

Preventing mother-to-child transmission of HIV

Unit 4.1

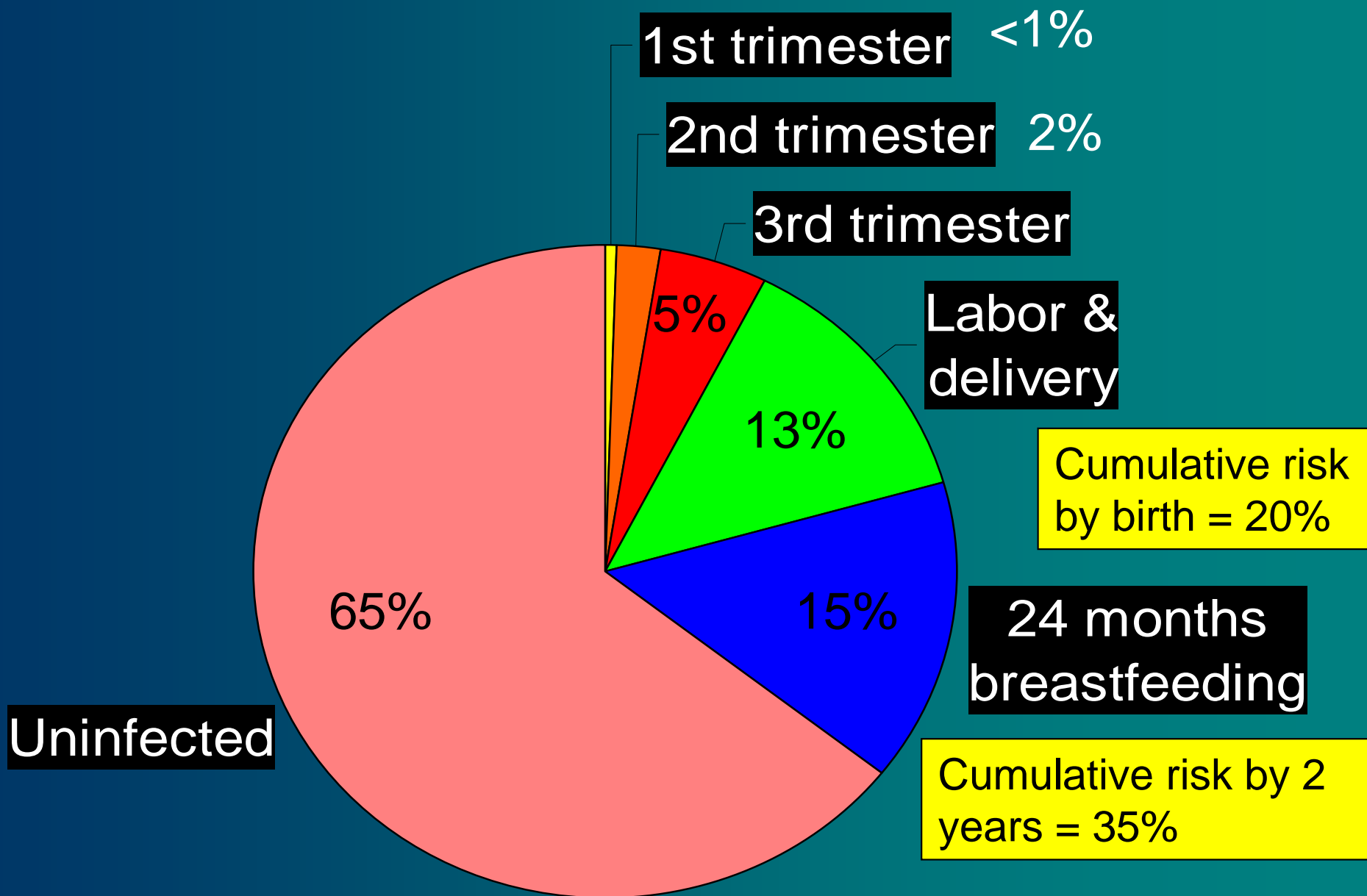
Paediatric Antiretroviral Therapy Workshop
Institute for Human Virology-Nigeria ACTION
Abuja
24-28 July 2006

Goals



- Know the risk of HIV transmission during pregnancy, labor, and delivery
- Identify the steps at which MTCT of HIV can be prevented
- Appreciate differences in effectiveness of PMTCT antiretroviral regimens
- Recognize the major risks of antiretroviral prophylaxis of MTCT of HIV

Risk of mother-to-child transmission of HIV during pregnancy, delivery, and breastfeeding



Challenges in PMTCT



- Preventing HIV in young women
- Preventing unintended pregnancy in HIV+ women
- Diagnosing HIV *early* in pregnant women
- Getting ARV prophylaxis started before transmission can take place
- Reducing transmission risk at term
- Preventing transmission from breast milk *while protecting child against diarrhea and malnutrition*
- Avoiding ARV resistance

PMTCT: Four targets for a comprehensive approach



- Prevent young women from becoming infected
- Prevent unintended pregnancy in HIV-infected women
- Prevent HIV-infected women from transmitting HIV to their infant
- Provide HIV care, treatment, and support to HIV+ women, their infants, and their families

Primary Prevention of HIV in Young Women: The ABCs



- **Abstinence**
 - Delay age of onset of sexual activity
 - Avoid intergeneration sex
 - Empower women: freedom from coercion
- **Be faithful**
 - A single sexual partner
 - HIV testing of both
 - For women *and men*
- **Condoms**

Intergenerational sex and HIV infection of young women



- Transmission of HIV from older to younger people is necessary to maintain virus in population- without sex between older and younger populations epidemic would fade as infected persons age
- Pressures on young women to have sex or marry older men
 - Dominance of older males in society
 - Family pressure
 - Economic
 - Social status

Case 1



- 14 Dec- 19 year old presents to an antenatal clinic with LNMP 21Aug. ELISA/WB confirms HIV.
- 25 Jan- told she has HIV and is prescribed ZDV/3TC.
- 19 Mar- Noted that ZDV/3TC prescription not filled. Viral load 15,487 c/ml. Pt. denies HIV diagnosis. Referred to UMMS.
- 5 Apr- Initial UMMS visit. Viral load 5,216. CD4 = 543/ul.
- 9 Apr- Post-test counseling. "Not ready" to start treatment.
- 16 Apr- Receiving ZDV/3TC/NVP
- 7 May- Viral load = 84 c/ml.
- 19 May- Presents in labor, given IV ZDV, delivers, infant started on ZDV.
- Child ends up HIV+

Preventing mother-to-child transmission of HIV



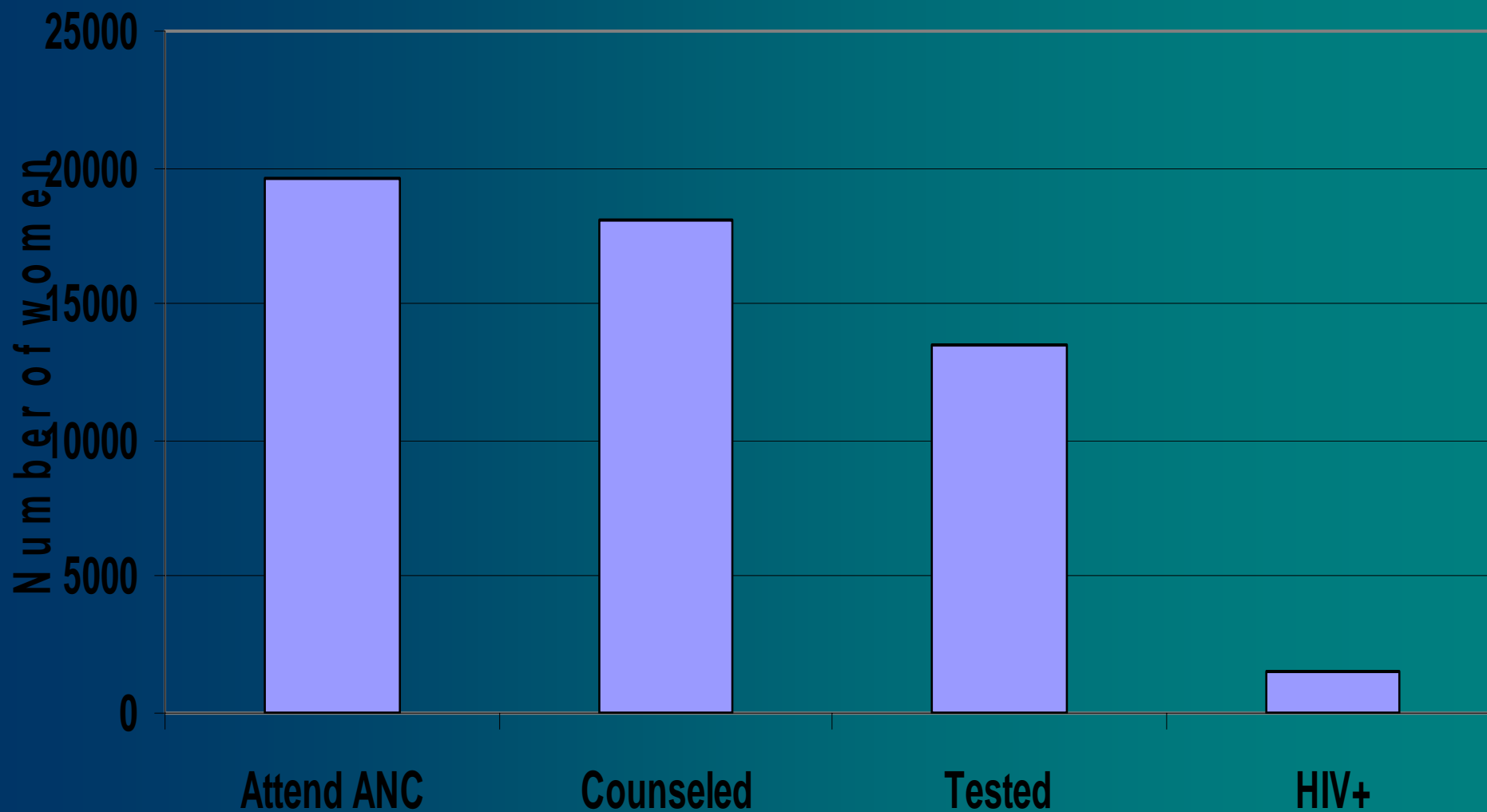
- Identify, engage, and track infected women
- Prenatal, intrapartum, and neonatal antiretroviral prophylaxis
 - Reduce maternal viral load to undetectable
 - Load fetus and newborn with prophylactic drugs
- Obstetric: A safe delivery
 - Avoid relying on C-section
 - Prematurity and prolonged rupture of membranes increase risk
- Care of exposed infant
 - Nutritional support
 - Quickly identify infected infants
 - Antiretroviral and PCP prophylaxis & therapy

Lessons from perinatal prevention trials

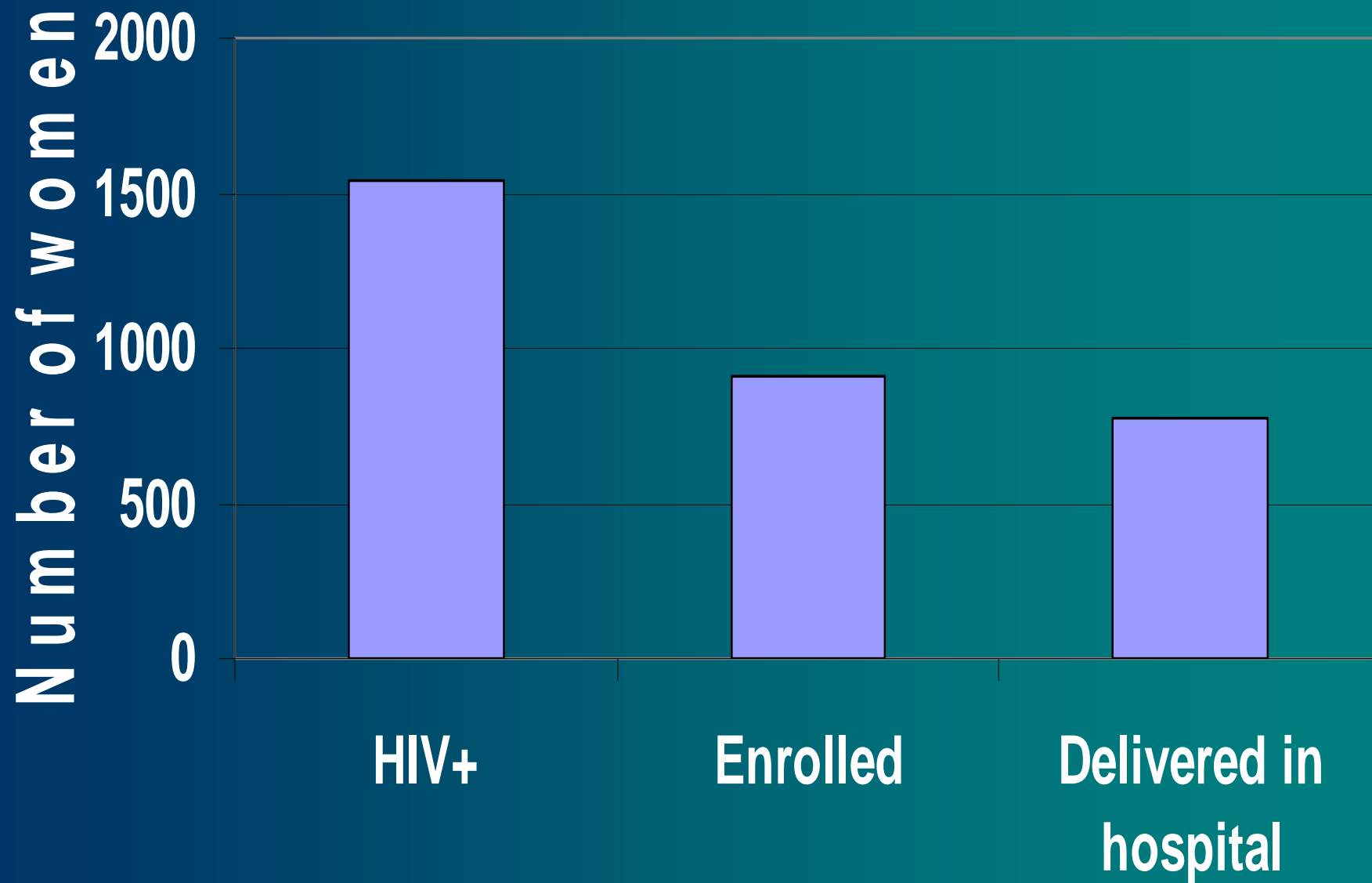


- Timing of infection: 1st < 2nd < 3rd trimesters < L&D = breastfeeding
 - About 25% of transmission occurs prior to labor and 35% postnatal: *no intrapartum intervention can affect this*
- Prophylactic efficacy related to *duration* and *intensity* of maternal antiretroviral therapy
- *Elective* C-section reduces risk to infant *at risk*
- Duration & intensity of neonatal prophylaxis not critical *if* mother received prenatal treatment

Uptake into PMTCT program, Nsambya Hospital, Kampala (Bassani 2004)



Treated women in PMTCT program, Nsambya Hospital, Kampala (Bassani 2004)



Enrolling and retaining women and children in PMTCT



- Public awareness of value of VCT & PMTCT: this will take time
- Training and support at antenatal clinics
 - VCT: Acceptance of tested related to quality of counseling
 - Laboratory
 - Information management
- Bridging the gap between the ANC and maternity services
 - At what point to transfer care?
 - Ensuring that woman and information make the transition

Enrolling and retaining women and children in PMTCT (2)



- Ensuring intrapartum prophylaxis
 - Most deliveries at night or on weekends: information and drug must be available
 - Fear of breach of confidentiality
- Infant dosing and feeding
 - Counseling on feeding choices should have been done at prenatal visits
 - If infant to go home on medication: demonstration, drug supply, etc. prior to leaving maternity site.

Enrolling and retaining women and children in PMTCT (3)



- Follow up of infants
 - Must monitor infants to measure program outcome
 - Nutritional support
 - Testing for HIV
 - TMP/SMX (Bactrim) prophylaxis
 - An avenue to getting mothers, fathers, & siblings tested or into care

Antiretroviral prophylaxis against mother-to-child transmission of HIV



- Prenatal: Preventing infection of the fetus
- Intrapartum: Preventing infection during labor and delivery
- Postpartum neonatal: Preventing intrapartum infection from becoming established
- Infant : Preventing transmission during breastfeeding

How do antiretrovirals prevent mother-to-child transmission?



- Reduction of maternal viral load
- Loading fetus with prophylactic drug that prevents transmitted virions from replicating

Antiretroviral (ARV) Treatment versus Prophylaxis



- *ARV Treatment*
 - Long-term use of antiretroviral drugs to treat maternal HIV/AIDS and prevent PMTCT
- *ARV Prophylaxis*
 - Short-term use of antiretroviral drugs to reduce HIV transmission from mother to infant

- Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- Zidovudine ZDV, AZT
- Stavudine D4T
- Lamivudine 3TC
- Didanosine DDI
- Abacavir ABC
- Tenofovir TDF

* A nucleotide RT inhibitor.

A quick introduction to ARVs (2)



- Non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs)
 - Nevirapine NVP
 - Efavirenz EFV
- HIV protease inhibitors (PIs)
 - Lopinavir/ritonavir LPV/r
 - Nelfinavir NFV
 - Saquinavir SQV
 - Indinavir IDV
 - Ritonavir (low dose) r

Effectiveness of antiretrovirals for PMTCT: Infection rates at 1 month



- Effectiveness depends on DURATION- how early in pregnancy treatment started, and on INTENSITY- how many drugs used
- No intervention: 20 % infected
- Single-dose NVP: 12 % infected
- ZDV from 28 weeks: 7 % infected
- 2 drugs: 1-4 % infected
- HAART: <1 % infected

Summary of Efficacy of ARVs for PMTCT



Intervention (IP = intrapartum)	% HIV+ at 1 month
None	~18-22%
Neonatal NVP or ZDV	13-21, 9.3-16.6
Neonatal ZDV/3TC or ZDV/NVP	14.2-15.3
Intrapartum/neonatal NVP	10.4-11.9
Intrapartum/neonatal ZDV	10-20
Intrapartum/neonatal ZDV/3TC	7.9-8.9
ZDV start 36-37 wk + IP + neonatal	9.6-15.1
ZDV start 35 wk + IP + neonatal	8.6-10.4
ZDV start 23-28 wk + IP + neonatal	4.3-8.3
ZDV/3TC start 36, 34, 23-32 wk	5.9, 2.8, 1.6
ZDV 34 wk ± IP NVP + neonatal NVP	4.3, 3.7
ZDV 28 wk + IP NVP ± neonatal NVP	1.1, 2.0
HAART 34 wk	3.6
Early HAART	<1

Caesarian delivery for PMTCT



- *Scheduled* Caesarian delivery reduces MTCT in infants *at risk of HIV transmission because mother is on no prophylaxis or inadequate prophylaxis (ZDV monotherapy only)*
- No evidence of efficacy after onset labor
- Increased morbidity in women with HIV
- Under conditions where safe, scheduled C/S can be performed, adequate ARV prophylaxis should be feasible

Antiretroviral therapy in pregnancy: Possible scenarios for HIV-infected women



- Women who may become pregnant
- Women who become pregnant while receiving antiretroviral therapy
- Women who have indications for starting HAART

WHO guidelines for ARVs for pregnant women and PMTCT:

1. Pregnant woman who is HAART eligible



- CD4 < 250
 - 2 NRTI + NVP
 - 2 NRTI + PI
 - 2 NRTI + EFV *3rd trimester only*
- CD4 >250
 - 2 NRTI + PI
 - 2 NRTI + EFV *3rd trimester only*
 - 2 NRTI + NVP *avoid; monitor carefully if used*

A: HIV+ women who may become pregnant and who require ART

- Standard WHO-recommended HAART
- Currently: D4T or ZDV + 3TC + NVP
- Avoid EFV if contraception cannot be assured

B: HIV+ women receiving HAART

- Continue HAART
- If 1st trimester
 - Replace EFV with NVP or PI
 - Use PI if CD4 > 250
- Continue TDF (*may change with TDF safety data*)
- Continue HAART in labor
- Neonatal ZDV X 1 wk, SD NVP, or both

C: HIV+ women with indications for ART (CD4 <200 or stage III-IV) or for whom ART should be considered (I or II and CD4 < 350, especially 200-250)

- May consider delay until end 1st trimester
- Otherwise, start HAART
- Include ZDV if not contraindicated
- If NVP contraindicated use PI
- (Risk if CD4 > 250 may not be as great as thought)

D: HIV+ women *without* indications for ART

Same regimen recommended for HAART
available or not available:

Antepartum: ZDV starting 28 weeks

Intrapartum: SD NVP* + consider 3TC

Postpartum: Consider ZDV + 3TC X 7 days

Infant: ZDV + 3TC X 7 days

(Extend ZDV to 4 weeks if < 4
weeks maternal ZDV)

*(consider omission of NVP if mother received > 4 weeks ZDV)

F: Options for women with TB

- “Triple NRTI”
 - (presumably ZDV/3TC/ABC but note rifampicin decreases ZDV +/- ABC exposure)
- EFV- based regimen “2nd and 3rd trimesters”
+ post-partum contraception if continued
- PI- based regimen: guidelines to be determined

G: Options for women of unknown HIV status or HIV+ presenting in labor without prior ARV

Option 1:

Intrapartum: ZDV + SD NVP

Infant: SD NVP + ZDV X 4 weeks

(Note: SD NVP to mom does not have NVP “tail” covered)

Option 2:

Intrapartum: ZDV + 3TC

Postpartum: ZDV + 3TC X 7 days

Neonate: ZDV + 3TC X 7 days

Option if minimal ARV capacity:

Intrapartum: SD NVP

Neonate: SD NVP

H: Infants of HIV+ women who did not receive ARVs prior to delivery

- Infant: SD NVP + ZDV X 4 weeks
 - (2004: SD NVP + ZDV X 1 week)
- Unlikely to be of benefit > 2 days after delivery
- (Note this regimen does not cover NVP “tail”- including neonatal 3TC would)
- (ZDV/3TC for 1 week in infant has efficacy similar to SD NVP)

Resistance to ARVs after PMTCT-1

- NVP single dose
 - 20-40% of mothers with detectable resistance
 - 46% of infants who fail prophylaxis have resistant virus
- Women who receive SD NVP and start on NVP-based HAART post partum have 49% treatment success versus 68% of those not receiving SD NVP
 - Starting HAART later may be more effective
- ZDV from 28 weeks + single dose NVP: 32-44% NVP resistance
- SD NVP *to women receiving ZDV/3TC from 32 weeks gestation until 3 days post partum*: 1% NVP, 8% 3TC resistance
- ZDV/3TC given to mom for 3-7 days after SD NVP reduces NVP resistance to 5-10%.

Resistance to ARVs after PMTCT-2



- ZDV monotherapy from 2nd trimester: little resistance
- ZDV/3TC: 3TC resistance depending on duration (about 30% after 3 months exposure)
- HAART regimens
 - No resistance if full suppression achieved
 - Varies according to regimen: NNRTI failure associated with rapid resistance- and failure rates at 1 year are 10-40%

Fetal & infant ARV toxicity- 1

- Placental transfer
 - Nucleoside RT inhibitors and NNRTIs cross placenta well
 - PIs cross in small amounts
- Teratogenicity
 - Concern mainly in 1st trimester
 - Efavirenz highly teratogenic in monkeys, similar cases in humans (not as common)
 - Others: no clear pattern of defects
- Infantile lactic acidosis
 - Persistent high lactate levels
 - Most associated with DDI

Fetal & neonatal ARV toxicity- 2



- Neurodegenerative mitochondrial disease in infants
 - Associated with continuous use of ZDV/3TC from 23-32 weeks gestation through 6 weeks postnatal
 - Not seen if ZDV/3TC given to mother only
 - Not seen in infants with HIV treated early in life with ZDV/3TC
- Other fetal or neonatal effects
 - Anemia: zidovudine
 - ? Potential for increased bilirubin: atazanavir, indinavir, TMP/SMX
 - ? Bone toxicity: TDF

Maternal ARV toxicity

- GI upset: most protease inhibitors (except nelfinavir)
- Anemia: zidovudine
- Hepatic toxicity
 - Nevirapine, especially if CD4 >250 and female
 - Other ARVs
 - D4T+DDI in combination: hepatic steatosis, hepatic failure around term: *contraindicated in pregnancy*
- Glucose intolerance: PIs (except atazanavir)

Summary of key points-1



- Early, potent ART almost eliminates MTCT of HIV up through delivery
- 2-3 drug ARV prophylaxis intrapartum minimizes intrapartum MTCT
- Resistance to NVP is common in mothers and in infants failing SD NVP prophylaxis *given without 2 more drugs*
- Continuing NRTIs for ~1 week after SD NVP minimizes risk of resistance

Summary: Antiretroviral prophylaxis and treatment in pregnancy



- Antenatal, intrapartum, and postpartum care of woman, infant, and family must be coordinated
- If a pregnant woman needs HAART, then start HAART
- Options for women who do not require HAART:
 - HAART (stop after deliver)
 - ZDV or ZDV/3TC *plus* SD NVP in labor *plus* 2 weeks ZDV/3TC postpartum
 - Postnatal choices may be different if mother breastfeeds infant

Summary: Antiretroviral prophylaxis for infant



- If mom received ARV during pregnancy: infant prophylaxis less important
 - (Nigerian guidelines: SD NVP + ZDV X 6 weeks)
- If mom did not receive prophylaxis until near term, in labor, or not at all:
 - SD NVP + ZDV/3TC X 1 month
 - ZDV/3TC X 7 days (8.3% transmission)
 - (Nigerian guidelines: SD NVP + ZDV X 6 weeks)