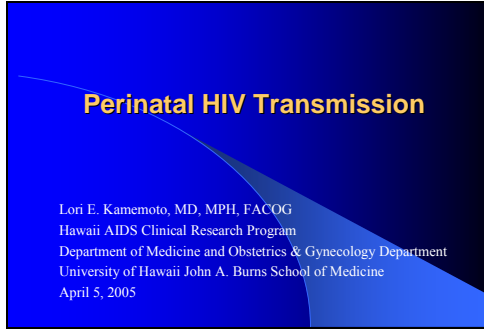
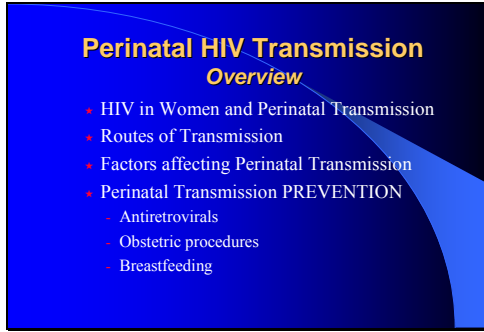


Slide 1



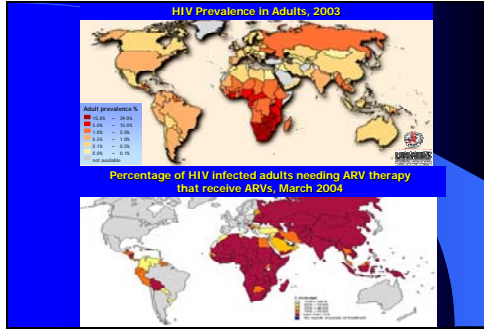
Slide 2



Slide 3




Slide 4



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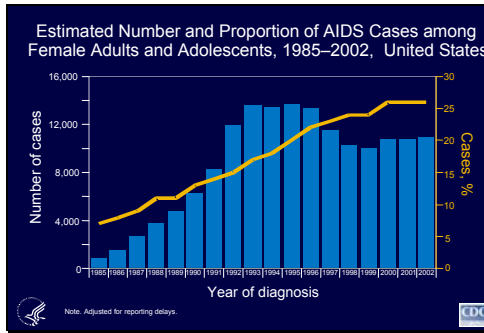
HIV/AIDS

The Changing Face of HIV

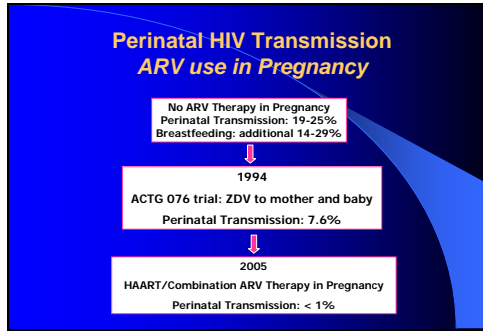


- Worldwide-increasingly female disease
 - 1985: 35% of all HIV infected persons were women
 - Today: 48% are women
- Sub-Saharan Africa
 - close to 60% are women
- South and Southeast Asia
 - close to 30% are women

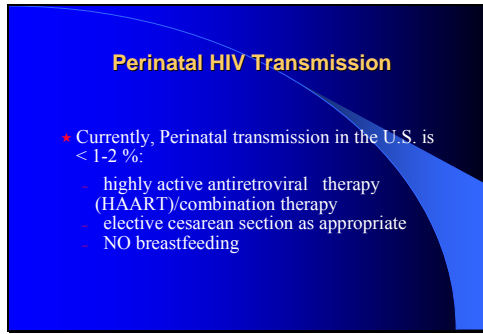
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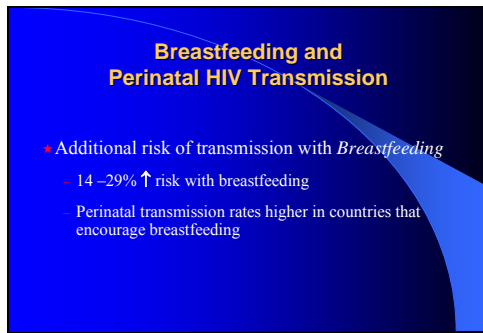
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Slide 12



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**Perinatal HIV Transmission
Risk Factors**


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HIV in the Female Genital Tract

- HIV detected in cervicovaginal lavage and cervical mucus
- Associated with an increase in female genital tract (FGT) viral load:
 - Cervical inflammation and ectopy
 - STDs: chlamydia, gonorrhea, herpes
 - Menstrual cycle, pregnancy, oral contraceptives?
- ARVs: decrease in FGT viral load

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**Perinatal HIV Transmission
Mode of Transmission**



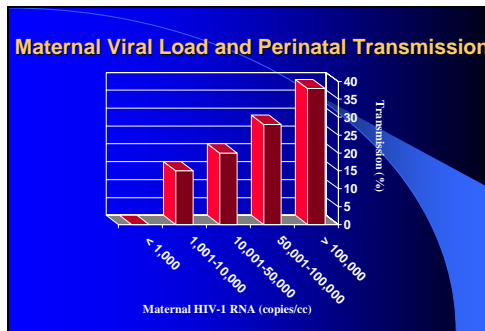
- In-utero transmission: 25-40%
- Intrapartum transmission: 60-75%
- Additional transmission risk with Breastfeeding
 - 14% risk with established infection
 - 29% risk with primary infection

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Factors Influencing Perinatal Transmission

- **Maternal Factors**
 - HIV-1 RNA levels
 - CD4+ lymphocyte count
 - Other co-infections, bacterial vaginosis
 - Maternal Vitamin A deficiency
 - ARV during pregnancy decrease risk
- **Obstetric Factors**
 - Length of ruptured membranes/chorioamnionitis
 - Labor/contractions
 - Vaginal delivery
 - Invasive procedures
- **Infant Factors**
 - Prematurity

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Ruptured Membranes and Perinatal HIV Transmission

Rupture of membranes

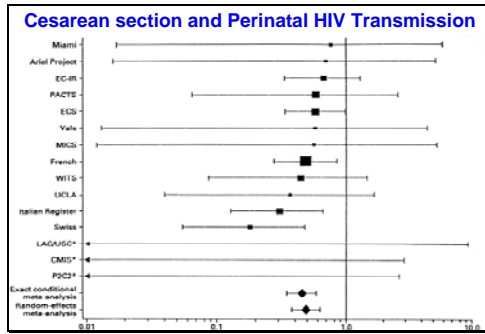
- Landesman (1996)
 - ROM < 4 hours: 14% transmission
 - ROM > 4 hours: 25% transmission
- Minkoff (1995)
 - Mothers with low CD4 counts with ROM > 4 hours:
 - ↑ risk transmission (RR 4.53)

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Twin Studies and Perinatal HIV Transmission

- 66 pairs of twins
- Vaginal delivery
 - First born: 50% transmission
 - Second born: 19% transmission
- Cesarean section
 - First born: 38% transmission
 - Second born: 19% transmission

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Cesarean section and HAART

	Elective C-S	Vaginal delivery or emergency C-Section
HIV-1 RNA > 1000 copies/mL		
Single drug	1.8%	7.4%
Multi-drug HAART	2.3%	1.8%
HIV-1 RNA < 1000 copies/mL		
Single drug	1.8%	4.3%
Multi-drug HAART	0.8%	0.5%

Shapiro, PACTG 367, February 2004 CROI (3,081 deliveries)

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Complications of Cesarean section

- Risk of complications with c/s in HIV+ (vs. HIV-) (Semprini, 1995)
 - Increased fever and minor complications (wound infections, UTI, endometritis)
- Women and Infants Transmission Study
 - 686 vaginal deliveries, 139 non-elective c/s, 52 elective c/s
 - Elective c/s (before ROM) had same morbidity as vaginal delivery
 - Non-elective c/s associated with a 6-fold increase in infectious complications

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Cesarean section and Perinatal HIV Transmission

- Cesarean section and ZDV: appears to decrease risk by ~ 50% if viral load is $\geq 1,000$
- If VL $\geq 1,000$:
 - Offer c/s at 38 weeks, BEFORE rupture of membranes and labor
- If VL $< 1,000$:
 - Benefit unknown

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Preterm Delivery and Perinatal HIV Transmission

- ↑ Preterm deliveries
 - European Collaborative Study: baseline CD4+ < 200 (OR 2.36), PI-containing HAART (OR 4.17)
- Preterm babies are at increased risk of transmission
 - Preterm birth (< 37 weeks): 31% transmission
 - Term birth: 8% transmission

Thorne, ECS, February 2004 CROI

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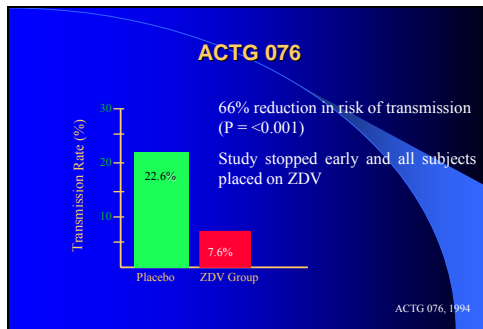
ACTG 076

Randomized, placebo-controlled trial of zidovudine (ZDV) for the prevention of maternal-fetal HIV transmission.

Treatment Regimen

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

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Follow-up of Uninfected ACTG 076 Infants ZDV vs. Placebo

- No significant difference in growth
- No difference in CD4 and CD8 counts between groups
- Mild neonatal anemia
- No other short term safety abnormalities identified
- No differences in Bayley developmental scores in uninfected infants (ACTG 219)
- Follow-up of infants with exposure to nucleoside analogues ongoing due to the potential for mitochondrial toxicity
- In the US, no cases of mitochondrial toxicity identified so far

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Follow-Up of Women in ACTG 076

- Median follow-up 4.2 years
- No differences in postpartum CD4 count, time to progression to AIDS, or death in women who received ZDV compared to placebo

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Timing of ZDV Prophylaxis

ZDV Started	Transmission (%)	RR (95% CI)
Prenatal	6.1	0.23 (0.16, 0.34)
Intrapartum	10	0.38 (0.18, 0.81)
Within 48 hrs of birth	9.3	0.35 (0.19, 0.65)
≥ 3 days old	18.4	0.69 (0.35, 1.36)
None	26.6	

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Short Course ARV Therapy in Pregnancy

- Oral ZDV from 36 weeks and during labor (Thailand)
Transmission rate: 9.4% ZDV vs. 18.9% placebo
- PETRA study—intrapartum/postpartum oral ZDV/3TC (Uganda, S. Africa, Tanzania)
Transmission rate: 5.7% ZDV/3TC vs. 15.3% placebo
- HIVNet 012—intrapartum/neonatal nevirapine (NVP) vs. short course/neonatal ZDV (Uganda)
Transmission rate: 12% NVP vs 21% ZDV
NVP resistance developed in ≈ 15% of mothers
- Thailand MOPH—US CDC Study—ZDV started at 34–36 weeks and intrapartum NVP
Transmission rate: 4.6%


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Reducing Intrapartum HIV Transmission: Nevirapine

- More recent data: NNRTI resistance develops after single dose NVP in 15-39% of mothers
- ↑ Hepatotoxicity with chronic NVP in non-pregnant women with CD4+ > 250 cells/mm³ (11-13%)
- Need for further studies on PI regimens in resource-poor settings

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Nevirapine Resistance with Single dose NVP in labor



- Mothers:
 - 15%-39% of women develop NVP resistance mutations after single dose NVP (with and without other antepartum ARV)
- HIV infected babies:
 - 17%-52% of infected infants develop resistance to NVP
- Therapeutic NVP levels noted in 56% up to 3 weeks after SD NVP in labor (Jourdain, XV Int'l AIDS, 2004)

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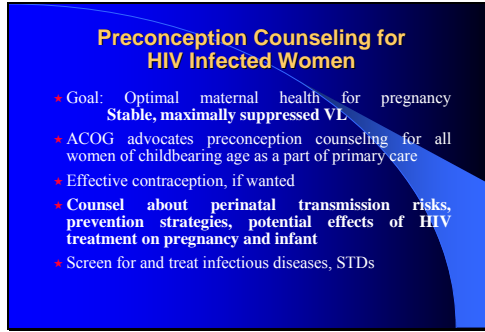
Breastfeeding and Perinatal HIV Transmission

- Additional risk of transmission with *Breastfeeding*
 - 14-29% ↑ risk with breastfeeding
- HIV detected in cellular and cell-free components
- Intermittent breastfeeding may be associated with a greater transmission risk than breastfeeding alone
- Transmission risk may be greater in early months of life

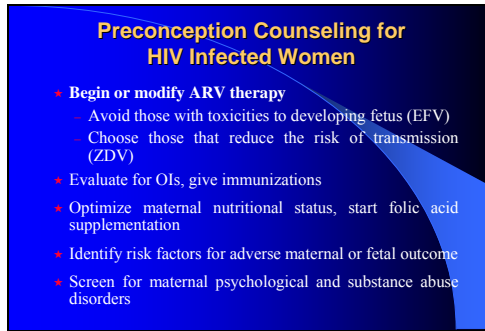
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HIV Testing in Pregnancy

- CDC/USPHS recommendations:
 - Routine HIV screening for ALL pregnant women using "opt out" approach
 - Labor and delivery: consider rapid testing for women whose HIV status is unknown
 - Postnatal: Rapid testing for all infants whose mother's status is unknown
- Barriers to testing: No prenatal care (15% of HIV+), Doctor too busy, Patient afraid to get tested
 - When health care provider strongly recommends testing, 3 x more likely to consent to HIV test

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HIV Testing in Pregnancy

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FDA-approved Rapid HIV Tests

	Sensitivity (95% C.I.)	Specificity (95% C.I.)
OraQuick Advance		
- whole blood	99.6 (98.5 - 99.9)	100 (99.7-100)
- oral fluid	99.3 (98.4 - 99.7)	99.8 (99.6 - 99.9)
- plasma	99.6 (98.5 - 99.9)	99.9 (99.6 - 99.9)
Uni-Gold Recombigen		
- whole blood	100 (99.5 - 100)	99.7 (99.0 - 100)
- serum/plasma	100 (99.5 - 100)	99.8 (99.3 - 100)

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FDA-approved Rapid HIV Tests

	Sensitivity <i>(95% C.I.)</i>	Specificity <i>(95% C.I.)</i>
Reveal G2		
- serum	99.8 (99.2 – 100)	99.1 (98.8 – 99.4)
- plasma	99.8 (99.0 – 100)	98.6 (98.4 – 98.8)
Multispot		
- serum/plasma	100 (99.9 – 100)	99.9 (99.8 – 100)
- HIV-2	100 (99.7 – 100)	

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Positive Predictive Value of a Single Test Depends on Specificity & Varies with Prevalence

HIV Prevalence	Predictive Value, Positive Test			
	OraQuick	Reveal	Uni-Gold	Single EIA
10%	99%	92%	97%	98%
5%	98%	85%	95%	96%
2%	95%	69%	87%	91%
1%	91%	53%	77%	83%
0.5%	83%	36%	63%	71%
0.3%	75%	25%	50%	60%
0.1%	50%	10%	25%	33%
Test Specificity	99.9%	99.1%	99.7%	99.8%

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HIV Screening with OraQuick in Labor and Delivery: the MIRIAD Study

- Testing of pregnant women in labor for whom no HIV test results are available; 12 hospitals in 5 cities: Atlanta, Chicago, Miami, New Orleans, New York
- To date
 - 4894 women screened
 - 34 (0.7%) new HIV infections identified
 - 4 false positive OraQuick tests, no false negatives
 - 11 false-positive EIAs: 5 p24 only, 6 WB negative
- Positive Predictive value: OraQuick 90%; EIA 76%

Bulterys et al. JAMA July 2004


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Remember the tradeoffs...

- Good News: More HIV-positive people receive their test results.
- Bad News: Some people will receive a false-positive result before confirmatory testing.
- http://www.cdc.gov/hiv/rapid_testing

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**Perinatal HIV Transmission
ARV Recommendations**



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USPHS Perinatal Transmission Guidelines

- USPHS Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and to Reduce Perinatal HIV-1 Transmission in the United States
- Developed in 1994 in response to ACTG 076
- Updated recommendations available online at AIDSInfo website (www.aidsinfo.nih.gov)

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Goals of ARV Therapy

- General Goals for ALL HIV infected patients
 - Prolong and improve quality of life
 - Suppress HIV viral load for as long as possible
 - Preserve immune function
- Additional Goal for Pregnancy
 - Prevent perinatal transmission

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Rationale for Combination ARV

- Synergistic or additive effects
- Prevent emergence of resistance
 - Resistance may develop as quickly as weeks to months with monotherapy
- Attack HIV virus at multiple points in the life cycle
- Pregnancy: lower viral load associated with decreased perinatal transmission

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Risks of ARV Therapy during Pregnancy

- Little human data available
- May have as yet unknown risks on the fetus
- ZDV associated with maternal and neonatal anemia
- Possible increased risk of glucose intolerance with PIs
- Benefit (↓↓↓ perinatal transmission) outweighs risk at this time

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Perinatal HIV Transmission and Maternal Viral Load

- Correlation between maternal HIV-1 RNA level (VL) and risk of transmission, even in pregnant women treated with ARVs
- Risk of transmission in women with undetectable VL is extremely low, but transmission has occurred at all VL levels
- Other factors beside VL also appear to play a role in transmission
- ZDV decreases transmission regardless of VL level
- **ZDV prophylaxis should be given even to women with very low or undetectable VL levels**

Slide 50

Women without prior ARV therapy

- **Recommend**
 - 3-part ZDV regimen to reduce perinatal transmission for all pregnant women, regardless of VL
 - Combination ARV therapy that includes 3-part ZDV regimen for all women
- Can consider delaying start of therapy until after 10–12 weeks of gestation

Slide 51

Women on ARV therapy prior to Pregnancy

- Discuss benefits and potential risks of ARV during pregnancy
- Add or substitute ZDV
- Intrapartum and neonatal ZDV
- Discontinue teratogenic drugs (EFV)
- Can consider continuing or stopping current therapy based on gestational age (<14 weeks)
- If therapy is stopped, stop and restart all ARV simultaneously
- Resistance testing for suboptimal viral suppression

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Changing HIV Therapy During Pregnancy

- Poor VL response after one month of therapy
- Poor CD4⁺ response
- Drugs with potential teratogenicity
- Poor adherence to regimen
- Evidence of viral resistance

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Follow-Up of HIV infected Pregnant Woman

- CD4⁺ and viral load at least once every trimester
 - ARV therapy for maternal health
 - Alteration in therapy
 - VL at 34-35 weeks to determine need for C/S
- Side effects or toxicities
- Adherence to therapy
- Long-range planning for continuity of medical care, team approach (ID, OB, Pediatrician, Social services)

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HIV-infected Woman in Labor with No Prior Treatment

- Four treatment options
 - Intrapartum IV ZDV and 6 weeks ZDV to the baby
 - Oral ZDV/3TC for mother at onset and during labor followed by 1 week oral ZDV/3TC for the newborn
 - Single dose NVP for mother at onset of labor followed by single dose of NVP for the newborn at 48-72 hrs of age*
 - The 2-dose NVP regimen as above combined with intrapartum IV ZDV and 6 week ZDV for the newborn*

*rapid development of resistance after one dose NVP to mother in ≈ 20-40% and hepatotoxicity with CD4⁺ > 250

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Mitochondrial Toxicity and NRTIs

- Nucleoside analogs (such as ZDV) induce mitochondrial dysfunction
- Lactic acidosis/hepatic steatosis reported in very few women with HIV infection
 - Pregnant women with HIV infection on nucleoside analogues should have liver enzymes and electrolytes monitored in 3rd trimester
 - Severe disease is very rare
- d4T and ddI combination should not be used in pregnancy

Slide 59

Chronic Nevirapine in Women

- Non-pregnant women with CD4 counts > 250 on long-term NVP, have a 9 to 10 fold higher risk of hepatic toxicity (11-13%) compared to men
- Associated Press: "Woman died in Government AIDS study", December 16, 2004
 - Hepatic failure and death among a very small number of pregnant patients
 - Usually occurs early in therapy, often with little warning
 - Use chronic NVP with caution in pregnancy, generally only when other options not available or acceptable
- The above caution applies to **chronic** NVP

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Perinatal HIV Transmission Obstetric Recommendations

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Cesarean Section to Reduce Perinatal HIV Transmission

- Pregnant women with VL \geq 1,000 counseled re: potential benefit of scheduled C/S
- Unknown whether scheduled C/S offers any benefit to women on HAART with VL < 1,000
- Complications of elective C/S may be similar to HIV uninfected women (in the U.S.)
- Patient's decision should be respected

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Obstetric Prevention Strategies

- Prenatal procedures
 - Avoid Amniocentesis/CVS
- Mode of Delivery
 - Consider cesarean section
- Decrease exposure of fetus to maternal body fluids
 - Do not rupture membranes
 - Avoid scalp electrode/scalp pH/internal monitoring
 - Avoid operative delivery (forceps/vacuum)
 - Avoid lacerations/episiotomy if possible
 - "Bloodless cesarean section"
 - Wash baby at delivery

Slide 63

Breastfeeding and HIV Infection

- Women with HIV infection in the United States should NOT breastfeed
- Women considering breastfeeding should know their HIV status

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JAMA
The Journal of the American Medical Association

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Volume 282(6) 11 August 1999 pp 577-579

Can Perinatal HIV Infection Be Eliminated in the United States?
[Editorial]

Mofenson, Lynn M. MD

Barriers to Prevention of Perinatal HIV Transmission:

1. Prenatal HIV Testing
2. Inadequate or no prenatal care
3. Substance abuse
4. Prophylaxis offered to women that are HIV infected

Slide 65

Strongly Recommend that ALL Pregnant women be tested for HIV as part of their routine prenatal labs.

Consider rapid HIV testing in women with no prenatal care.

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Prevention of Perinatal Transmission

- Prevention of HIV infection in women
- Adequate contraception for those who do not want children
 - 4 in 10 pregnancies in developing world are unintended pregnancies (76 million out of 183 million pregnancies in 2003)
 - 29% of women at risk for unintended pregnancy use no contraception
 - Use of Family Planning clinics as introduction to HIV prevention AND as perinatal HIV transmission prevention intervention
- Avoid breastfeeding where possible
- Cesarean section with VL \geq 1,000 where possible
- Avoidance of invasive procedures at vaginal delivery
- Antiretroviral Therapy during pregnancy
TREATMENT = PREVENTION

Slide 67

Antiretroviral Pregnancy Registry

- A collaborative project managed by PharmaResearch Corporation on behalf of an advisory committee (specialists in OB/GYN, ID, teratology, epidemiology, and CDC and NIH members) and sponsored by:
Abbott Laboratories, Agouron Pharmaceuticals, Inc., Boehringer Ingelheim Company, Bristol-Myers Squibb, Co., Gilead Sciences, Inc., GlaxoSmithKline, F. Hoffmann-LaRoche Ltd., Merck & Co., Inc. and PharmaResearch.
- Purpose: To assess safety of ARV drugs during pregnancy
- Telephone: (800) 258-4263 Fax: (800) 800-1052 available at <http://www.apregistry.com>

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