The Sexually Transmitted Diseases

Infections in pregnancy

Infections in Pregnancy

- STDs/HIV and other infections (B strep, malaria)
- Direct infection of fetus/infant
- Indirect effects of inflammatory response in fetus or mother

Routes of Intrauterine Infection

Pregnancy

- Hematogenous Transplacental
  - Syphilis, HIV, malaria
- Ascending Infections
  - Gonorrhea, Chlamydia, BV

Chorioamnionitis

Intrapartum

- HIV, Hepatitis B, HSV-2, HPV
- Gonorrhea, Chlamydia, Group B Strep

Lactation

- HIV
- Syphilis

Maternal-Infant Infections During Pregnancy

STDs

- Viruses (HIV, HSV-2, HPV)
- Bacteria (Syphilis, Gonorrhea, Chlamydia)
- Trichomonas

Other Genital Tract

- BV
- Group B Strep

Other Systemic Infections

- Parastitic (Malaria)
- Viruses (Rubella, Hepatitis B, CMV)
- Bacterial (TB)

Fetal/Infant outcomes

- **Pregnancy Loss, perinatal and infant Death**
- Direct infection of fetus/new born (congenital)
- Effects via preterm birth and low birth weight

Birth Outcomes

Outcomes:

- Preterm Delivery <37 weeks (PTD)
- Premature rupture of membranes (PROM)
- Low birth weight (< 2500 gm)

Etiology:

- HIV
- Syphilis
- Gonorrhea/Chlamydia
- BV
- Trichomonas
- Chorioamnionitis

Frequency of transmission to infants

- Syphilis ~ 70% of infants affected in primary, secondary and early latent maternal syphilis
  - SAB/stillbirth/infant death
  - congenital syphilis
- Gonorrhea ~ 45% ophthalmia → blindness
- Chlamydia ~ 50% low grade ophthalmia or pneumonia
- HIV: 14-44% infants infected without treatment

Pregnancy outcome with treated and untreated active syphilis, Tanzania

Pregnancy outcome	Untreated active syphilis %	Treated active syphilis %
Stillbirth	24.6	2.3
Low birth weight	32.7	6.3
Preterm	20.0	8.5

Watson-Jones *et al JID* 2002;186:186 and 194

Placental membrane infections

- Chorioamnionitis, funistis (cord), amniotic fluid infection, fetal infections
- Probably due to organisms from the vagina which ascend into the uterus early in pregnancy
- Often asymptomatic
- Direct effects of infection
- Indirect inflammatory effects

Anatomy of Chorioamnionitis, Amniotic Fluid and Fetal Infections (Goldenberg NEJM 2000)

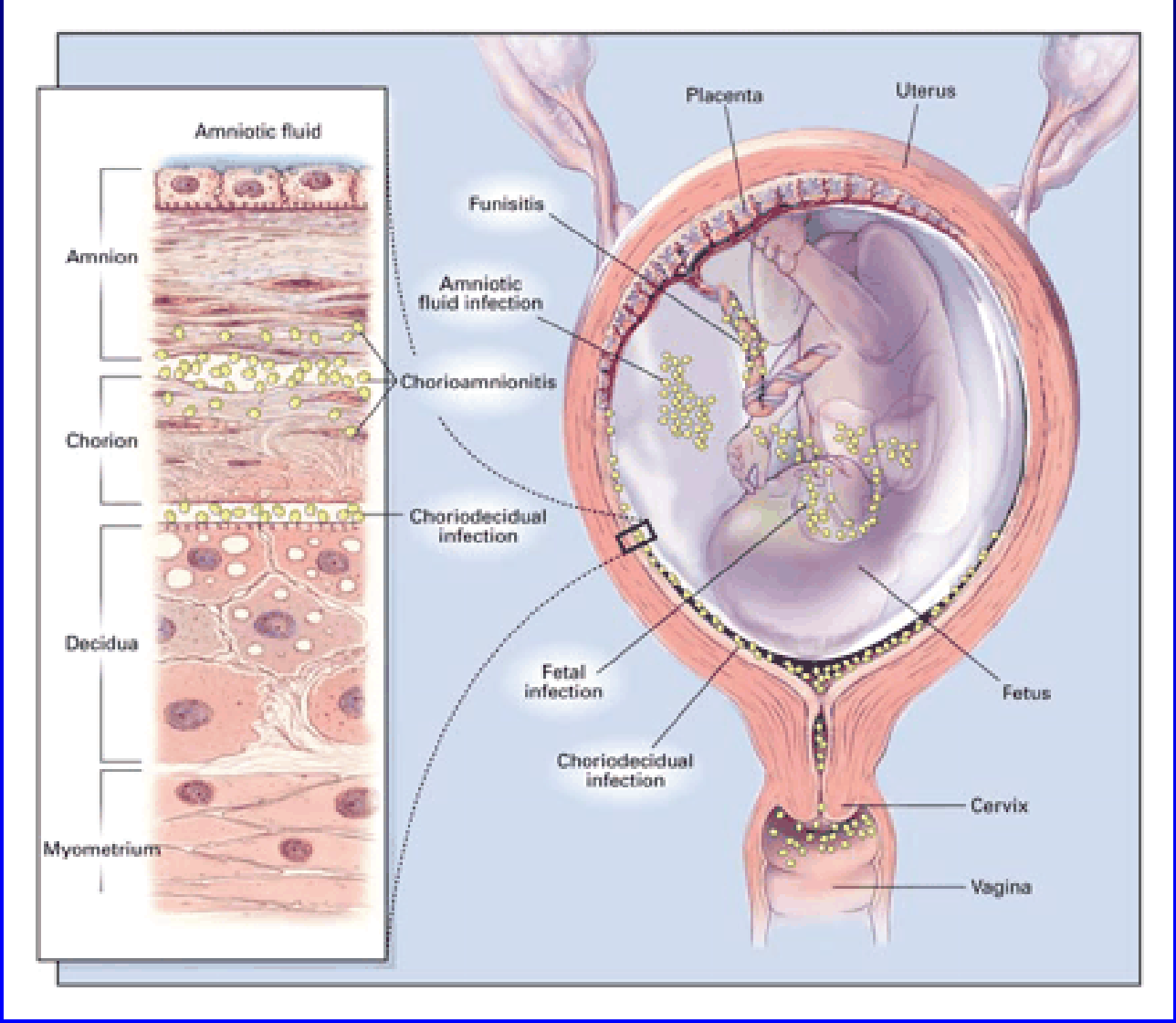
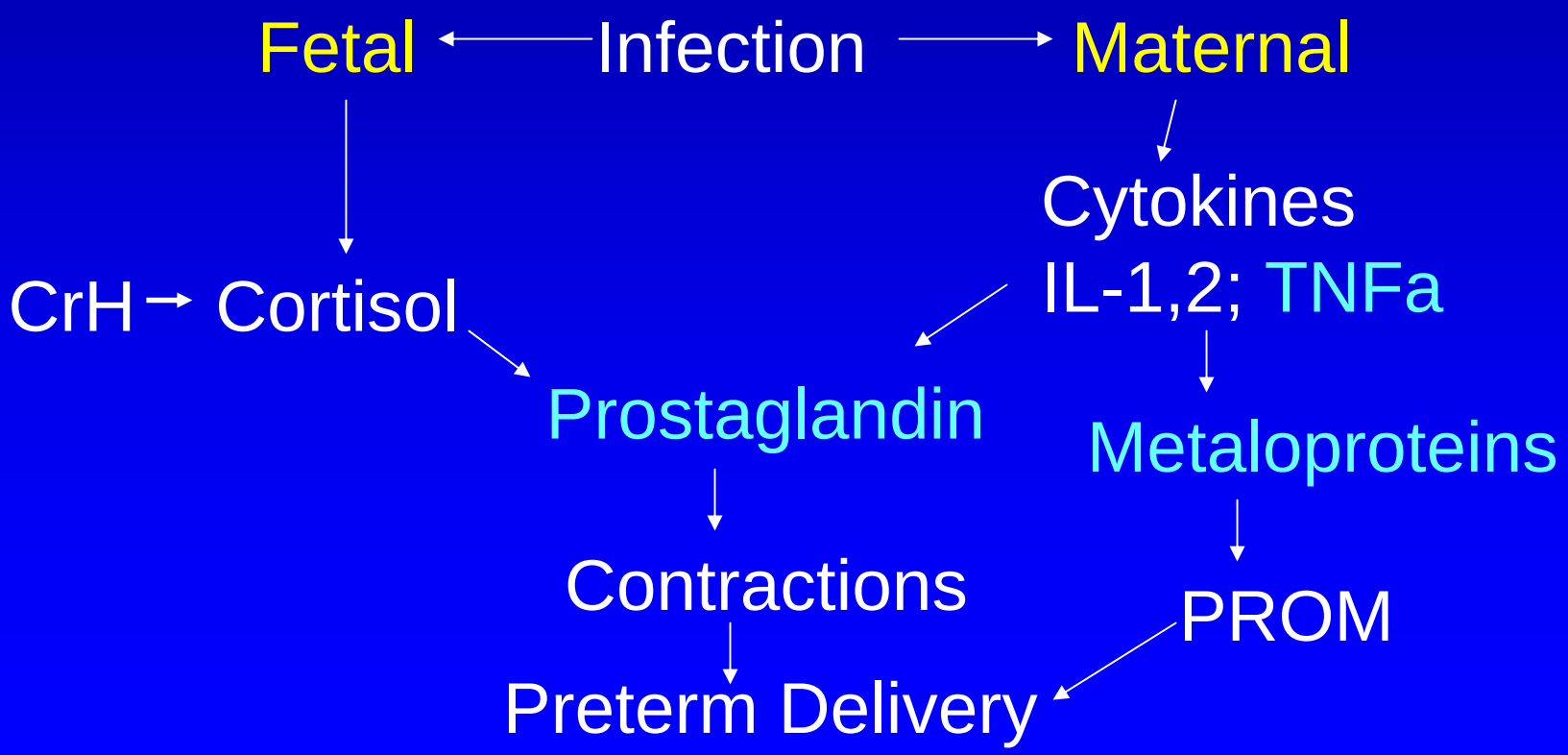


Figure 1. Goldenberg RL, et al. Intrauterine Infection and Preterm Delivery. NEJM 2000;342:1500-1507.

Inflammatory Response in Fetus and Mother

- **Inflammatory response to infection**



Preterm Delivery (PTD)

- Delivery < 37 weeks
- ~ 10% births in US (higher in African American mothers)
- 70% perinatal deaths are PTD
- 50% of long-term neurologic morbidity PTD
- Most serious morbidity/mortality in PTD < 32 weeks and very low birth weight (VLBW < 1500 g)

Bacterial Vaginosis (BV)

- BV is the most common vaginal infection
  - 10-50%
- Disturbances in the vaginal flora
  - loss of peroxide producing lactobacilli,
  - increase in predominantly anaerobic flora,
  - increase in vaginal pH
- Most women are asymptomatic
- BV implicated in chorioamnionitis, PTD PROM, and PID

BV Diagnosis

- Clinical (Amsel criteria)
  - **Raised (alkaline pH)**
  - **Discharge**
  - **Amine odor (KOH whiff test)**
  - **Clue cells**
- Gram stain morphology (Nugent's score)
  - **0-4 normal**
  - **4-6 intermediate**
  - **7-10 BV (low or no Lactobacilli, anaerobes, Mobiluncus)**

BV and Preterm Delivery (PTD) or Low Birth Weight (LBW)

- **Observational studies**
- BV and PTD RR ~1.6
- BV associated with chorioamnionitis and amnionotic fluid infections
  - Elevated cytokines
  - Elevated prostaglandin ⟶ PTD

Treatment of BV

- Metronidazole or Clindamycin ~ 70-85% cure over 1 month
- Treats anaerobic overgrowth, but does not restore Lactobacilli
- BV tends to be recurrent following treatment because of depletion of lactobacilli
  - Role of bacteriophages?

Trials in high risk women (prior preterm delivery or other risk factors)

References	Treatment in pregnancy	RR of PTD
McGreggor AJOG 1995	Clindomycin	0.52*
Ugwumadu Lancet 2003	Clinindomycin	0.42*
Morales AJOG 1994	Metronidazole	0.46*
Mc Donald BJOG 1997	Metronidazole	0.14*
Hauth NEJM 1995	Metronidazole	0.63*
Andrews AJOG 2006	Metronidazole (preconception	1.1

Trials in low risk women or general populations

References	Tmt	RR PTD
Carey NEJM 2000	Mtz	1.0
Goldenberg AJOG 2006 HIV+ HIV- (LMP subgroup)	Mtz	 1.0 1.0
McDonald BJOG	Mtz	0.96

BV and PTD Conclusions

- BV treatment during pregnancy reduces PTD in high risk women with BV in most trials
- PTD not reduced in lower risk women
- Metronidazole alone less efficacy than combined metronidazole plus macrolide antibiotics (clindomycin, erythromycin, azithromycin)
  - Possibly via suppression of TNFa

Treatment of Trichomonas in pregnancy

Metronidazole in women with Trichomonas (MFNU Study)

(Klebanoff NEJM 2001;345:487)

- 617 women asymptomatic trichomonas randomized to Metronidazole 16-23 weeks & 24-29 wks.

- PTD
  - Metronidazole = 19.0%
  - Placebo = 10.7%
  - RR = 1.8 (1.2-2.7)
- VLBW <1500 gm
  - Metronidazole = 5.4%
  - Placebo = 3.8%
  - RR = 1.4 (0.7-3.0)

Rakai Trial; Trichomonas Treatment (Kigozi AJOG 2003)

- Subanalysis of women with Tv in Rakai trial
  - Treatment arm n = 94
  - Control arm n = 112
- LBW RR = 2.49 (1.12-5.50)
- PTD RR = 1.28 (0.81-2.02)
- Mortality RR = 1.58 (0.99-2.52)

Other treatment of infection in pregnancy

- Presumptive treatment
- Birth canal cleansing
- Syndromic management

Presumptive STD Treatment in Pregnant Women (Gray AJOG 2001)

- Intervention arm -single, oral, directly observed therapy:
  - azithromycin 1 gm, cefixime 400mg., and metronidazole 2 gram
- Control arm
  - -iron/folate
- Serologic syphilis IM benzathine penicillin 2.4 million units
  - Home tmt in intervention
  - Referral for free tmt in control

Baseline Maternal Infections in Pregnancy (Rakai, Uganda)

Infection	Prevalence (%)
BV	50%
Trichomonas	25%
Syphilis	10%
Gonorrhea	2%
Chlamydia	3-4%

Maternal STDs Postpartum

Maternal STDs	Intervention vs Control RR (CI)
Syphilis	1.0 (0.8-1.3)
BV	0.75 (0.7-0.8)
Trichomonas	0.3 (0.2-0.5)
Gon/Chlamydia	0.4 (0.3-0.7)

Infant Outcomes

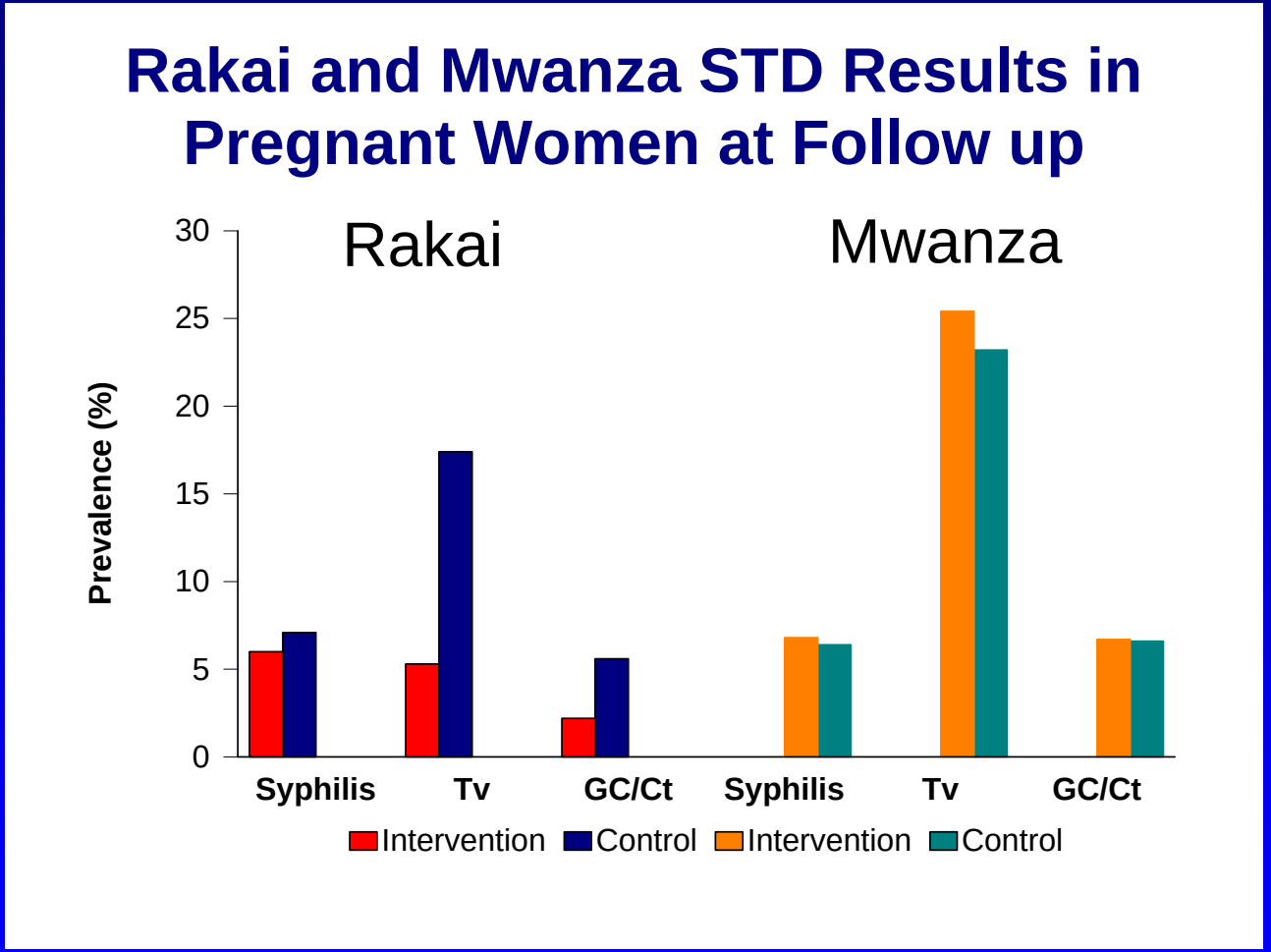
Outcomes	Intervention vs control RR (CI)
Gonorrhea/chalmydia	0.38 (0.2-0.7)
Low birth weight	0.70 (0.51-0.96)
Preterm	0.73 (0.54-0.99)
Neonatal death	0.83 (0.71-0.97)

Presumptive Ceftrioxone in pregnancy

(Temmerman J Repro Med 1995)

- Nairobi trial 209 women ceftrioxone IMI, 191 control, at 28-32 weeks
- Birthweight
  - Ceftrioxone = 3209 g
  - Placebo = 3056 g (p = 0.01)
- Low Birth weight
  - Ceftrioxone = 4.0%
  - Placebo = 9.2% (p = 0.08)

Presumptive treatment (Rakai) vs syndromic management (Mwanza) in pregnant women



Presumptive treatment more effective than syndromic management in reducing STIs

Infections at Time of delivery

- **Maternal genital tract infections contaminate infants during passage through birth canal during labor and delivery**
  - ingestion/inhalation
  - transdermal
- Antisepsis during labor can reduce infections with STDs and other pathogens (e.g., Grp B strep)
- Viral STIs (HSV-2, HPV, HBV)
  - Antiviral drugs
  - C-section

Genital Tract Cleansing During Labor

(Taha Brit Med J 1997;315:216-9)

- Randomized trial of Chlorhexadine (0.25%) washing of birth canal in labor.n=3,500 per arm
- Neonatal sepsis admissions RR= 0.44 ($p<0.002$)
- Neonatal mortality RR = 0.78 ($p<0.06$)
- Mortality due to sepsis RR = 0.33 ($p<0.005$)
- Maternal re-admissions RR = 0.33($p<0.02$)

Group B Streptococcus (GBS)

- 15-30% of women asymptomatic carriers
- Transmission rate to baby 40-75%
- Neonatal sepsis Early onset (< 1 week)
  - Incidence = 0.3%, case/fatality = 10-50%, common in preterms
  - Late Onset (> 1 week)
  - Incidence = 0.05%, case/fatality = 10-15%
- Common infection but rare outcomes
- Treatment ampicillin, penicillin
- **Prevention trials all unsuccessful**

Prevention of Infection in Pregnancy

- Primary prevention:
  - Prophylaxis (condom use)
  - Safe sex
- Secondary prevention
  - Screening and treatment (e.g. syphilis HIV)
  - Mass treatment (e.g., metronidazole + macrolide in populations with high BV?)
  - Cleansing of birth canal during labor
- Treatment of new born
  - Screening and diagnosis can be problematic

HIV incidence during pregnancy

(Gray et al Lancet 2005)

	Pregnant	Lactating	Neither preg/lact
Incident cases/ women years (wy)	23/997	40/3043	275/24,161
Incidence/100 wy	**2.3**	1.3	1.1
Adjusted IRR (95%CI)	**2.0 (1.3-3.1)**	1.2 (0.8-1.6)	1.0

HIV incidence during pregnancy was also significantly higher than during lactation Adj IRR = 1.76 (1.05-2.94)

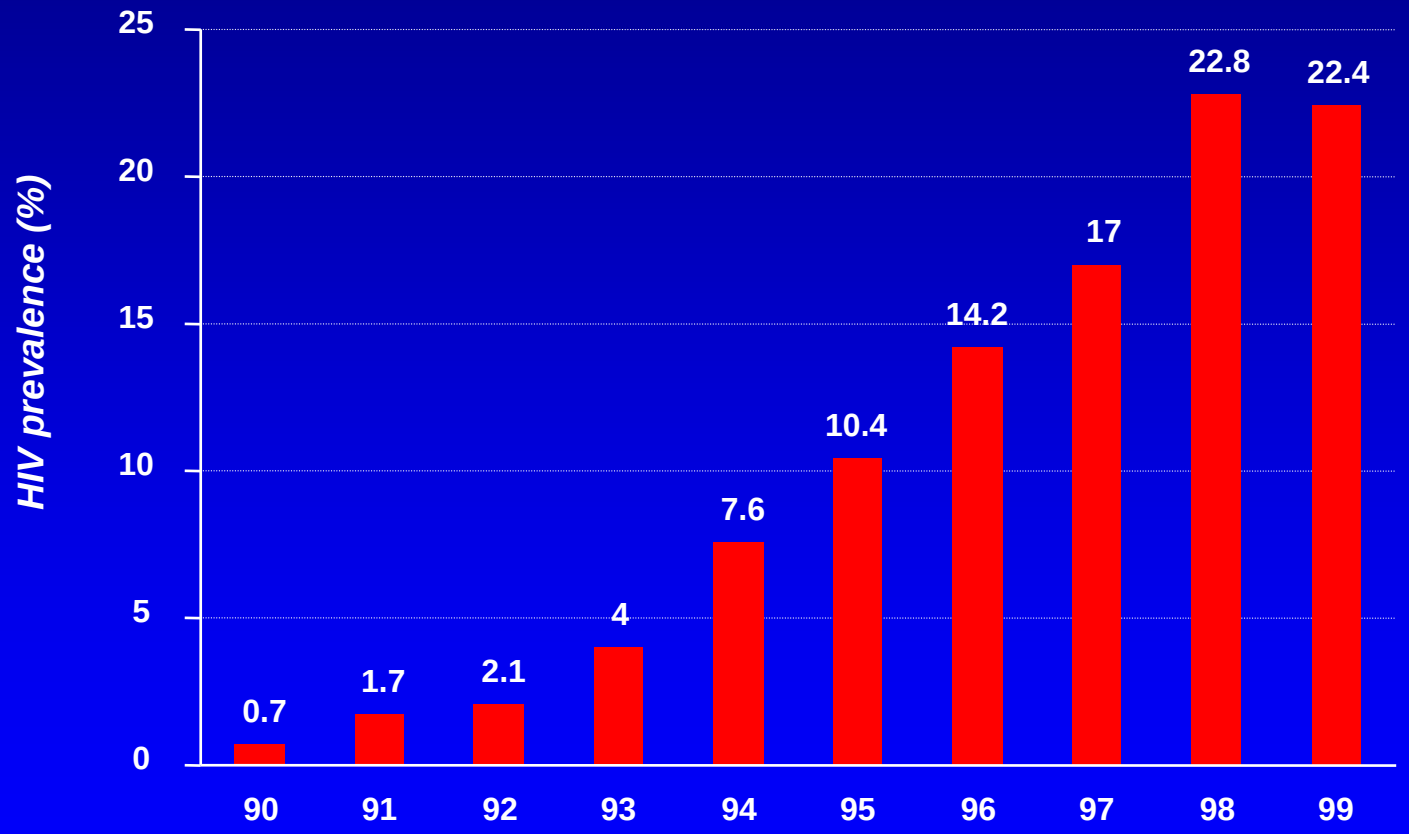
Mother to child HIV transmission (MTCT)

- Rates and timing of transmission
- Prevention trials
- Breast milk transmission

Epidemiology

- Most children with HIV are infected by vertical transmission
- HIV seroprevalence rates of 30-35% among pregnant women in some African settings
- In countries with very large populations, lower seroprevalence rates can still result in large numbers of infected children

HIV prevalence among pregnant women in South Africa, 1990 to 1999



Source: *Department of Health, South Africa*

Timing and rate of MTCT no breastfeeding

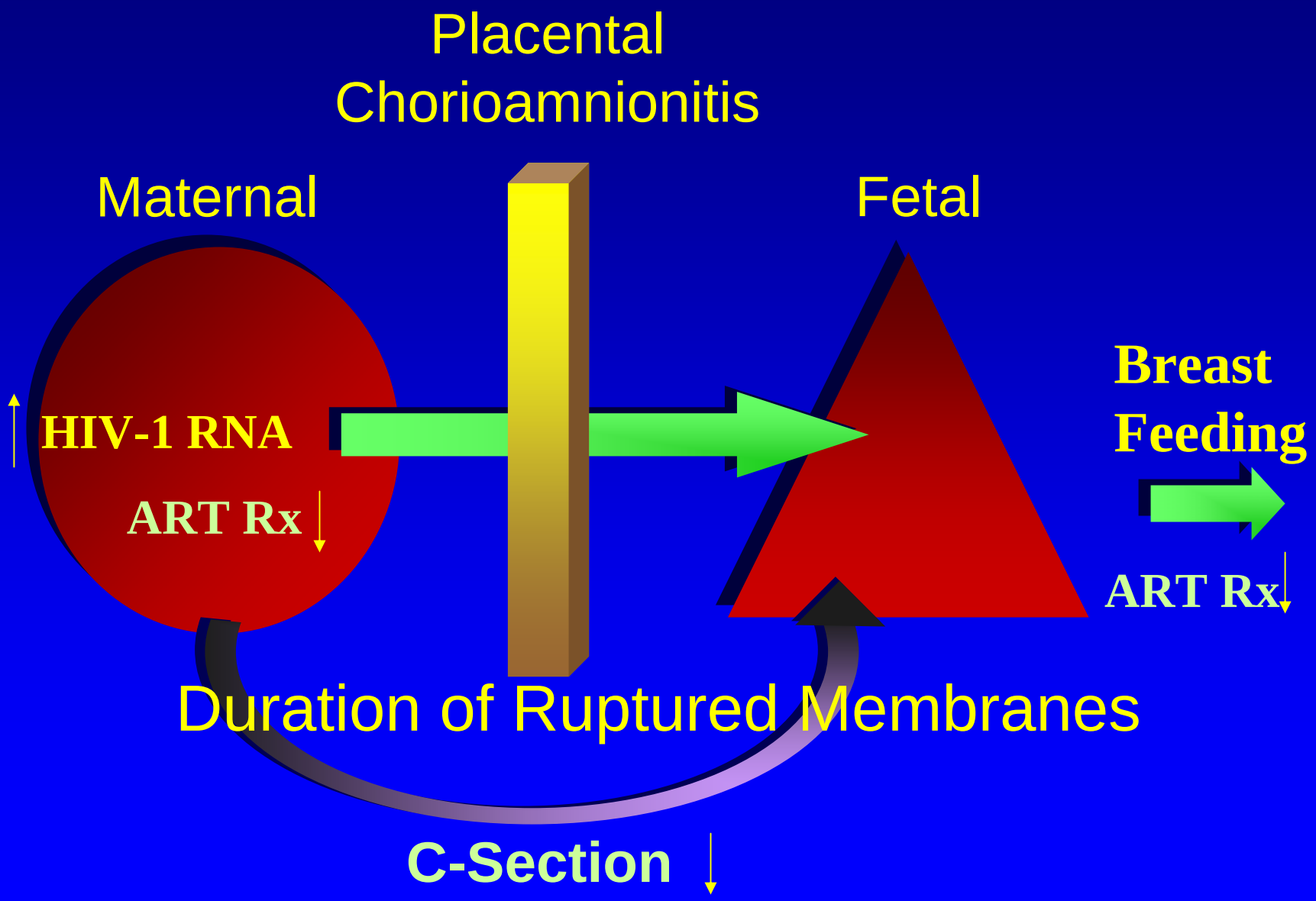
Timing	Absolute rate	Relative proportion of all transmissions
Intrauterine	5-10%	25-35%
Intrapartum	10-20%	65-75%
Total	15-30%	100%

DeCock JAMA 2000;283:1175

Timing of transmission with breastfeeding for 18-24 months

Timing	Absolute rate	Relative proportion of transmissions
Intrauterine	5-10%	20-35%
Intrapartum	10-20%	35-50%
Breast 2 months	5-10%	20-25%
Breast> 2 mths	5-10%	20-25%
Total	30-45%	100%

Perinatal Transmission of HIV



Maternal Factors and perinatal MTCT

- Stage of maternal infection
- HIV viral load (1 log increase in VL RR of MTCT RR ~2.5)
- Viral subtypes
- Antiretroviral therapy
- Coinfections (STIs, chorioamnionitis, malaria)
- Factors associated with delivery (instrumentation, C/S)

HIV diagnosis in infants

- Complicated by presence of maternal antibodies
- Under 18 mths of age use:
  - HIV DNA PCR
  - HIV RNA PCR
- > 18 months use EIA/WB

ACTG 076 Trial

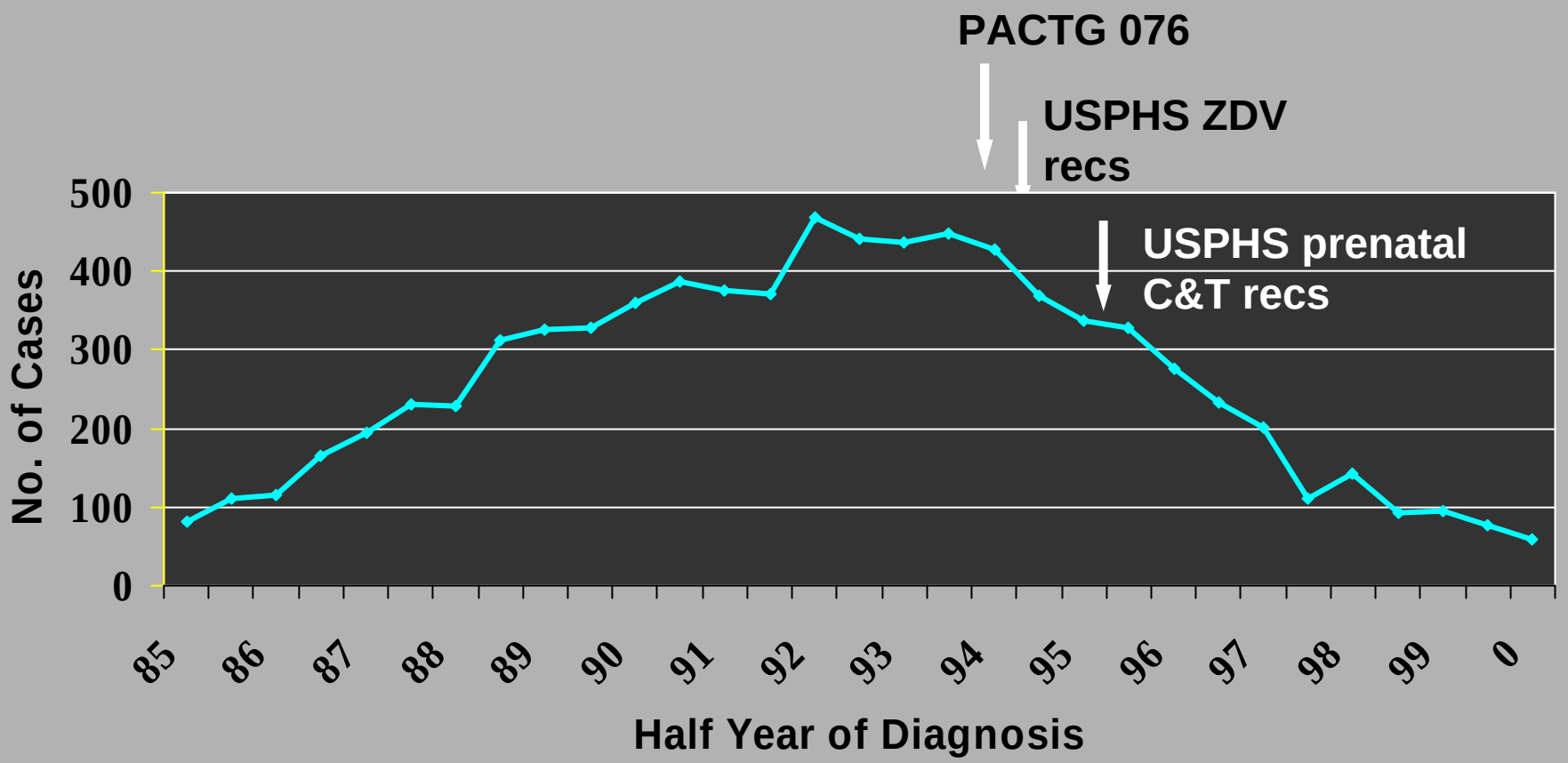
- Multicenter clinical trial conducted in US and France

- Placebo vs AZT:
  - AZT beginning at 14 wks gestation
  - Given intravenously during labor
  - Given to infant for 6 weeks

ACTG 076 - Outcome

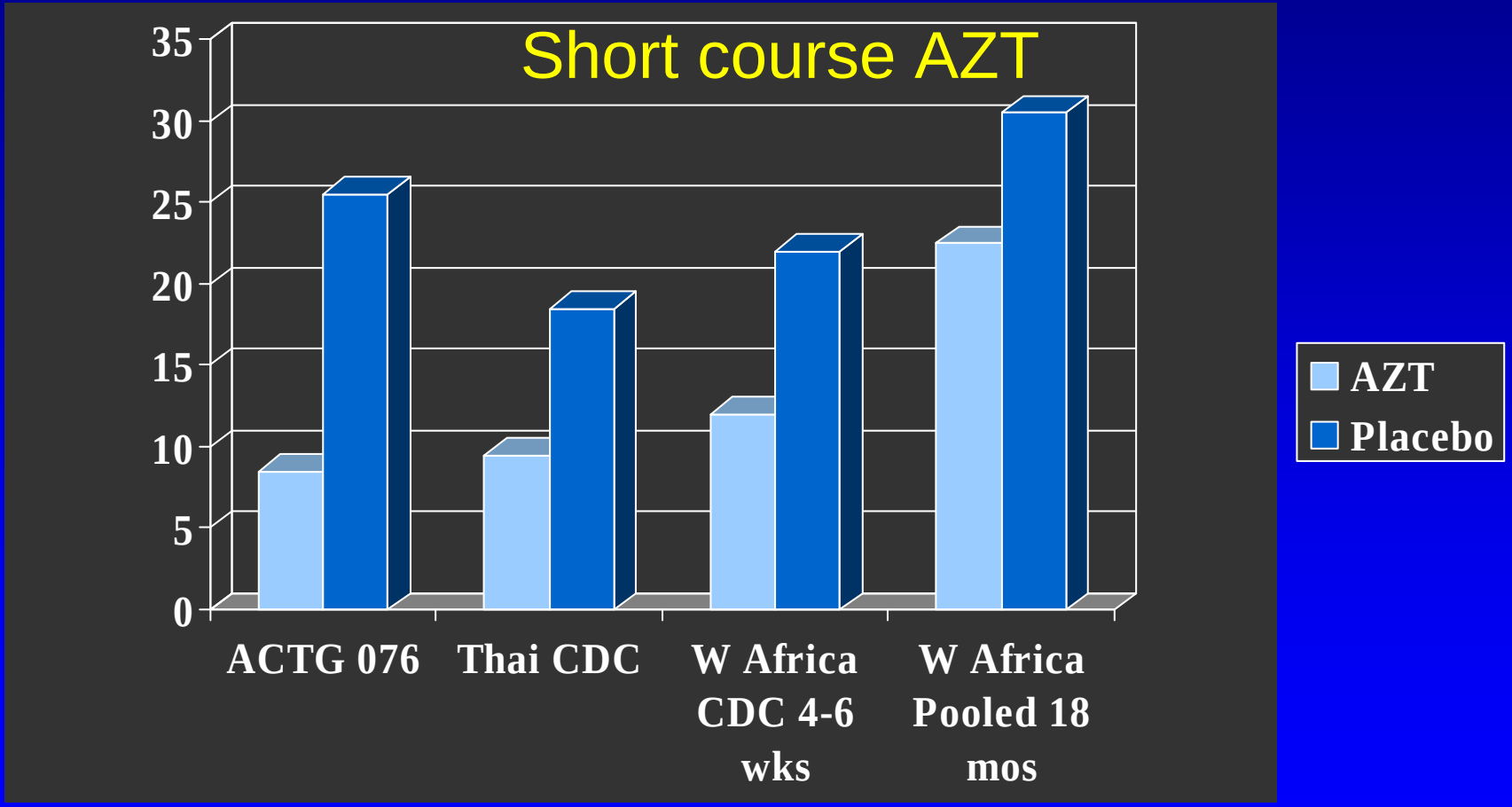
- Target sample size 748 women
- Interim analysis done with 364 women, trial stopped
- Transmission rate in AZT arm was 8.3% compared to 25.5% in placebo arm
- Reported adverse events balanced between two groups, although mean Hgb levels lower in infants receiving AZT

Incidence of Perinatally-Acquired AIDS United States, 1985-June 2000*

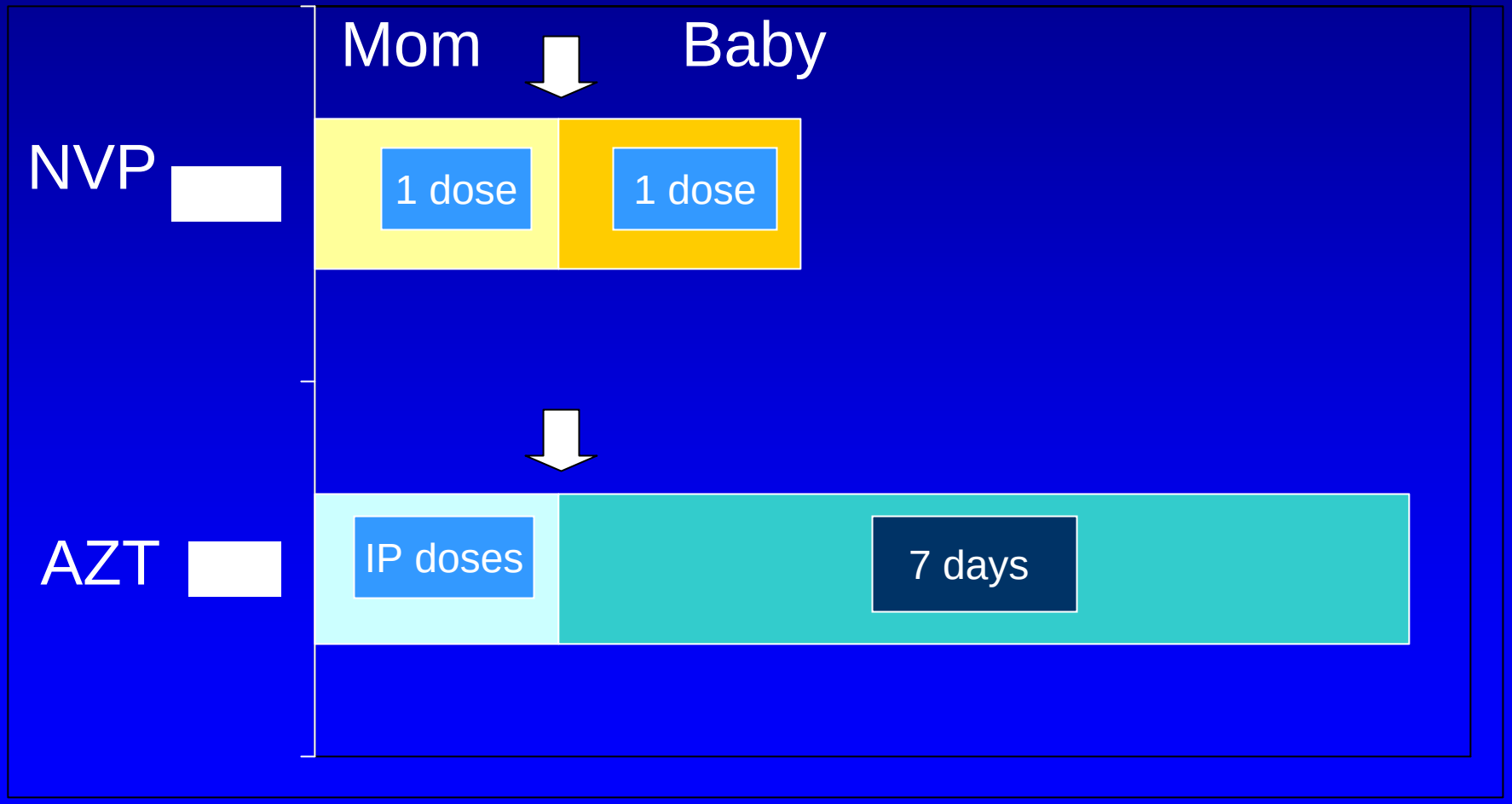


*Reported through December 2000

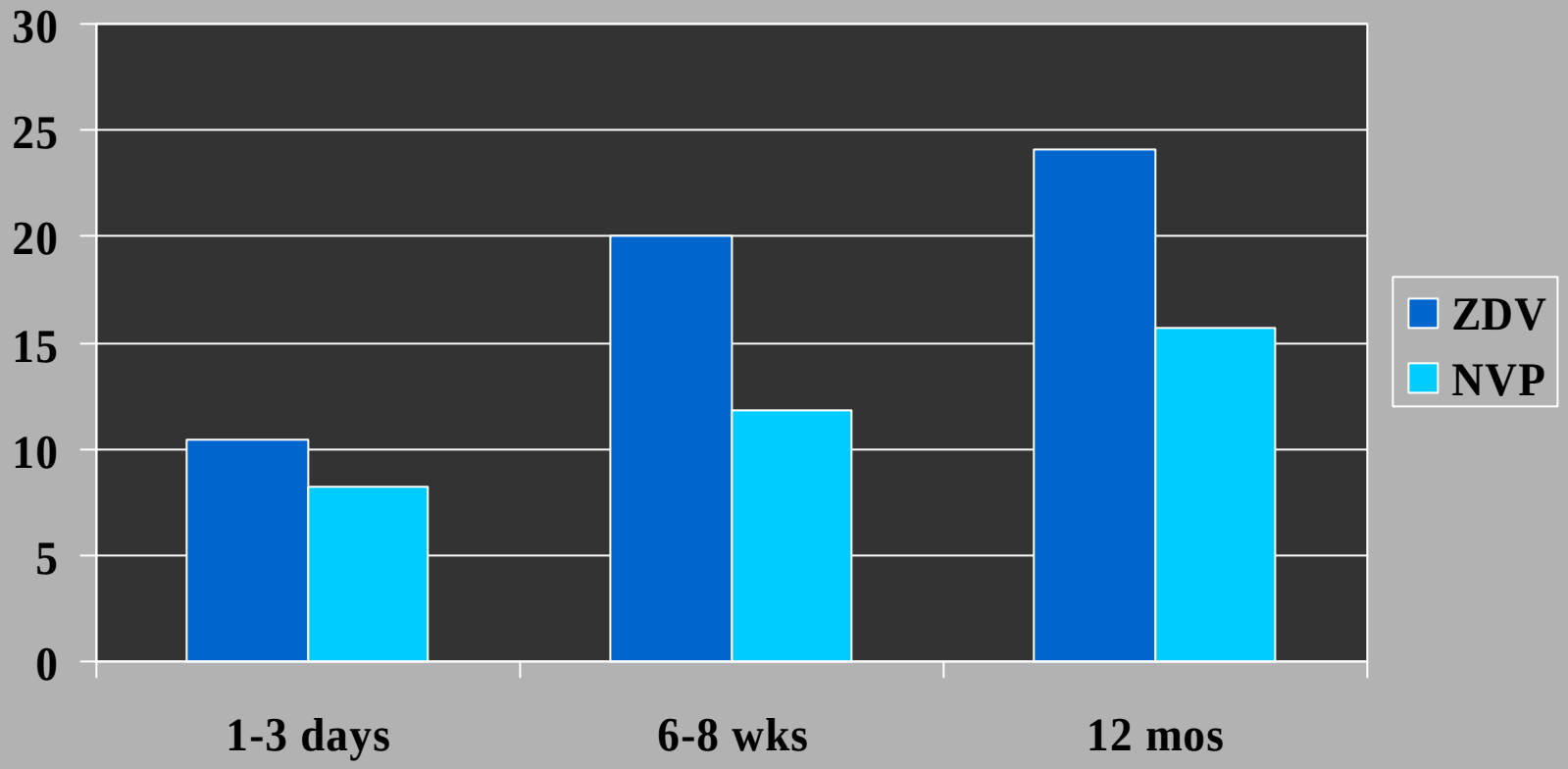
HIV Perinatal Transmission Rates in short-course AZT Trials



HIVNET 012 trial, Uganda



HIVNET 012: Cumulative transmission during long-term follow up



Sustained reduction in MTCT, despite breast milk transmission

Chorioamnionitis and MTCT Observational studies

Study (Country)	Transmission Rate with Chorio (%)	RR of Transmission (Chorio/no chorio)
St. Louis JAMA 1993; 269:2858 (Zaire)	40	4.2 (1.3-13.7)
Temmerman, Am J Obstet Gynecol 1995:172:700 (Kenya)	---	7.9 (1.3-47.4)
Landesman NEJM 1996:334:1617 (US)	45.5	2.45 (1.3-4.8)
Wabwire-Mangen AIDS Retrovirol 1999: (Uganda)	25.5	2.87 (1.0-7.9)

Trials of chorioamnionitis and MTCT

- Two trials of presumptive treatment of chorioamnionitis showed no effect on MTCT

- Rakai Uganda (Gray Amer J Obstet Gynecol 2001)

- NIH (trial stopped prematurely due to no impact)

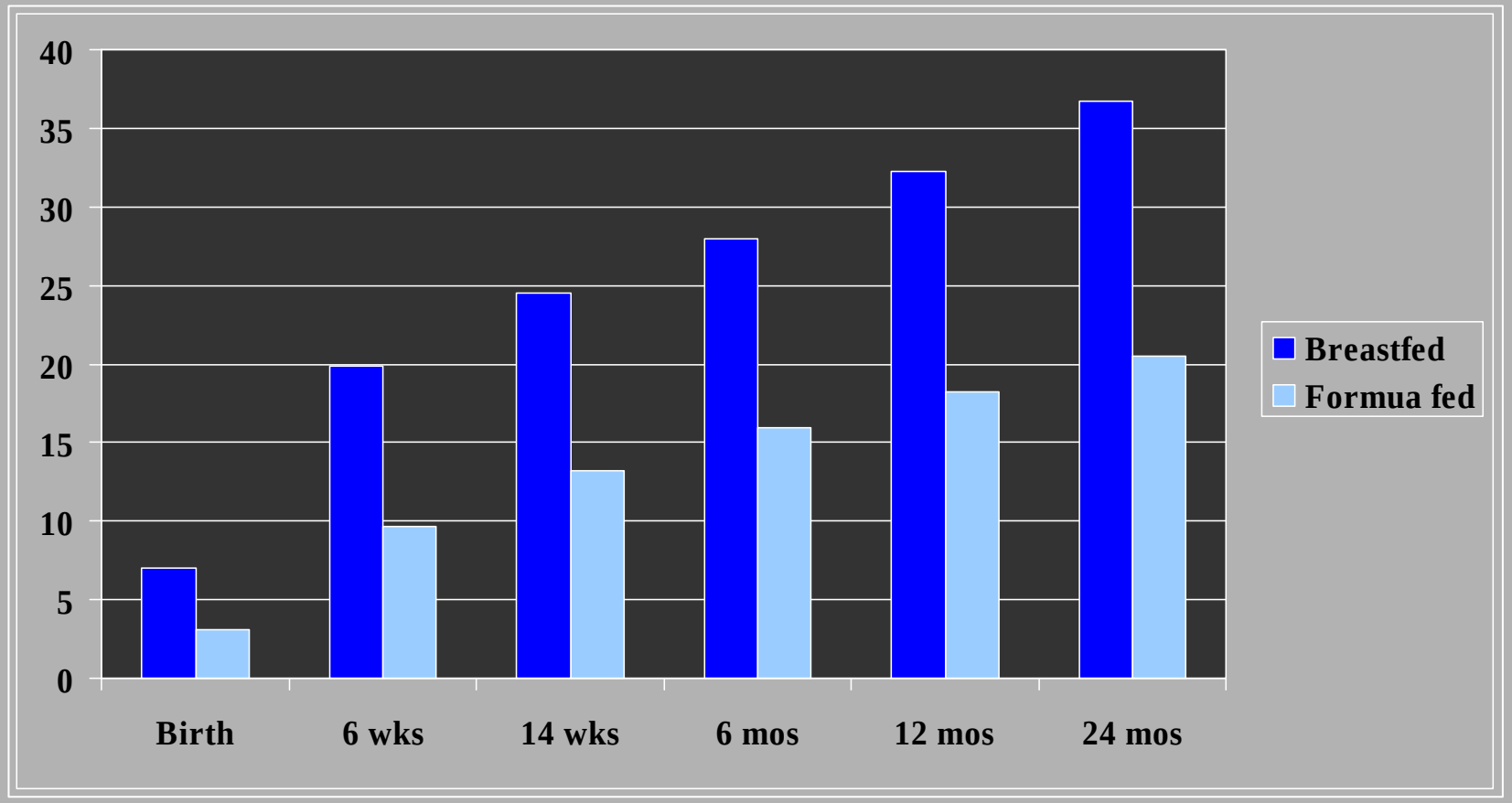
Factors Associated with Transmission Through Breastfeeding

- Maternal viral load and CD4 count
- Duration of breastfeeding
- Type of breastfeeding
- Subclinical and clinical mastitis
- Breast milk viral load
- Low vitamin A (no effect)

Randomized Trial of Breastfeeding vs Formula Feeding Nduati *et al: JAMA*

- 425 HIV infected women in Nairobi randomized to breast or bottle feeding
- Median follow-up of 24 months
- Data from 401 mother-infant pairs in final analysis
- Compliance was 96% in breastfeeding arm and 70% in the formula arm

Transmission Rate by Feeding Method *(Nduati et al, JAMA 2000)*

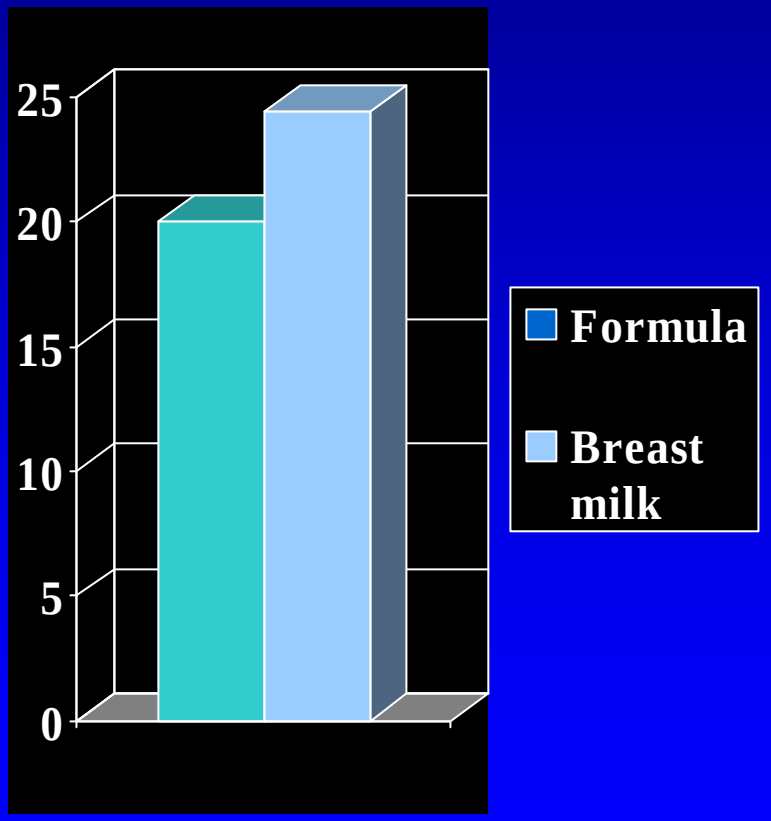


Morbidity and Mortality in Breastfed and Formula-Fed Infants of HIV-Infected Women

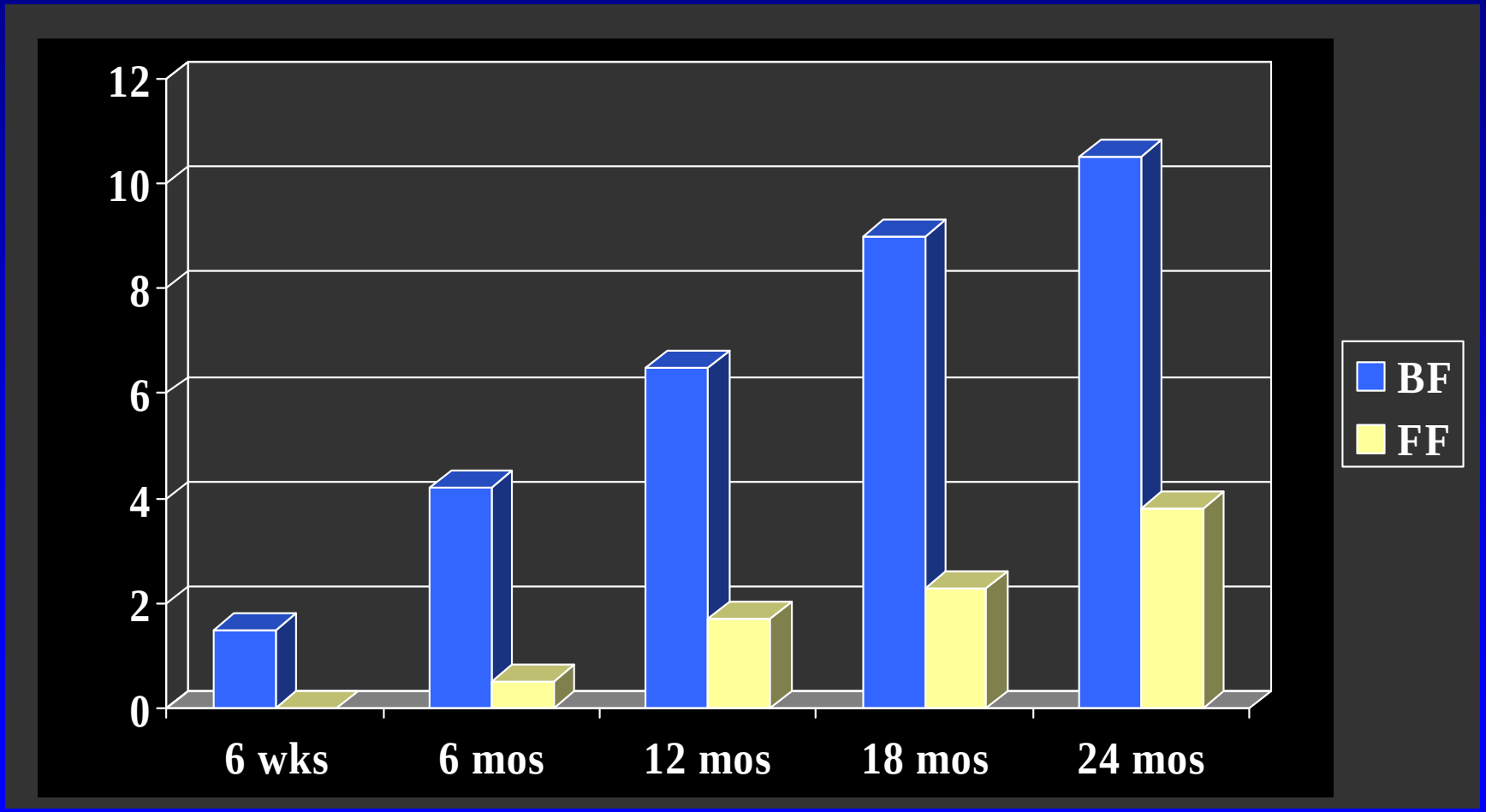
(Mbori-Ngacha, JAMA 2001;286:2413-20)

Two year mortality rates similar in the 2 arms even after adjusting for HIV infection status.

(Is 2 years too short?)



% Mortality among HIV-Infected Women by Feeding Method



Nduati et al Lancet

Why breast feeding might increase maternal mortality

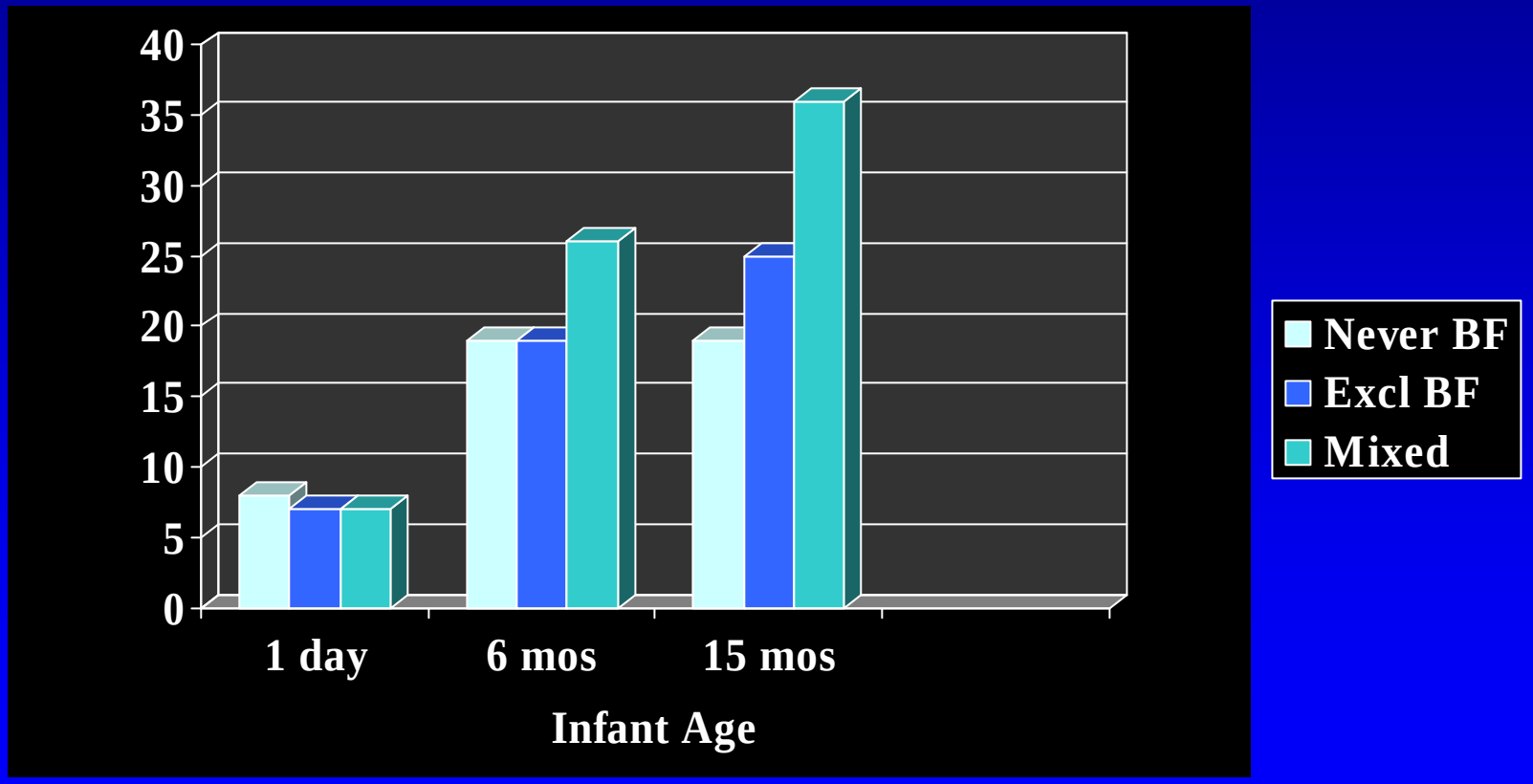
- Depletion of nutritional reserves
  - More rapid weight loss
  - More OIs
- No effects of breastfeeding on maternal deaths in SA trial (Kuhn AIDS 2005)

Method of Infant Feeding and breast milk HIV Transmission

*(**Coutsoudis et al:** AIDS 2001;15:379-387)*

- Conducted a vitamin A intervention trial in South Africa
- Evaluated transmission rates by feeding practice among 551 mother-infant pairs
- Compared the following:
  - Never breastfed (n = 157)
  - Exclusively breastfed (n = 118)
  - Mixed feeding (n = 276)

MTCT by Feeding Practice



Why mixed feeding may increase MTCT

- Mixed feeding increases risk of
  - Intestinal infection (gastroenteritis, diarrhea)
  - Allergies
  - Recruitment of HIV target cells into gut

Breast feeding vs formula feeding

- The objective is to maximize AIDS free survival of infants

- UNICEF recommends women be informed of risks and advised to:
  - Formula feed
  - Exclusively breast feed for 4-6 months then abruptly wean

Randomized trial of abrupt weaning at 4 months vs continued breast feeding: Zambia (Sinkala CROI 2007, Abst 74LB)

- 998 HIV+ women who exclusively breastfed randomized to:
  - Abrupt weaning at 4 mons
  - Continued breast feeding
- At 24 months HIV/death:
  - Abrupt weaning 17%
  - Continued breast feeding 19%
- Among HIV-infected infants mortality was reduced by breastfeeding

Post-weaning gastroenteritis mortality, Malawi (Kafulafula CROI 2007, Abst 773)

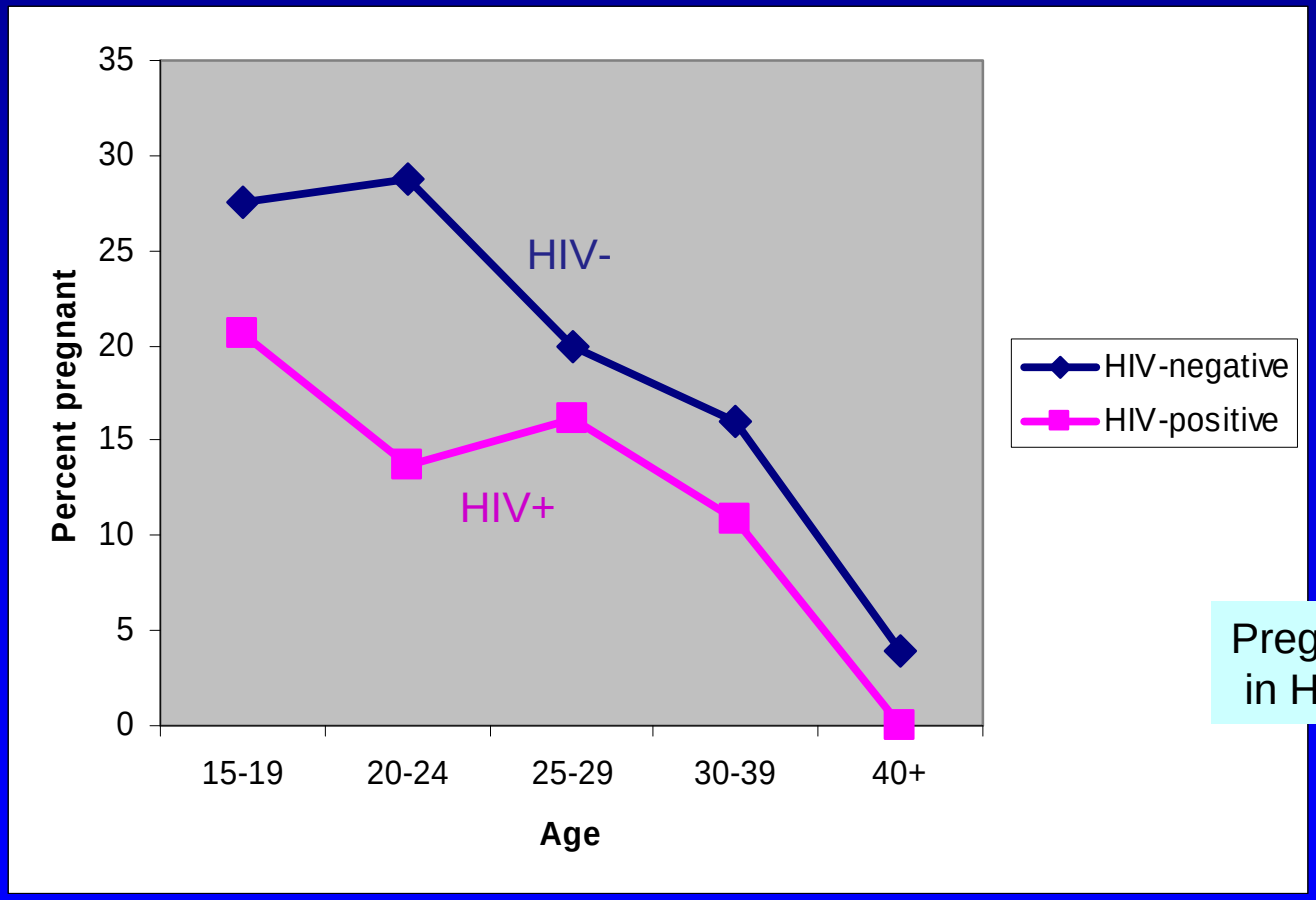
	Gastroenteritis mortality/1000 by age			
	3 mth	6 mth	9 mth	12 mth
Early weaning	4	6	23	28
Delayed weaning	1	3	7	7

HIV and Fertility

- Studies in Uganda and US show lower pregnancy rates and increased rates of pregnancy loss in HIV+ women (Gray et al Lancet 1998)

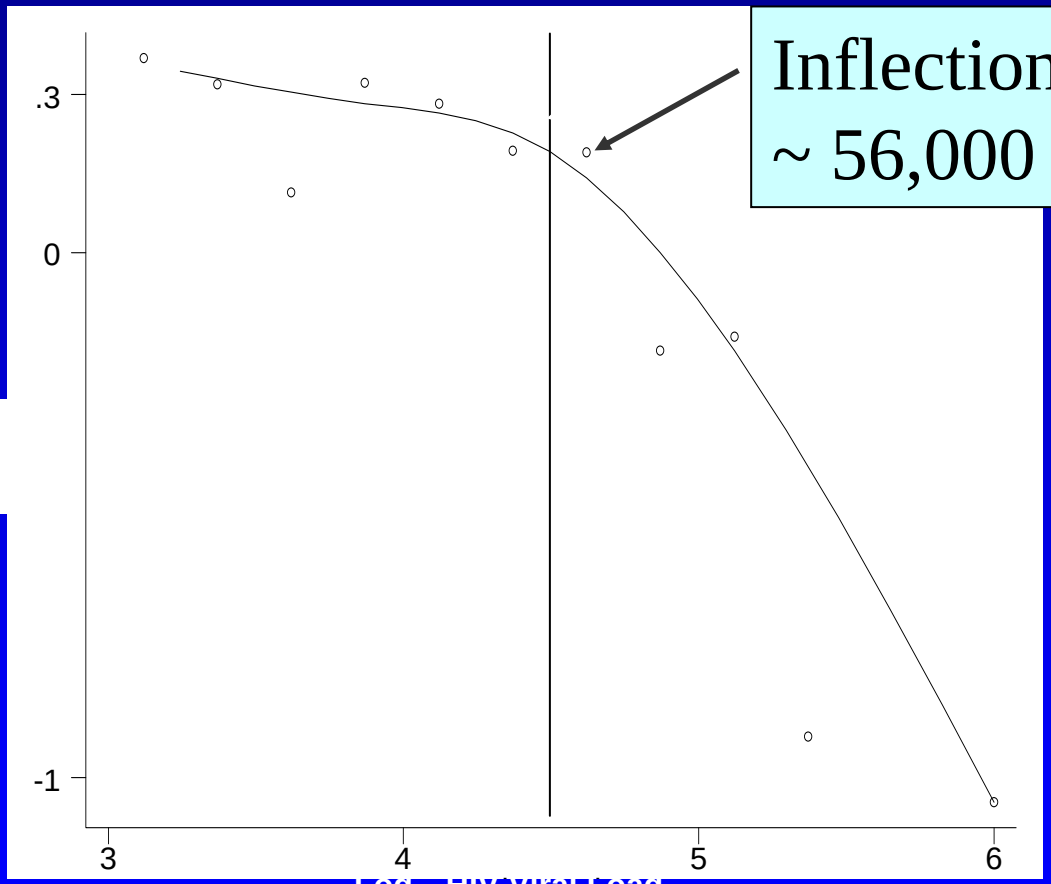
- Reduction in pregnancy rates are associated with duration of HIV infection and viral load

Prevalence of Pregnancy in HIV+ and HIV- women Rakai (Gray et al Lancet 1998)



Pregnancy rates are lower in HIV+ than HIV- women

Odds of pregnancy associated with HIV viral load, Rakai (Ngyen et al 2006)



Policy Implications
Reduced Fertility in HIV-Infected Women

- HIV Surveillance
  - Antenatal surveillance underestimates HIV prevalence in reproductive age women
  - 70% of UNAIDS data from antenatal surveillance, underestimates the global burden of HIV

Malaria and pregnancy

- Malaria associated with
  - LBW
  - PTD
  - SAB and stillbirth
- Effects mainly in nulligravid women (but in HIV+, malaria effects at all gravidities)
- Routine malaria prophylaxis in pregnancy

Malaria and HIV in pregnancy

- Malaria more common and parasitemia is higher in HIV+ than HIV-

- **MTCT and placental malaria (pm)**
  - Placental malaria MTCT = 33%
  - No placental malaria MTCT = 14%
  - Adjusted RR = 5.6, p = 0.02
- HIV Viral load higher in women with malaria