Maternal to Child Transmission of HIV-1

Idaho Perinatal Project
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Objectives
- Know the epidemiology of HIV infection in women and risk factors for maternal to child transmission
- Understand the diagnosis and management of HIV during pregnancy
- Know the strategies employed to decrease fetal and neonatal HIV infection
- Know the monitoring and treatment for HIV–exposed infants

Disclosures
- No conflicts to disclose
- Some of the medications discussed in this talk are not specifically approved for use in pregnancy
Note: For comparison with data for 1999 and later years, data for 1987−1998 were modified to account for ICD-10 rules instead of ICD-9 rules.
About 6,300 new HIV infections a day in 2012
- About 95% are in low- and middle-income countries
- About 700 are in children under 15 years of age
- About 5,500 are in adults aged 15 years and older, of whom:
  - Almost 47% are among women
  - About 39% are among young people (15–24 years)

World-wide data—UNAIDS

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A 25 y/o woman comes to you for prenatal counseling. She recently found out she was HIV infected and is currently not on any antiretroviral medication. She is worried about taking any medication during pregnancy and wants to know the risk of transmission to her baby if she doesn’t.

- a. 80–90%
- b. 50–60%
- c. 20–30%
- d. 5–10%
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### Rate of HIV-1 MTCT in the Absence of Intervention

<table>
<thead>
<tr>
<th>Study</th>
<th>Transmission Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaire</td>
<td>~8% prenatal (primarily after 28 weeks)</td>
</tr>
<tr>
<td>ACTG 076</td>
<td>Primary maternal HIV-1 infection</td>
</tr>
<tr>
<td>Cote d'Ivoire</td>
<td>Maternal viral load</td>
</tr>
<tr>
<td>Bangkok</td>
<td>Illicit drug use</td>
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<tr>
<td>US-PACTS</td>
<td>Chronic chorioamnionitis</td>
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<tr>
<td>US-WITS</td>
<td>Maternal CD4 count</td>
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<td>French Collaborative</td>
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<td>Swiss &amp; Thai/CDC study</td>
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<tr>
<td>European Collaborative</td>
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</tbody>
</table>

### Risk Mother–to–Infant HIV–1 Transmission

- ~8% prenatal (primarily after 28 weeks)
  - Primary maternal HIV–1 infection
  - Maternal viral load
  - Illicit drug use
  - Chronic chorioamnionitis
  - Maternal CD4 count
The woman in Q1 is just starting her second trimester of pregnancy and her CD4 count is 450 cells/m2. She asks you about starting antiretroviral therapy. You recommend:

a. Starting a three-drug regimen at the beginning of the third trimester since most transmission occurs later in pregnancy
b. Starting zidovudine only now, since her CD4 count is high
c. Starting a three-drug regimen now and continuing throughout her pregnancy
d. Including nevirapine in her three-drug regimen because it has high placental transfer
Q 2
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Q 3
Antiretroviral medications work to decrease the risk of transmission of HIV from mother to infant by:
a. Decreasing the amount of virus in maternal blood and genital secretions
b. Providing pre-exposure prophylaxis by passing through the placenta and achieving adequate systemic levels in the infant
c. Providing post-exposure prophylaxis protecting from virus that may have entered the fetal/infant circulation via maternal-fetal transfusion during labor or from swallowed maternal blood/secretions
d. all of the above
Placebo Controlled Trial of ZDV to prevent MTCT of HIV-1 (ACTG 076)

- ZDV mother
  - 100mg po 5x/d after 14 wk gestation
  - 2mg/kg iv x1 & 1 mg/kg iv/hr in labor
- ZDV infant: 2mg/kg po q6h x 6w
- placebo n=183; ZDV n=180
- Transmission placebo 25.5%
- Transmission ZDV 8.3%

Connor EM et al. NEJM 1994;331:1173-80

General considerations treatment of HIV+ pregnant women

- Women who require ARVs for their own health should start as soon as possible
- If not indicated for their own health, can start after the first trimester
- Women on ARV when they get pregnant should stay on their ARVs
- Drug resistance should be performed if viral load >500
- Always emphasize adherence
- Counsel regarding decreasing general risk behaviors – eg smoking, drug use, unprotected sex

General considerations for ARV therapy in HIV+ pregnant women

- Avoid efavirenz in the first trimester
- Nevirapine should not be used in ARV naïve women with CD4 cell counts >250 cells/mm³
- Zidovudine should be included in the regimen unless significant anemia, neutropenia, intolerance or woman already suppressed.
- If zidovudine is not included at least one agent should have good placental passage
  - lamivudine, emtricitabine, stavudine, tenofovir, abacavir
- IV zidovudine should be given during labor unless documented hypersensitivity
Approaches to Prevent HIV-1 MTCT Transmission

- Decrease HIV exposure
  - Decrease maternal viral load – plasma and genital
    - prepartum antiretroviral treatment
  - Decrease placental inflammation or breaks
  - Decrease infant exposure to maternal secretions
    - Cesarean delivery
    - avoid prolonged rupture of membranes

- Decrease HIV exposure
  - Avoid breastfeeding
  - Reduce viral load in breast milk
    - postpartum maternal antiretrovirals

- Infant prophylaxis
  - intrapartum and infant postpartum antiretroviral treatment
The National Perinatal HIV Hotline (1–888–448–8765)

The National Perinatal HIV Hotline is a federally funded service providing free clinical consultation to providers caring for HIV–infected women and their infants.

Recommendations for use of antiretroviral drug in pregnant HIV–1–infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States

Perinatal HIV Guidelines Working Group July 2012

http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf
Q 4
Which of the following is true about current recommendations for HIV screening during pregnancy?

a. All women should be screened for HIV early in pregnancy as part of their routine pregnancy labs unless they specifically decline
b. Only women who are known to have high risk behaviors should be screened for HIV
c. All women should be screened for HIV early in pregnancy if they sign a separate written consent for HIV testing

What are the current CDC testing guidelines?

- HIV screening should be included in the routine panel of prenatal screening tests for all pregnant women.
- HIV screening is recommended after the patient is notified that testing will be performed unless the patient declines (opt-out screening).
- Separate written consent for HIV testing should not be required
- Repeat screening in the third trimester is recommended
  - in certain jurisdictions with elevated rates of HIV infection among pregnant women
  - if the local epidemiology shows 1/1000 positive rate in pregnant women
  - Women with increased risk

Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health Care Settings. MMWR September 22, 2006; 55(RR14):1-17
The woman you have been counseling is now on antiretroviral therapy and doing well. She is in her third trimester and starting to think about her delivery. Which of the following is not a factor that may influence the risk of HIV transmission to her infant?

- mode of delivery
- receipt of immunizations during pregnancy
- duration of rupture of membranes
- presence of STDs
- plasma HIV RNA level at delivery
- breastfeeding

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- breastfeeding
Prevention of HIV-1 MTCT - obstetrical approaches

- Cesarean delivery – prior to onset of labor and rupture of membranes
- Avoid premature rupture of membranes
- Treat STDs to decrease risk of chorioamnionitis
- Avoid episiotomy or other interventions that increase risk of exposure to maternal blood

European Randomized Mode of Delivery Trial: Elective Cesarean at 38 Weeks vs Vaginal Delivery

- 11% Transmission
- 10% Transmission
- 9% Transmission

Randomized Assignment - Vaginal, Urgent Cesarean, Elective Cesarean

As Actually Delivered - Vaginal, Urgent Cesarean, Elective Cesarean

Scheduled cesarean delivery at 38 weeks gestation is recommended if HIV RNA levels >1,000 copies/mL near the time of delivery and for women with unknown HIV RNA levels near the time of delivery.

Controversial when present with ruptured membranes or in labor.

If HIV RNA is <1000 c/ml individualize use of CSx.

Use prophylactic antibiotics at the time of cesarean delivery.

Avoid AROM and fetal scalp monitors

Minimize use of forceps, vacuum extraction, episiotomy

Transmission from breastmilk

Meta-analysis of published studies – overall risk of HIV–1 transmission from breast milk 16%

21% risk in infants breastfed ≥3 months

13% risk in infants breastfed <2 months

Transmission risk after 3–6 months fairly constant at about 4%


Q 6
Your hospital has instituted rapid HIV testing in L&D for any woman who presents for delivery without a prior HIV test result documents. You are called because the rapid HIV test from a woman who just delivered returned positive. What should you do?

a. Nothing, the tests aren’t very reliable

b. Send an EIA and WB on the mother – if this confirms she is HIV positive, then start the baby on zidovudine

c. Start the infant on zidovudine and nevirapine while you wait for the confirmatory testing on the mother
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Rapid (point of care) HIV testing

- Should be recommended at presentation to L&D for any woman who was not HIV tested during pregnancy
- Should be confirmed with a repeat conventional EIA/WB
- Prophylaxis should be instituted for a woman/infant with a positive rapid test in labor/post–partum – can discontinue if doesn’t confirm as positive
- Infant should have PCR testing as soon as possible if rapid test is confirmed

Table 1. US Food and Drug Administration–approved rapid HIV antibody tests for HIV-1 detection

<table>
<thead>
<tr>
<th>Rapid HIV test</th>
<th>Specimen type</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>CLIA category</th>
</tr>
</thead>
<tbody>
<tr>
<td>OraSure® Advance Rapid HIV-1 Antibody test</td>
<td>Oral fluid</td>
<td>99.2% (98.4-99.7)</td>
<td>99.0% (99.5-100.0)</td>
<td>Waived</td>
</tr>
<tr>
<td></td>
<td>Whole blood (fingerstick or venipuncture)</td>
<td>99.6% (98.5-99.9)</td>
<td>99.9% (99.7-100.0)</td>
<td>Waived</td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>99.6% (98.9-99.9)</td>
<td>99.5% (99.6-99.9)</td>
<td>Moderate complexity</td>
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<tr>
<td></td>
<td>Serum</td>
<td>99.6% (99.5-100)</td>
<td>99.3% (99.6-99.9)</td>
<td>Moderate complexity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>99.6% (98.9-100)</td>
<td>99.5% (99.6-99.9)</td>
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</tr>
<tr>
<td></td>
<td>Whole blood (fingerstick or venipuncture)</td>
<td>100% (99.5-100)</td>
<td>99.7% (99.0-100)</td>
<td>Waived</td>
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<tr>
<td></td>
<td>Plasma</td>
<td>99.8% (99.5-100)</td>
<td>99.6% (99.4-99.9)</td>
<td>Moderate complexity</td>
</tr>
<tr>
<td></td>
<td>Serum and plasma</td>
<td>99.5% (99.1-100)</td>
<td>99.8% (99.3-100)</td>
<td>Moderate complexity</td>
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<tr>
<td></td>
<td></td>
<td>99.5% (99.0-100)</td>
<td>99.8% (99.2-100)</td>
<td>Moderate complexity</td>
</tr>
</tbody>
</table>

*Trade names are for identification purposes only and do not imply endorsement by the US Department of Health and Human Services or the Centers for Disease Control and Prevention.
CLIA = Clinical Laboratory Improvement Amendments of 1988
*Adapted from model Research and Education Task Force at http://www.aidsinfo.nih.gov/clinical_info/testing.
Exposure to antiretroviral medications during pregnancy has been associated with all of the following increased risks in the exposed infants except:

a. Anemia
b. neural tube defects
c. pre-term birth
d. hepatitis
e. increased lactate levels

ARV toxicity in exposed infants

- Zidovudine
  - Anemia
  - Neutropenia
- NRTIs mitochondrial dysfunction
  - Reported severe neurologic disease in ZDV/3TC exposed infants in France
  - Not confirmed in several other large cohorts
  - Some small studies have shown alterations in mitochondrial DNA levels in NRTI-exposed infants
  - Asymptomatic hyperlactatemia
- Tenofovir – potential for renal/bone
- Atazanavir – potential for hyperbilirubinemia
ARV toxicity in exposed infants

- Concern for neural tube defects with use of efavirenz in the first trimester – based on preclinical data
- Unclear if increased risk of preterm birth with combination antiretroviral therapy
- Cardiac toxicity – cardiomyopathy, heart block, acute renal failure, lactic acidosis, CNS depression – lopinavir/ritonavir (Kaletra) infants (<42 weeks postgestational age)
  - KALETRA oral solution contains the excipients alcohol (42.4% v/v) and propylene glycol (15.3% w/v).

Maternal toxicity and pregnancy complications

- PACTG 316 – 1,407 women
  - 34 ZDV treatment before or during first trimester (early)
  - 288 ZDV second or third trimester (late)
  - 175 combination NRTIs early
  - 327 combination NRTIs late
  - 263 combination NRTIs + PI early
  - 320 combination NRTIs + PI late


Maternal toxicity and pregnancy complications

- Symptoms or laboratory abnormalities of a moderate grade were < 5% in all groups
- 4% preterm labor
  - median gestational age all groups 38 weeks
  - median birth weight all groups 3070 grams
- Slight increase in gestational diabetes with PI use – not confirmed by AACTG 5084
Maternal toxicity and pregnancy complications

- All ARVs are FDA category B and C (except EFV which is category D)
- Increased hepatic toxicity from nevirapine in women with >250 CD4 cells
- Increased hepatic toxicity with d4T + ddI – fatal cases of lactic acidosis in pregnancy

Q 8
You are covering the newborn nursery and have just been informed of a term infant born to an HIV-infected mother. You find out that the mother was on combination antiretroviral therapy during her pregnancy with a suppressed viral load, so you judge the infant to be at low risk of infection. Standard treatment for this infant would include:

a. zidovudine 4mg/kg every 12 hours for 6 weeks
b. zidovudine 4mg/kg every 12 hours for 6 weeks plus three doses of nevirapine–birth, 48 and 144 hours
c. zidovudine 4mg/kg every 12 hours for 6 weeks plus lamivudine for the first 2 weeks
d. zidovudine 4mg/kg every 12 hours for 4 weeks
**ARV prophylaxis for HIV-exposed infants**

- Mother on antiretroviral therapy and a low viral load
  - Zidovudine 4mg/kg/dose q 12 hours for 6 weeks
- Mother with high viral load at time of delivery, known resistance, not on antiretrovirals, other risk factors for transmission
  - Consider additional antiretrovirals
  - Most frequently recommended additional ARV is nevirapine – 2mg/kg/dose – birth, 48 and 144 hours

**ZDV dosing in premature infants**

- <30 wks – 2mg/kg/dose po
  - (1.5mg/kd/dose IV) q 12 hours – advance to 3mg/kg/dose po (2.3mg/kg IV) q 8 at 4wks
- <35 – >30wks – 2mg/kg/dose po
  - (1.5mg/kd/dose IV) q 12 hours – advance to 3mg/kg/dose po (2.3mg/kg IV) q 8 at 15 days
- ≥35 wks – 4mg/kg/dose po
  - (3mg/kd/dose IV) q 12 hours

**Early management of HIV-exposed infants**

- Wash baby before giving HepB vaccine and Vit K
- Verify maternal HepB and HepC status
- Monitor for complications of premature delivery
- Check baseline CBC with differential, ALT
- Start zidovudine within 12 hours
You are seeing a 6 week old infant in clinic born to an HIV-infected mother. The mother had limited prenatal care and did not receive ARVs antenatally. The infant was treated with 6 weeks of zidovudine and 3 doses of nevirapine. The HIV DNA PCR from birth was negative, but an HIV RNA PCR done at 2 weeks was positive at 3,550 copies/ml. Of the following, the next best step in the management of this baby is:

a. order an HIV culture  
b. order HIV resistance testing  
c. repeat the HIV RNA PCR  
d. send a CD4 count  
e. start antiretroviral therapy

A pediatrician calls you in a panic. The HIV–exposed baby she is taking care of has a positive test.

What is the first question you should ask?
HIV diagnosis in infancy

- HIV EIA and WB reflect maternal antibody and cannot be used for infant diagnosis
  - 90-95% of uninfected infants will be EIA negative by 12 months, may still have bands on WB
  - EIA and WB should both be negative by 18 months
- HIV DNA PCR or HIV RNA PCR (not from cord blood)
- Some commercial HIV DNA PCR assays are less sensitive for non-type B virus

Management of the HIV-exposed infant

<table>
<thead>
<tr>
<th></th>
<th>birth</th>
<th>2-3 wks</th>
<th>4-6 wks</th>
<th>4-6 mos</th>
<th>12-18 mos</th>
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<tbody>
<tr>
<td>H &amp; P</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CBC with diff</td>
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<td>X*</td>
<td>X*</td>
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<tr>
<td>LFTs</td>
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<td>X*</td>
<td>X*</td>
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<td>PCP prophylaxis</td>
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<td>HIV RNA or DNA</td>
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<tr>
<td>HIV serology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X*</td>
</tr>
</tbody>
</table>


HIV infant diagnosis

- Presumptive exclusion
  - Two negative tests one ≥ 2 wks and one ≥ 1 month
  - One negative test ≥ 2 months
  - One negative serology ≥ 6 months
- Definitive exclusion
  - Two negative tests one ≥ 1 month and one ≥ 4 months
  - Two negative serology tests ≥ 6 months
PCP prophylaxis

- Start TMP–SMX for PCP prophylaxis at 4–6 weeks unless there is adequate virologic testing to presumptively or definitively exclude HIV infection