,323
Diagnoses of HIV Infection and Population in Children Aged <13 Years by Race/Ethnicity, 2017—United States

Note. Data for the year 2017 are preliminary and based on 6 months reporting delay.

* Hispanics/Latinos can be of any race.

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>Population, United States (%)</th>
<th>Diagnoses of HIV infection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian/Alaska Native</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Asian</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Black/African American</td>
<td>14%</td>
<td>26%</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>19%</td>
<td>26%</td>
</tr>
<tr>
<td>Native Hawaiian/Other Pacific Islander</td>
<td>&lt;1%</td>
<td>1%</td>
</tr>
<tr>
<td>White</td>
<td>10%</td>
<td>50%</td>
</tr>
<tr>
<td>Multiple races</td>
<td>6%</td>
<td>50%</td>
</tr>
</tbody>
</table>

N = 52,738,932

N = 99
Persons Living with Diagnosed Perinatally Acquired HIV Infection, Year-end 2016—United States and 6 Dependent Areas

N = 11,915

- American Samoa: 0
- Guam: 2
- Northern Mariana Islands: 0
- Puerto Rico: 244
- Republic of Palau: 0
- U.S. Virgin Islands: 9

Note. Data are based on address of residence as of December 31, 2015 (i.e., most recent known address).
Age Distribution of Persons Living with Diagnosed Perinatally Acquired HIV Infection, Year-end 2016—United States and 6 Dependent Areas  

N = 11,915
Diagnoses of Perinatally Acquired HIV Infection among Children Born During 2015, by Area of Residence—United States and Puerto Rico

N = 54
Diagnoses of Perinatally Acquired HIV Infection among Children Born in the United States and Puerto Rico, Birth Years 2010–2015, by Area of Residence

N = 348
Infected Infants Born in Memphis Area
Perinatal Transmission Today

• Approximately 8500 women living with HIV give birth each year
• Transmission risk <1%
• Between 1994 and 2010 an estimated 21,956 cases of perinatal HIV infection were prevented
• 99 children under the age of 13 received a diagnosis of perinatal HIV infection in 2017

https://www.cdc.gov/hiv/group/gender/pregnantwomen/index.html
So why can’t we prevent ALL cases of perinatal HIV infection?
Perinatal HIV Prevention Cascade
Source Report: Institute of Medicine, 1998

<table>
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<tr>
<th>Missed Opportunities</th>
<th>Prevention Opportunities</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected woman: known status</td>
<td>Primary HIV prevention for women and girls</td>
</tr>
<tr>
<td>HIV-infected woman: unknown status</td>
<td>Adequate preconception care and family planning services</td>
</tr>
<tr>
<td>No Preconception Care</td>
<td></td>
</tr>
<tr>
<td>Become Pregnant</td>
<td></td>
</tr>
<tr>
<td>No Prenatal Care</td>
<td>Accessible, affordable, welcoming prenatal care</td>
</tr>
<tr>
<td>No HIV Test</td>
<td>Universal prenatal HIV testing (routine, opt-out)</td>
</tr>
<tr>
<td>Inadequate ARV Prophylaxis</td>
<td>Providing ARV prophylaxis to all eligible</td>
</tr>
<tr>
<td>No Cesarean Delivery</td>
<td>Utilize Cesarean delivery if maternal viral load is &gt;1000 copies/ml</td>
</tr>
<tr>
<td>Breastfed Infant</td>
<td>Education and support on avoidance of breastfeeding</td>
</tr>
<tr>
<td>Child Infected Despite Treatment</td>
<td>Comprehensive services for mother and infant</td>
</tr>
</tbody>
</table>
IDENTIFICATION OF HIV INFECTION

Missed Opportunities for Prevention
HIV Testing in Pregnant Women

• Recommended by CDC since 1995
• Opt-out approach (used in TN):
  • Told that HIV test included in routine prenatal tests, but they may decline
  • Unless they decline, test performed
  • 85% acceptance rate in TN (2002)
• Opt-in approach
  • Receive pre-test counseling
  • Must agree to testing, usually in writing
Repeat Testing in Third Trimester

- CDC revised testing recommendations MMWR 2006;55 (No. RR-14)

- “A second HIV test during the third trimester, preferably < 36 weeks of gestation, is cost-effective even in areas of low HIV prevalence and may be considered for all pregnant women.”

- Second test recommended:
  - Reside in jurisdictions with elevated HIV incidence among women of child-bearing age (like Tennessee)
  - Facility with HIV incidence ≥ 1/1000 pregnant women/year
  - Known to be at risk
    - Injection drug use (self or partner), partner HIV+, exchange sex for money or drugs, new partner during pregnancy, > 1 partner during pregnancy, diagnosed with STI during pregnancy

**Infected Infants**

- Before pregnancy: 40%
- During pregnancy: 14%
- At birth: 7%
- After birth: 18%
- Unknown: 22%

**Exposed but not infected**

- N = 14,681
- 78%
  - 19%
  - <1%
  - 1%

- Infected Infants
  - Before pregnancy: 40%
  - During pregnancy: 14%
  - At birth: 7%
  - After birth: 18%
  - Unknown: 22%

- Exposed but not infected
  - Before pregnancy: 19%
  - During pregnancy: 19%
  - At birth: <1%
  - After birth: 1%
  - Unknown: 1%
Acute HIV Infection During Pregnancy – Higher Risk of MTCT


• 17% (12/70) transmission in Florida 2007-2014  (South Med J. 2017;110(2)L116-128)

• Enhanced Perinatal Surveillance, 15 sites in US 2005-2010  (Singh et al. CROI 2013)
  • 124 of 10,308 pregnant women seroconverted during pregnancy (1.2%)
  • 12.9% transmission (8x higher) among this group
1/3 of HIV-infected infants born in Memphis in 2002 were born to mothers who tested negative early in pregnancy (3 of 9)
Infected Infants Born in Memphis Area

- Early 2007 – The MED implemented routine 3rd trimester testing (if no documented result, test at L&D)
- Within ONE WEEK identified a woman who seroconverted during pregnancy
Must Have DOCUMENTATION

• HIV-infected women may not self-identify at L&D
  – Disclosure issues (family may not know)
  – May assume you know
• Testing at L&D has identified women who were known HIV+ but did not disclose diagnosis
  – One of the infants born in 2002 wasn’t diagnosed until 2009 – but her mother was known + in 2002
HIV Testing at Delivery

• Pending confirmatory testing of positive result:
  – Administer IV zidovudine intrapartum
  – Neonatal prophylaxis should be initiated ASAP, preferably within 6 hours of birth
  – Counsel against breastfeeding (may pump and discard)
Testing Infants for HIV Exposure

• Mandated in several states
• Laws vary from state to state
• Recent example:
  • No HIV test result documented for mother, so infant tested (positive Ab, started on ART)
  • Mother reported needle phobia – no labs during pregnancy
  • Later learned mother diagnosed with HIV two years previously in another state
<table>
<thead>
<tr>
<th>Time of ARV Administration</th>
<th>Infected</th>
<th></th>
<th>Exposed but not infected</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% of Row Total</td>
<td>No.</td>
<td>% of Row Total</td>
<td>No.</td>
</tr>
<tr>
<td>During Pregnancy (DP) only</td>
<td>3</td>
<td>2.6</td>
<td>112</td>
<td>97.4</td>
<td>115</td>
</tr>
<tr>
<td>During Labor and Delivery Only (L&amp;D) only</td>
<td>3</td>
<td>4.3</td>
<td>66</td>
<td>95.7</td>
<td>69</td>
</tr>
<tr>
<td>Infant received ARV after birth (Infant ARV) only</td>
<td>71</td>
<td>8.3</td>
<td>781</td>
<td>91.7</td>
<td>852</td>
</tr>
<tr>
<td>DP and L&amp;D</td>
<td>8</td>
<td>2.5</td>
<td>314</td>
<td>97.5</td>
<td>322</td>
</tr>
<tr>
<td>DP and Infant ARV</td>
<td>21</td>
<td>2.2</td>
<td>950</td>
<td>97.8</td>
<td>971</td>
</tr>
<tr>
<td>L&amp;D and Infant ARV</td>
<td>45</td>
<td>5.1</td>
<td>837</td>
<td>94.9</td>
<td>882</td>
</tr>
<tr>
<td>DP and L&amp;D and Infant ARV</td>
<td>113</td>
<td>1.3</td>
<td>8,896</td>
<td>98.7</td>
<td>9,009</td>
</tr>
<tr>
<td>No known ARVs</td>
<td>233</td>
<td>20.4</td>
<td>908</td>
<td>79.6</td>
<td>1,141</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>497</strong></td>
<td><strong>3.7</strong></td>
<td><strong>12,864</strong></td>
<td><strong>96.3</strong></td>
<td><strong>13,361</strong></td>
</tr>
</tbody>
</table>

Note. Data include persons with a diagnosis of HIV infection regardless of stage of disease at diagnosis.
Missed Opportunities for Prevention

MEASURES TO PREVENT MOTHER-TO-CHILD TRANSMISSION
Additional Measures for Prevention of Mother-to-Child Transmission

• If maternal viral load >1000 at near delivery
  • Schedule c-section at 38 weeks
  • Intrapartum IV zidovudine

• Counsel women during pregnancy about safe infant feeding practices
  • Breastfeeding not recommended in the US
  • Counsel against premastication
Breastfeeding not Recommended in the US

• ART does not eliminate risk of transmission via breast milk (may not correlate with serum VL)
• Safe and affordable feeding alternatives available
• Lack of safety data on most ART regimens
Counseling about Breastfeeding

- Discuss with women prior to/during pregnancy
- Stigma for many who don’t breastfeed – concern about disclosure
- First addressed in guidelines March 2018 - still not recommended, but provide recommendations re: harm reduction counseling
Breastfeeding Management Plan

• Maintain viral suppression – VL every 1-2 months while breastfeeding
• Breastfeed exclusively for up to 6 months, then wean slowly as foods introduced
• Prompt treatment of maternal mastitis and infant thrush
• Additional testing, prophylaxis for infants
Premastication

- 2008 – 3 cases of HIV transmission linked to premastication
  - Miami (2), Memphis (1)
  - Diagnosed at 9, 15 and 39 months
  - HIV-infected caregiver: mother (2), great-aunt (1)
  - 2 cases associated with oral bleeding
  - Phylogenetic analyses supported conclusion in 2 of 3 cases

Gaur et al, Pediatrics, August 2009
Prevalence of Premastication

• 14% among the general US population

• CDC survey of HIV-infected caregivers Dec 2009-Feb 2010
  • 9 sites (GA, TX, TN, FL, LA, NJ, PR, DC)
  • 31% HIV-exposed children received premastticated food

MMWR March 11, 2011
MANAGEMENT OF THE HIV-EXPOSED NEWBORN
For All HIV-Exposed Newborns

- Obtain baseline CBCD
- Begin antiretroviral prophylaxis ASAP, preferably within 6 hours of birth
- All infants receive zidovudine prophylaxis at a minimum
Infant Zidovudine Dosing

• ≥35 weeks gestation at birth
  • 4 mg/kg/dose every 12 hours

• <35 weeks gestation at birth
  • 2 mg/kg/dose every 12 hours
  • Increase to 3 mg/kg/dose every 12 hours:
    – At 2 weeks of age if ≥30 to <35 weeks gestation at birth
    – At 4 weeks of age if <30 weeks gestation at birth

• IV dose is 75% of oral dose
Infants at Low Risk of Perinatal HIV Acquisition

- Mothers received standard ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence
- ARV prophylaxis: 4 weeks of zidovudine (ZDV)
Infants at Higher Risk of Perinatal HIV Acquisition

- Mothers who did not receive ARVs during pregnancy (regardless of whether they received intrapartum prophylaxis)
- Mothers with detectable VL near delivery, particularly if delivery was vaginal
- Mothers with acute HIV infection during pregnancy or breastfeeding
- Breastfed infants
Additional ARVs for Exposed Infants

• Now recommended for infants at increased risk of HIV acquisition
• Additional prophylaxis v. empiric therapy
• Limited treatment options available
  – Data sufficient for term and preterm newborns for only 3 drugs to be given at birth: zidovudine, lamivudine, nevirapine
Combination Prophylaxis for Infants

- NICHD-HPTN 040/PACTG 1043 enrolled 1746 infants born to mothers who did not receive antepartum ARVs
- Compared 3 regimens:
  - ZDV for 6 weeks
  - ZDV + 3 doses nevirapine
  - ZDV + 2 weeks of lamivudine/nelfinavir
- Transmission significantly lower in combination arms
  - 2.2% and 2.5% v. 4.9%
- Neutropenia significantly higher in 3-drug arm
- Nelfinavir powder no longer commercially available in the US

Additional Combination Therapy for Infants – “Mississippi Baby”

• HIV-exposed infant began receiving ART 30 hours after birth
• Infection confirmed by PCR testing
• Treatment discontinued at 18 months of age
• At 30 months, in absence of treatment, VL remained undetectable, HIV antibody negative
• Viral rebound at 27 months after stopping ART

Persaud et al, NEJM, November 7, 2013
ARVs for Neonates at Higher Risk of Perinatal Infection

• ARV Prophylaxis (Combination):
  – 6 weeks ZDV, plus
  – 3-dose course of nevirapine (NVP) (prophylactic dose)

OR:

• Empiric HIV Therapy
  – ZDV + lamivudine (3TC) + NVP (treatment dose)
1, 2, or 3 Drugs?

- Level of viremia that would trigger combination therapy is unknown
- Some would use combination therapy for any detectable VL
- Transmission possible at low-level viremia*
  - 0.05 – 0.3% with VL <50 at delivery
  - 1.1 – 1.5% with VL 50 – 399
  - 2.8 – 4.1% with VL >400

Duration of Empiric Therapy?

- Optimal duration unknown
- Some give 3 drugs for 6 weeks
- Some stop 3TC/NVP after newborn testing negative (continue zidovudine for 6 weeks)
Lamivudine (3TC) Dosing

• ≥32 weeks gestation at birth
  – Birth – Age 4 Weeks:
    • 2 mg/kg/dose orally twice daily
  – Age 4 – 6 Weeks:
    • 4 mg/kg/dose orally twice daily
Nevirapine: Treatment Dosing

- ≥37 weeks gestation at birth
  - 6 mg/kg/dose orally twice daily

- 34 to <37 weeks gestation at birth
  - Birth – Age 1 Week:
    - 4 mg/kg/dose orally twice daily
  - Age 1 – 6 Weeks:
    - 6 mg/kg/dose orally twice daily
Nevirapine: Prophylaxis Dosing

• **NOTE:** no calculation is required for prophylaxis dosing
• Birth weigh >2 kg: 12 mg dose
• Birth weight 1.5 – 2 kg: 8 mg dose
• Dosing schedule
  – 1\textsuperscript{st} dose: at birth – 48 hours of life
  – 2\textsuperscript{nd} dose: 48 hours after 1\textsuperscript{st} dose
  – 3\textsuperscript{rd} dose: 96 hours after 2\textsuperscript{nd} dose
Considerations for ARVs in Infants

• Community pharmacies may not stock liquid formulations of ARVs
• DO NOT administer in bottle of formula – use syringes
• Provide marked syringes
Newborns with Presumed HIV Exposure

- Mothers with positive test at L&D or postpartum
- Infants with positive HIV Ag/Ab test
- Treat as for infants at higher risk of acquisition
- ARV should be discontinued immediately if supplemental testing is negative for HIV
Breastfed Infants

• At least 6 weeks of ARVs
  – Standard zidovudine prophylaxis, and/or
  – Nevirapine as per PROMISE study
    (age-based dosing, continued until 42 days after cessation of breastfeeding)

• Discontinue at 6 weeks if maternal viral load undetectable
  – Some continue until 1 month after weaning

Additional Labs for Infants Receiving Combination Therapy

- CBCD
  - Repeat at 4 weeks if receiving ZDV/3TC
- LFTs
  - Monitor if receiving NVP
    - Baseline, at 2 and 4 weeks
HIV TESTING IN INFANTS
HIV Testing

• HIV antibody testing
  – Not useful for diagnosing infants due to transplacental transfer of maternal antibody
  – Infants who are uninfected should “serorevert” by 18 months of age

• HIV DNA PCR
  – Preferred test in infants

• HIV RNA PCR (“viral load”)
  – Acceptable, concerns about sensitivity in infants exposed to antiretrovirals
PCR Testing – All Infants

- At 1-3 weeks of age
- At ≥ 1 month of age
- At ≥ 4 months of age

Birth PCR not routinely recommended – detects in utero transmission, and most perinatal infection occurs intrapartum
Additional PCR Testing for Certain Infants

• For infants at higher risk of perinatal infection
  • PCR after birth (within 48 hours)
  • Consider at 2-4 weeks after cessation of ARVs (i.e., at 8-10 weeks of age)

• For breastfed infants
  • Every 3 months while breastfed
  • After cessation of breastfeeding:
    – 4-6 weeks later
    – 3 months later
    – 6 months later
Excluding HIV Infection in Infants

• HIV infection may be *presumptively* excluded
  – PCRs not detected ≥ 14 days and ≥ 4 weeks of age (or one ≥ 8 weeks or one negative antibody test ≥ 6 months)
  – It is not necessary to prescribe TMP-SMX prophylaxis if HIV infection presumptively excluded

• HIV infection may be *definitively* excluded
  – PCRs not detected ≥ 1 and ≥ 4 months of age (or two negative antibody tests ≥ 6 months)
Antibody Testing in Perinatally Exposed Children

• Many clinicians obtain antibody testing after 1 year of age to document seroreversion with loss of maternal antibody
• Seroreversion may take up to 18 months or more
4th Generation HIV Antigen/Antibody Testing

- If (+) → HIV-1/-2 antibody differentiation
- If HIV-1/-2 antibody differentiation (-):
  - Consistent with seroreversion in perinatally-exposed child
  - Lab normally proceeds to nucleic acid testing to assess for recent infection
- If HIV-1/-2 antibody differentiation (+):
  - Confirms infection in adolescents/adults (lab does not proceed to NAT)
  - May reflect maternal antibody in perinatally-exposed (can request lab to add NAT)
LONG-TERM OUTCOMES
Potential Long-Term Effects

- Mitochondrial toxicity
  - Neurologic, cardiac, increased lactate
- Cancer risk with exposure to nucleoside analogues
- Immunologic dysfunction
- Increased morbidity & mortality
Pediatric HIV/AIDS Cohort Study

• PHACS was established in 2005 to address two critical pediatric HIV research questions:
  • the long-term safety of fetal and infant exposure to prophylactic antiretroviral (ART) chemotherapy; and
  • the effects of perinatally acquired HIV infection in adolescents and young adults
PHACS SMARTT Study

• Surveillance Monitoring for ART Toxicities
• Enrolls up to 400 perinatally-exposed infants a year
PHACS Key Findings To Date re: Children Perinatally Exposed to HIV

• Hearing loss more common
• High risk of language impairment not related to ARV exposure
• High rates of mental health problems
• Data presented at IDSA 2018 showing trend toward increased adverse neurologic outcomes in children exposed to efavirenz and dolutegravir in utero
Thank You for Your Attention!