

KITSO AIDS Training Program

Lecture 12:

**Mother-to-Child-Transmission
and its Prevention**

- Outline**
1. HIV testing for pregnant women
 2. Interaction between HIV and pregnancy
 3. Mother-to-child-transmission (MTCT)
(timing and targeting prevention)
 4. Factors affecting MTCT
(maternal, obstetric, fetal, infant)
 5. Interventions to prevent MTCT
(ARVs, obstetric practices, infant feeding practices)

- HIV Testing for Pregnant Women**
- Pregnant women who test HIV-negative must receive ongoing counseling regarding safe sex, in order to avoid HIV infection during pregnancy, which could be transmitted to the baby. Such women should be advised to have repeat HIV testing if they have possible exposure to HIV infection during pregnancy.
 - Pregnant women who initially test HIV negative at ante-natal care registration should be retested either at 36 weeks gestation or at onset of labor, whichever comes first, in order to detect intercurrent HIV infection during pregnancy. If HIV positive, the patient should be managed as below, depending upon her eligibility for HAART.
 - Pregnant women with discordant rapid tests must have urgent and expedited HIV testing to rule out HIV infection (Lecture 3).

**Interactions
Between HIV and Pregnancy**

- **Effects of Pregnancy on HIV:** i.e., does pregnancy worsen HIV-related disease, including rate of progression to AIDS?
- **Effects of HIV on Pregnancy:** i.e., does HIV infection increase pregnancy complications and worsen outcomes?

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**Effect of Pregnancy on HIV:
Conflicting Conclusions**

- In the USA and Europe, there is no effect of pregnancy on the progression of HIV disease. (Absolute CD4 count may decline secondary to hemodilution of pregnancy, but CD4% remains stable.).

Versus

- In many developing countries, pregnancy accelerates HIV disease progression.
 - Poverty, malnutrition, hygiene problems, and civil unrest may be confounding factors.
 - Small samples, selection bias (stage of disease?)

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**Effects of HIV on Pregnancy:
Increased Risk of Adverse Events**




Increased risk:

- Prematurity
- Intrauterine Growth Restriction
- Stillbirth
- Infections
 - STI's, pneumonias, UTI's, OIs
 - Ectopic pregnancy
 - Amnionitis

However, there is no increased risk of congenital anomalies: HIV itself is not teratogenic.



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Timing of Transmission: Targeting Prevention
 (In untreated breastfeeding populations, total transmission rate is up to 40%)

- Pregnancy -----  (5 - 10%)
- Delivery -----  (10 - 15%)
- Breastfeeding -----  (10 - 15%)

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Timing of Transmission: Targeting Prevention
 (In untreated non-breastfeeding populations, total transmission rate is up to 25%)

- Pregnancy -----  (5 - 10%)
- Delivery -----  (10 - 15%)

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Timing of Transmission (3)

- As a general rule, it has been thought that the greatest HIV transmission occurs intra-partum, at delivery.
- However, data suggest that subtype C, the predominant subtype in Botswana, is associated with greater *in utero* transmission than other subtypes, especially in the weeks prior to delivery. This data stresses the importance of beginning non-HAART PMTCT with short-course ARVs at 28 weeks gestation, if the woman is not eligible for HAART for her own HIV infection.
- Data also suggest that subtype C is associated with greater MTCT rates and NVP resistance after sd-NVP prophylaxis.

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Factors Affecting Transmission

1. Maternal
2. Obstetric
3. Fetal
4. Infant

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1. Maternal Factors Increasing the Risk of Transmission

- High viral load: the most important maternal risk factor
 - Acute infection
 - Advanced Disease
- Impaired immunity (low CD4 count)
- Impaired nutritional status
- STIs, particularly HSV

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2. Obstetric Factors Increasing the Risk of Transmission

- Prolonged rupture of membranes (> 4 hrs): deliver the baby as soon after membrane rupture as possible.
- Intrapartum hemorrhage
- Invasive obstetrical procedures
 - Amniocentesis
 - Invasive fetal monitoring
 - Forceps

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3. Fetal Factors Increasing the Risk of Transmission

- Prematurity: a premature neonate's immune system is even more immature than at the time of normal term delivery.
- Multiple fetuses
 - First born infant has increased risk compared to subsequently delivered infant(s)

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4. Infant Factors Increasing the Risk of Transmission

- Breastfeeding
 - Mixed breast feeding
 - Exclusive breast feeding
- Oral Thrush: breakdown of mucosal barrier may facilitate acquisition of HIV both during delivery and with breast feeding.
- Prematurity: with prematurity, the infant's immune system is profoundly under-developed, and thus unable to avoid HIV infection.

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Prevention of Mother-to-Child-Transmission (PMTCT)

1. Antiretroviral Medications:
 - Treatment of the mother's HIV infection (HAART), which coincidentally also significantly prevents MTCT
 - Prophylaxis, to prevent transmission only (short-course ARVs to mother and infant)
2. Modifying Obstetric Practices
3. Modifying Infant Feeding Practices

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ARVs and PMTCT: General Principles

- ARVs reduce transmission
 - Lower viral load
 - AZT is most studied, and *by itself has PMTCT effects independent of its effect on viral load*. Thus, if possible, AZT should be included in HAART or in short-course prophylaxis for a pregnant woman, even if the woman has failed a prior AZT-containing regimen.
 - AZT, 3TC, NVP, and LPV/r considered safest
- ARVs for MTCT can be administered as:
 1. Maternal treatment program (HAART)
 2. Maternal/infant prophylaxis program (short-course ARVs to mother and infant)

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HAART and PMTCT: Advantages

- VERY low transmission rates (<1%).
- Use of multiple ARVs decreases the risk of developing resistance.
- HAART has PMTCT effects independent of its effect on viral load.
- In industrialized nations, HAART is recommended for all pregnant women with HIV RNA levels >1000 copies/mL, regardless of CD4 count.
- Pregnant women already on HAART should continue HAART, with any necessary regimen modification to protect both the mother and/or fetus (see below).

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HAART and PMTCT: 2008 Guidelines

- All HIV-infected pregnant women not already on HAART must receive priority scheduling for CD4 count and WHO staging, for evaluation for HAART eligibility. Failure to do so is a major dereliction of professional responsibility.
- HAART eligibility for all pregnant women is the same as that for other adults.
- In all cases, pregnant women who are eligible for HAART for their own HIV infection—i.e., women with CD4 counts < 250 cells/μL or with WHO stage 3 or 4 conditions--must be started on HAART, without exception. Because the woman's immune status is poor, HAART must not be deferred until the second trimester.

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**HAART and PMTCT:
 2008 Guidelines (2)**

- If CD4 count is < 200 cells/μL or a WHO stage 3 or 4 condition is present, the pregnant woman *must* be started on CTX prophylaxis: pregnancy is NOT a contraindication to CTX prophylaxis, nor is breastfeeding.
- Any pregnant woman who is not on HAART, and who presents for care at 28 weeks gestation or more must immediately be started on AZT 300 mg BD. The patient must then have urgent priority CD4 and clinical screening to determine whether or not she is eligible for HAART.
 - If eligible, and if baseline preparations are complete, then begin HAART, regardless of how late the pregnancy is. Unless active labor has started, there is no point in a pregnancy where it is too late to begin HAART.
 - If not eligible for HAART, continue AZT 300mg BD and refer to PMTCT program for short-course ARV prophylaxis (below).

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**HAART and PMTCT:
 2008 Guidelines (3)**

For pregnant women who are eligible for HAART (either by CD4 count or WHO clinical conditions), the recommended ARV regimen depends upon the baseline CD4 count:

- If baseline CD4 cell count is < 250 cells/μL:
 AZT + 3TC + NVP
- If baseline CD4 cell count is > 250 cells/μL:
 AZT + 3TC + LPV/r
- After patient preparation, begin HAART promptly, *regardless of the stage of pregnancy.*
- If baseline HgB is < 7gm/dL, d4T should be used in place of AZT.

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Management of Patients on HAART During Labor

- At the onset of labor, all women on HAART must still receive high-dose AZT:
 - At onset of labor, supplemental AZT 300mg po every 3 hours until delivery, to a maximum of 1500mg.
 - Sd-NVP should not be administered.
 - If the woman is on d4T-containing HAART at the time of labor, one of two options should be chosen:
 - Discontinue d4T and begin AZT 300mg po every 3 hours until delivery, to a maximum of 1500mg. This approach is preferred, if the patient is able to tolerate AZT. Transfuse the patient as needed.
 - Continue d4T and do not administer AZT.

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Safety of HAART in Pregnancy

- AZT + 3TC + NVP is recommended as 1st line regimen, if the CD4 count is < 250 cells/ μ L. If the CD4 count is > 250 cells/ μ L, use AZT + 3TC + LPV/r.
- In pregnancy, ddl and d4T increase the risk of lactic acidosis and pancreatitis.
 - If there is no prior history of possible AZT resistance, then replace d4T/ddl with AZT/3TC.
 - If a patient is on ddl+d4T, and has a history of probable resistance to AZT and 3TC (e.g., 1st line regimen failure), consult an HIV Specialist regarding possible ARVs to replace d4T/ddl.
 - If no alternatives exist, d4T/ddl can be used in pregnancy, but with close follow-up and patient education re: symptoms of lactic acidosis and pancreatitis.

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Safety of HAART in Pregnancy (2)

- SQV and RTV are alternative PIs.
- Do not use NFV because of September 2007 FDA prohibition re: presence of carcinogenic and teratogenic impurities.
- Do not use EFV re: teratogenicity.
- Compared to no therapy, HAART confers no additional risk of PTD, LBW, low Apgar scores, or stillbirth.
- There is possible association of PI containing regimens and increased risk of VLBW.

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HAART and PMTCT: Special Considerations

- First trimester exposure to EFV is not a medical indication for abortion, since the risks of teratogenicity are very small. The risk of EFV during the 2nd and 3rd trimesters is unknown, and its use during later pregnancy is not recommended.
- Routine IPT should not be initiated during pregnancy. If the woman has been on IPT for at least 3 months when she becomes pregnant, the IPT can be continued to conclusion.

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**HAART and PMTCT:
 Special Considerations (2)**

- Nausea and vomiting secondary to pregnancy must be addressed promptly and intensively, to minimize non-adherence and/or decreased ARV absorption.
- The dosages of ARVs are unchanged during pregnancy, and HAART monitoring is the same.

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**Prophylaxis and PMTCT:
 Short-course ARV Programs for PMTCT**

- Regimens of short-course ARVs are given to reduce transmission of HIV from a mother to her baby. Such regimens do *not* treat the mother's HIV infection.
- If a pregnant woman is ineligible for HAART, then administer short-course AZT 300mg BD beginning at 28 weeks (or promptly at presentation beyond 28 weeks). Whether or not single-dose NVP (sd-NVP) is given at delivery depends upon the duration of AZT received prior to delivery:
 - If the woman has received at least 4 weeks of AZT, sd-NVP should NOT be given at labor.
 - If the woman has received < 4 weeks of AZT, sd-NVP 200mg should be given at onset of labor (do not repeat).
 - If the history and clinic records are unclear as to how long the patient has been on AZT, then give sd-NVP.

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**Prophylactic Short-Course ARVs for
 PMTCT: the Mother**

Mother: From 28 weeks gestation: AZT 300mg PO every 12 hrs
 At the onset of labor, administer supplemental AZT 300mg PO every 3 hours (to a maximum 1500mg).
 Use of sd-NVP will depend upon the duration of AZT prophylaxis prior to labor:

- > If the woman has received at least 4 weeks of AZT prior to labor, do NOT give sd-NVP.
- > If the woman has not received at least 4 weeks of AZT prior to delivery, then give sd-NVP 200mg po at the beginning of labor (*do not repeat*).
- > If duration of AZT prophylaxis is unknown, give sd-NVP.

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Prophylactic Short-Course ARVs for PMTCT: the Mother (2)

- PMTCT protocol for mothers identified positive only in labor:
 - sd-NVP 200mg PO at the beginning of labor (do *not* repeat),
 - Supplemental AZT 300mg PO every 3 hours (to a maximum of 1500mg)
 - Post-partum referral for CD4/clinical screening, to determine HAART eligibility and to begin routine care.
- If mother is unable to take AZT orally during labor, give IV: 2mg/kg loading dose, followed by 1mg/kg every hour until delivery.

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Prophylactic Short-Course ARVs for PMTCT: the Infant

Regardless of whether or not the mother received any ARVs during pregnancy or delivery, short-course ARVs to the infant will further decrease MTCT. These interventions must be made as soon as possible after delivery, to maximize PMTCT:

- NVP syrup 6mg as a single dose as soon as possible after delivery, but no later than 72 hours after birth. Preterm (< 35 weeks gestation) and low birth weight (< 2.5 kg) babies: give 2mg/kg NVP.
- AZT 4mg/kg every 12 hours for 4 weeks. Preterm or low birth weight babies: AZT 2mg/kg every 12 hours for 2 weeks, and then 2mg/kg dose every 8 hours (TDS) for the final 2 weeks. If unable to take AZT po, then give per NG tube.
- If the infant is brought in > 72 hours after birth, do not give either sd-NVP or AZT.
- Infant Formula, provided for up to the first 12 months of life

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Special PMTCT Considerations (2): Severe Anemia

- Anemia during pregnancy may complicate use of AZT for PMTCT, both with HAART and with short-course prophylaxis. Such anemia can occur at baseline and/or after initiation of AZT.
 - Every effort should be made to use AZT, because of its demonstrated PMTCT efficacy. Both for the viability of the pregnancy and for allowing use of AZT for PMTCT, transfuse the patient as needed.

(continued)

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PMTCT and Severe Anemia (continued)

- If transfusion is not possible, or if AZT-induced anemia is not manageable with transfusion, then switch to full d4T-containing HAART (both for women on AZT-containing HAART *and* for women only on short-course AZT prophylaxis).
 - Baseline CD4 cell count must determine whether the HAART is NVP- or LPV/r-based, especially for women on AZT prophylaxis.
 - If anemia improves on d4T-containing HAART, consider later switching to AZT-based HAART, with close monitoring of HgB. If AZT cannot be used pre-partum, then still try to use it during delivery, with transfusion support as needed.
 - After delivery, women who were initially eligible for HAART should be switched to TDF-containing HAART. Women who were not initially eligible for HAART must be discussed with an HIV Specialist regarding whether HAART should be discontinued, until they eventually become eligible.

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**Prophylaxis Regimens:
Safety and Resistance Issues**

- Safety and drug resistance in the fetus
 - AZT: > 10 yr f/u with no adverse effects
 - sd-NVP: several year follow-up, with no adverse effects, except for high incidence of NVP resistance, which may seriously compromise any subsequent NNRTI-based HAART for such children. When HAART is eventually required, HIV-infected children with a history of sd-NVP should be initiated on LPV/r-based HAART.
- Drug resistance in the mother
 - AZT : because of high genetic barrier, minimal resistance, if any
 - sd-NVP: 50-90% develop NVP resistance mutations, which may compromise NNRTI-based HAART, especially if initiated within 6 months of sd-NVP.

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Obstetric Practices and PMTCT

- Avoid artificial rupture of membranes.
- Minimize interval between membrane rupture and delivery.
- Avoid invasive procedures/instrumented deliveries, whenever possible. If instruments required, use plastic suction cups.
- Avoid episiotomy, whenever possible.
- Perform vaginal cleansing.

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Obstetric Practices and PMTCT: (2)

- In the west, *elective* cesarean section is advised when the viral load is >1000 copies / ml. Limited resources preclude this practice in Botswana, except in the private sector.
 - In some studies, C-section has up to 60% increased complication rate in HIV-infected women.
 - 2008 guidelines permit *elective* C-section in the private sector when maternal viral load is > 1000 copies/mL.
- There may arise in the public sector rare instances where *elective* C-section may be medically indicated for the health of an HIV-infected woman and/or her baby (e.g., known placenta previa, abnormal fetal position). When intravenous AZT is not available for administration during the procedure, AZT 600mg po should be given 3 hours before the elective C-section.

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Infant Feeding Practices

- Formula Feeding
 - (-) Complete avoidance of breast feeding and its nutritional and immunological benefits; possible stigma
 - (+) Avoids post-natal HIV transmission
- Exclusive Breast feeding
 - Situational avoidance of breast feeding (infections, skin breakdown)
 - Early cessation of breastfeeding with rapid weaning at 6 months (to avoid mixed feeding)
 - (+) Reduces incidence of respiratory and diarrheal infections, improves nutrition, and avoids mixed feeding.
 - (-) Exposes infant to post-natal HIV transmission
- Mixed Feeding
 - Breast feeding with the addition of any other liquids/solids (including formula)
 - (-) Confers the risks of breast feeding without the benefits

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Infant Feeding Recommendations: 2008 Guidelines

First Best: Exclusive formula feeding, when clean water, patient education, and safe methods of formula preparation, including fuel for heating, are available. Exclusive formula feeding must be AFASS (next slide).

- Babies in this strategy should NEVER receive breast milk.
- Supplemental liquids (water, juice) and solids (tsabana, cereal) may be introduced at 6 months of age.

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**Successful Exclusive Formula Feeding:
“AFASS”**

- **Acceptable:** The mother perceives no significant barrier(s) to choosing a feeding option for cultural or social reasons, or for fear of stigma and discrimination
- **Feasible:** The mother has adequate time, knowledge, skills, social/family support, and resources to obtain formula regularly, to prepare feeds, and to feed the infant.
- **Affordable:** The mother and family, with available community and/or health system support, can pay for the costs of the replacement feeds – including formula, fuel (to boil water), and clean water – without compromising the family’s health and nutrition spending.
- **Sustainable:** The mother has access to a continuous and uninterrupted supply of formula until the infant is 12 months old.
- **Safe:** Formula is correctly and hygienically stored, prepared, and fed in nutritionally adequate quantities; infants are fed with clean hands and using clean utensils, preferably by cups.

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**Exclusive Formula Feeding:
Special Considerations**

- *Women deciding to use formula must be taught how to use formula safely: women should not simply be given formula and told to use it.*
- If refrigeration is available, prepared formula can be stored prior to use for up to 24 hours, after which time it should be discarded. However, if refrigeration is not available, each feed must be made fresh, to be used *within 1 hour of preparation.*

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**Exclusive Formula Feeding:
Special Considerations (2)**

- Bottles should be avoided, but if a woman decides to use a bottle, then both bottle and teat should be immersed in boiling water for 10 minutes before each use.
- Because monthly formula requirements often exceed standardized guideline “averages,” clinics which dispense formula must not turn away a mother who requests additional formula for her baby, and must provide additional formula. However, follow-up home visits should be done to access proper formula use.

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Infant Feeding Recommendations (2)

Second Best: Exclusive Breast feeding

- Mixed feeding is NOT recommended at any time. Non-breast milk liquids/foods can irritate the infants intestinal tract, thereby facilitating HIV infection.
 - Any liquid (including water) or solid food must NOT be given during exclusive breastfeeding.
 - Early solids during breastfeeding has been shown to increase MTCT.
- Stop breastfeeding at 6 months, to minimize exposure to HIV.

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WHO / UNICEF / UNAIDS (2000)

- Women should be empowered to make fully informed decisions regarding infant feeding.
- Women who have access to clean water and formula should be encouraged to exclusively formula feed.
- Overall, an informed mother is in the best position to decide how to feed her infant(s).

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Reproductive Choices and HIV

National Guidelines recognize the desire of HIV-infected couples (discordant and concordant) to have children:

- Couples should be counseled about adoption.
- Intercourse for conception should be confined to the fertile period, and ideally the HIV-infected partner(s) should have undetectable viral load(s) at the time. There should also be no genital ulcer disease, at the time of unprotected intercourse, as well as no "dry" sex.
- As a rule, the woman should be counseled to defer pregnancy until her general health has improved on HAART, with increased weight, high CD4 count, and undetectable viral load. However, the woman must ultimately control her own reproductive potential.
- Couples must be informed about risks of unprotected sex. Post-sexual prophylaxis is *not* indicated.

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2008 Guidelines: Pending Pilot Study on HAART for All Pregnant Women

- In the west, HAART is offered to all HIV-infected pregnant women, regardless of CD4 count or clinical stage, since HAART provides the greatest degree of PMTCT.
- With the release of the 2008 revised guidelines, the Ministry of Health will develop and implement a pilot study to explore the feasibility of HAART for all pregnant women, regardless of immune or clinical status. The site(s) of the pilot study will be announced once the details of the program have been developed.

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