



South to South



Overview of HIV in Pediatrics



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International Center for AIDS
Care and Treatment Programs
MAILMAN SCHOOL OF PUBLIC HEALTH
Columbia University

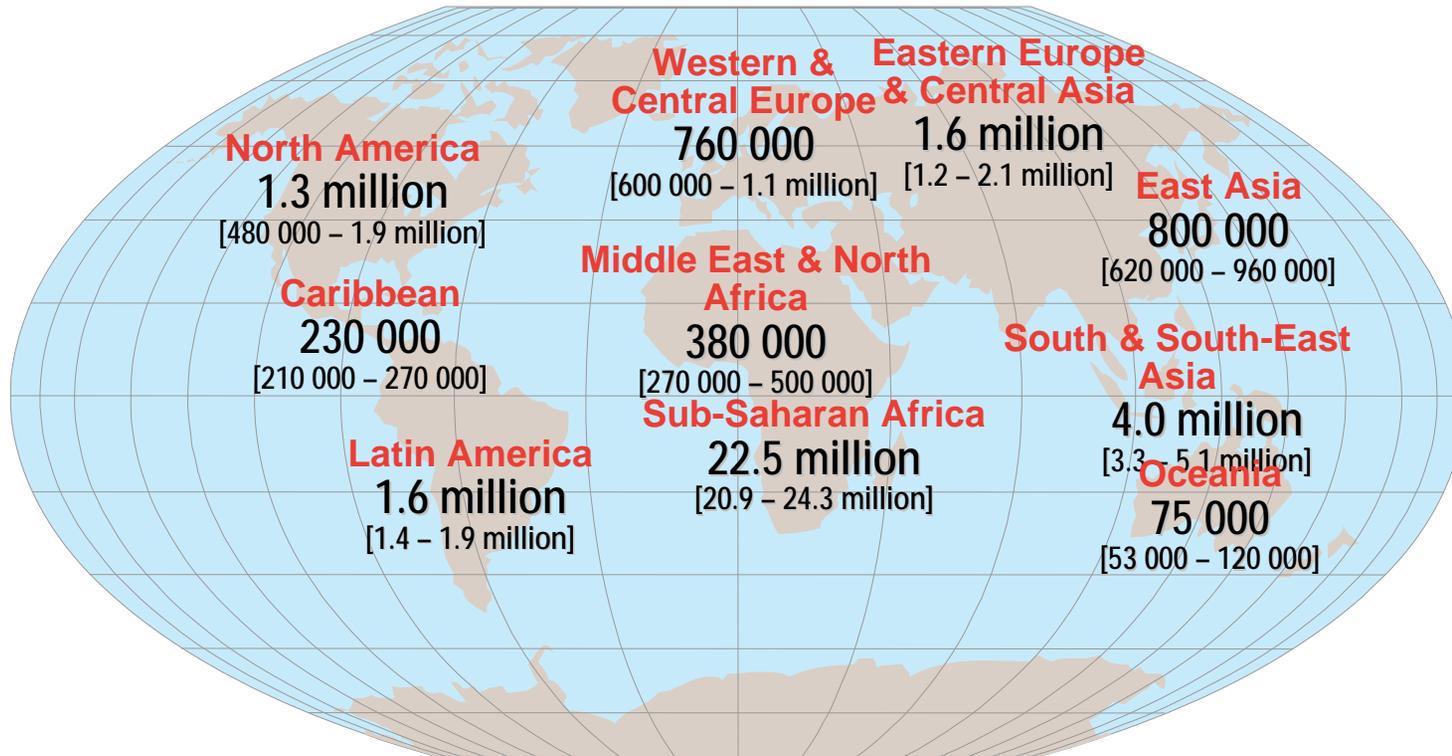


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Learning Objectives

- To review the global and national impact of HIV on children
- To understand that pediatric HIV is a preventable disease
- To develop a basic understanding of the HIV structure and lifecycle as introduction to antiretroviral treatment

Adults and children estimated to be living with HIV, 2007

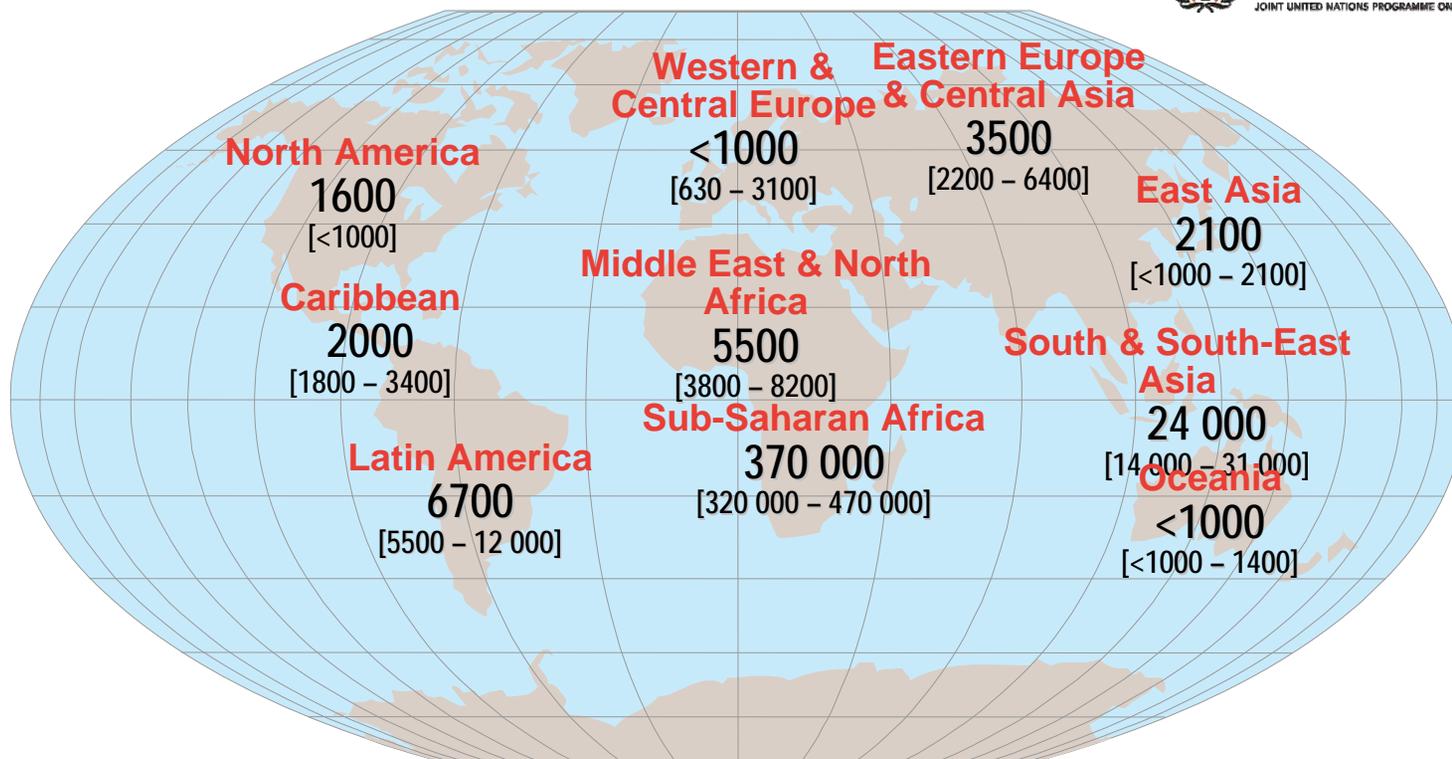


Total: 33.2 (30.6 – 36.1) million

WHO & UNAIDS 'AIDS Epidemic Update: special report on HIV/AIDS December 2007'



Estimated number of children (<15 years) newly infected with HIV, 2007

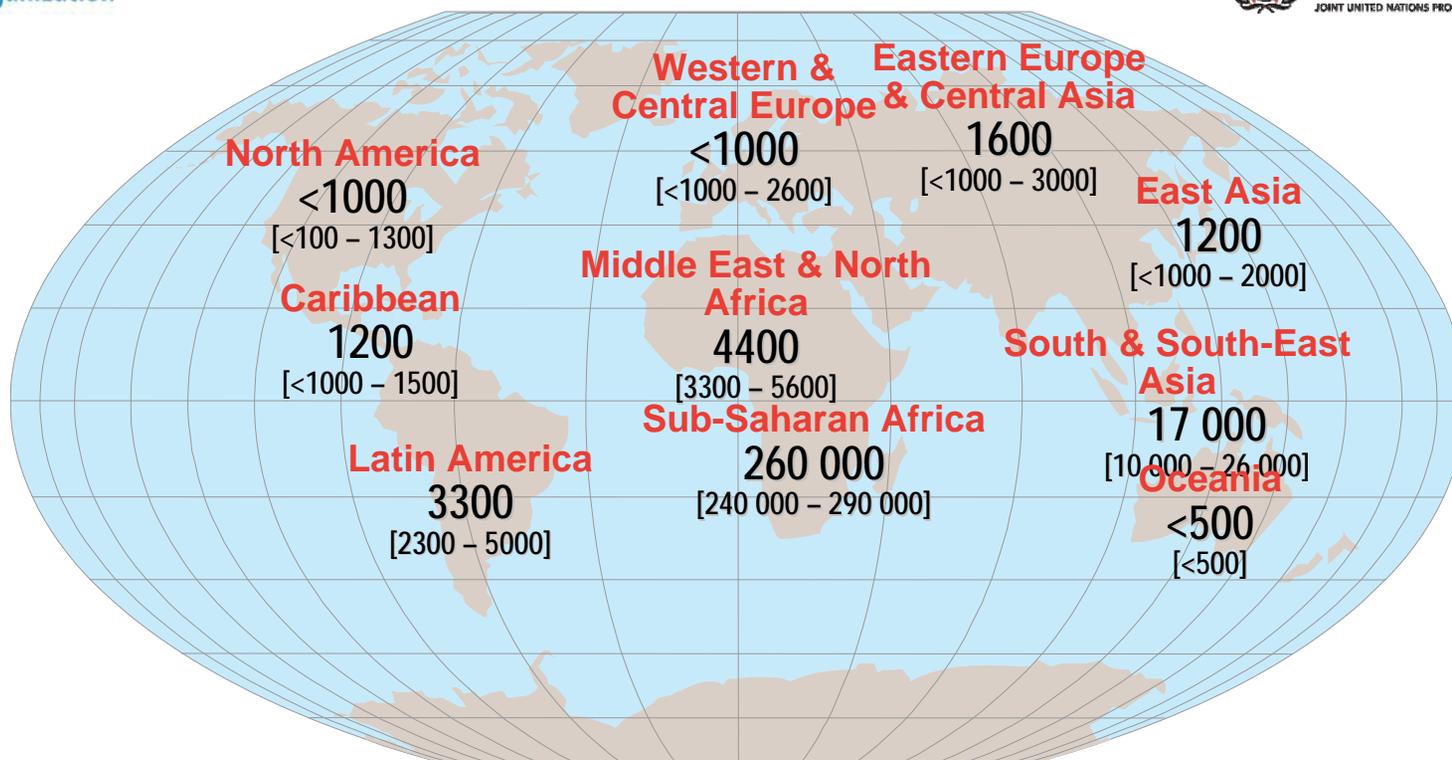


Total: 420 000 (350 000 – 540 000)

WHO & UNAIDS 'AIDS Epidemic Update: special report on HIV/AIDS December 2007'



Estimated deaths in children (<15 years) from AIDS, 2007

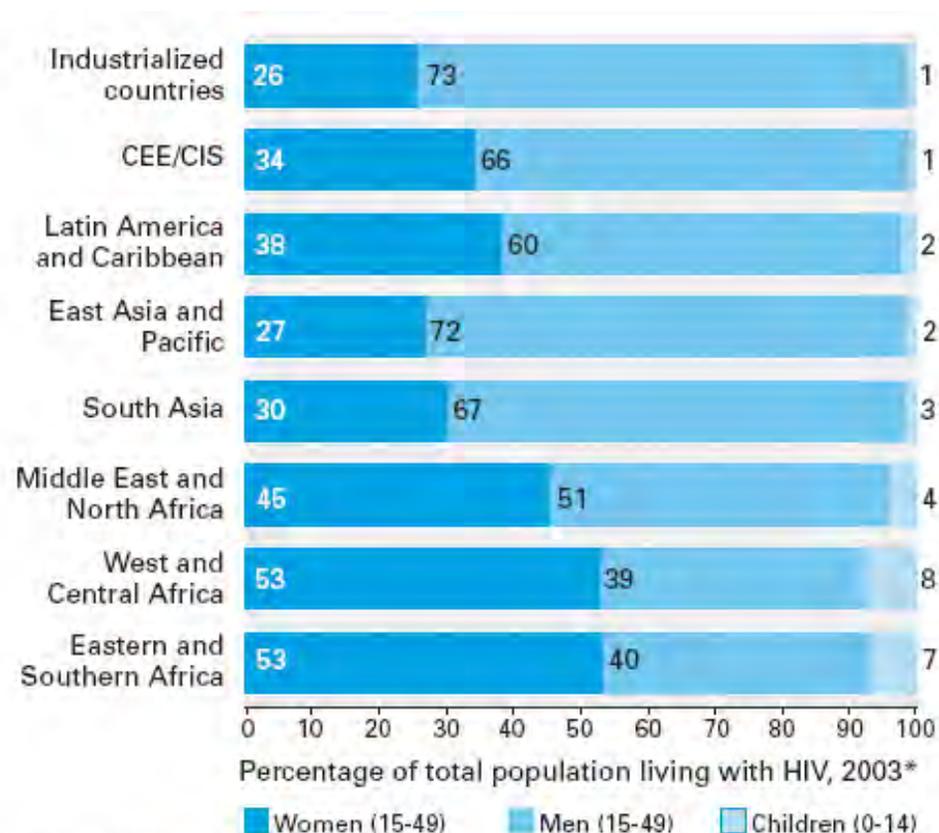


Total: 290 000 (270 000 – 320 000)



WHO & UNAIDS 'AIDS Epidemic Update: special report on HIV/AIDS December 2007'

In Africa children account for an increasing proportion of people living with HIV*



*Figures may not add up to 100% due to rounding.

Source: UNICEF calculations based on data from Joint United Nations Programme on HIV/AIDS, *Report on the Global HIV/AIDS Epidemic*, 2004.

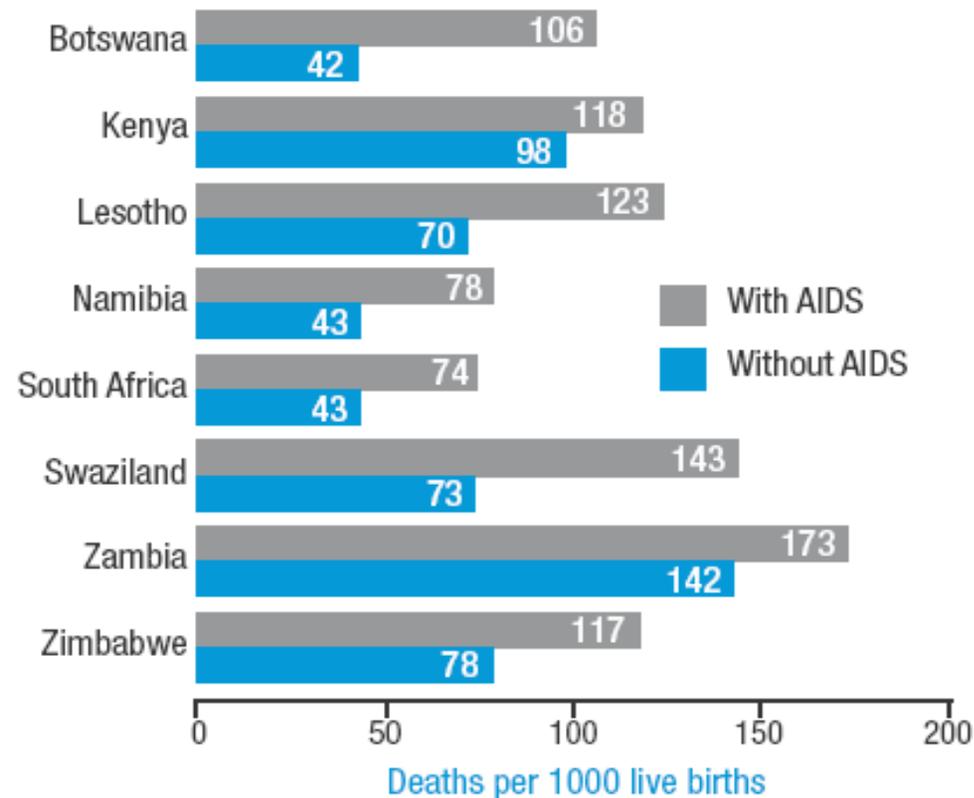
(SOURCE: p 26, "State of the World's Children 2006 - Report by UNICEF")

* 2008 report did not review these statistics

HIV/AIDS has led to an increase in child mortality

Impact of AIDS on child mortality

Estimated impact of AIDS on under-five mortality rates
2002-2005, selected countries in sub-Saharan Africa



Source: United National Population Division, World Population Prospects: The 2004 Revision, database (no subsequent report)

South Africa (2007 AIDS Epidemic update, UNAIDS)

- An estimated 5.7 million [4.9-6.6 million] people living with HIV
- An estimated 1.8 million people have died of AIDS-related disease since the start of the pandemic
- 18,3% adults (15-49 years) living with HIV in 2006 (DOH)
- HIV prevalence in pregnant woman 29% in 2006 (DOH)
 - (39% in KZN – 15% in NC)
- 275 000 HIV infected children in 2005
- 293 000 HIV infected children in 2006
- Deaths among children < 15 years of age increased by 72,9% between 1997 and 2004
- HIV contributed to a 42% increase in under 5 mortality in 2004
- 60% of hospital deaths HIV-related in 2005 (HIV & AIDS and STI Strategic Plan

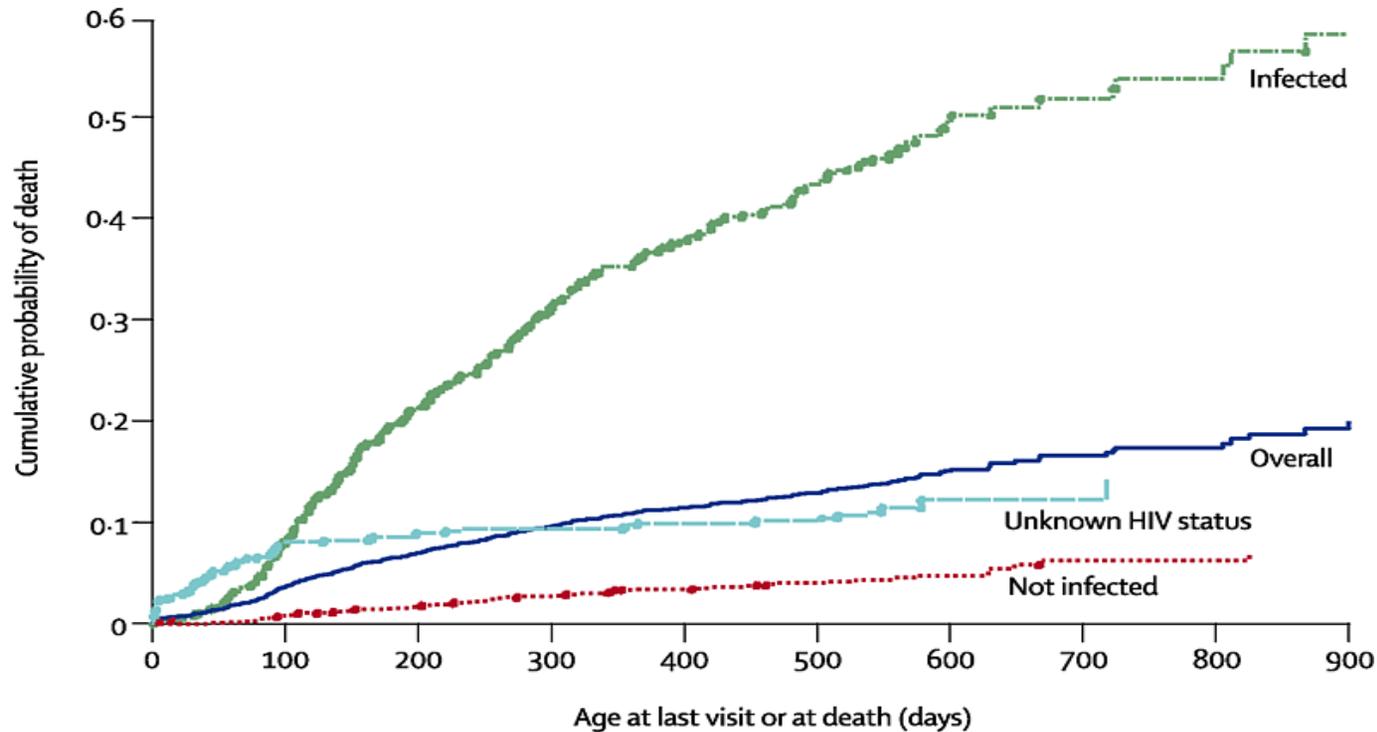
Mortality of infected and uninfected infants born to HIV-infected mothers in Africa

A pooled analysis of seven randomized MTCT intervention trials from sub-Saharan Africa in largely breastfeeding population

	Death by age 1 year	Death by age 2 years
HIV infected	35.2%	52.5%
HIV uninfected	4.95%	7.6%

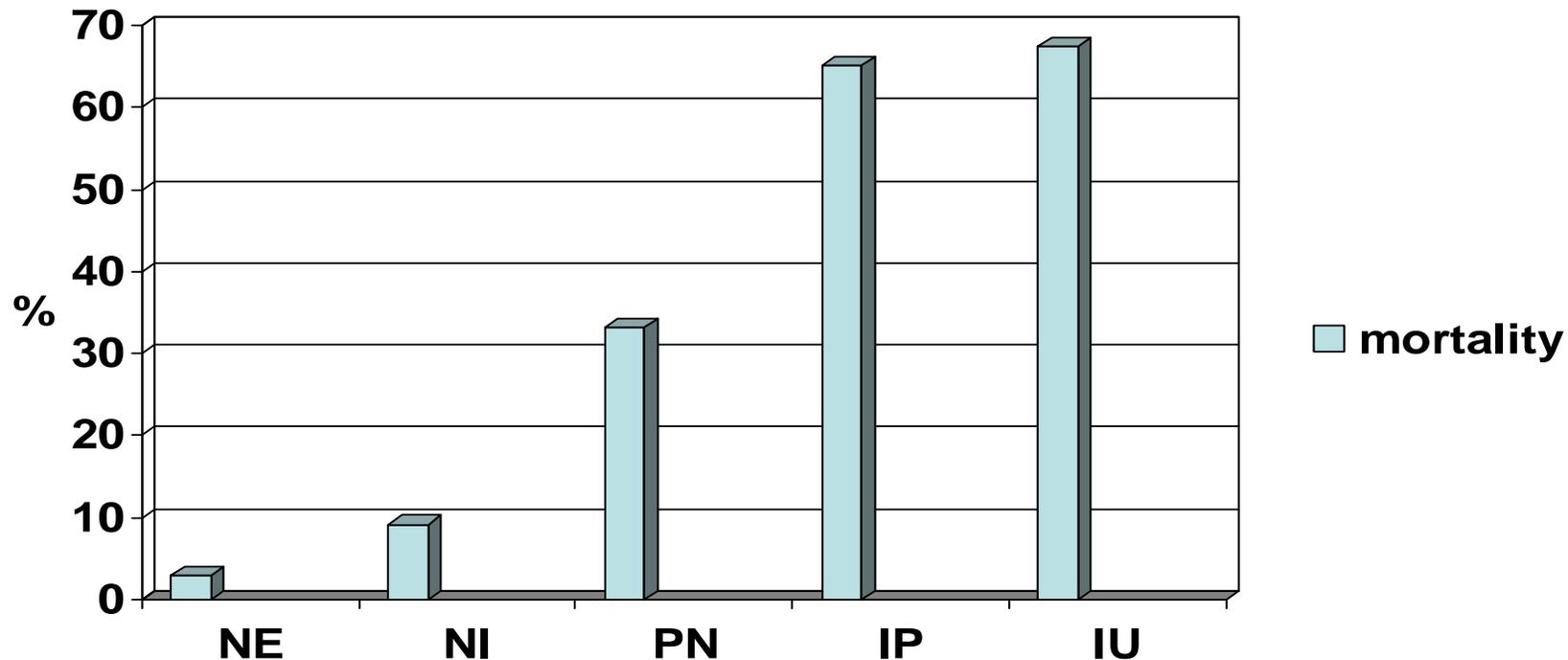
- Mortality associated with
 - Maternal death
 - Maternal CD 4 count <200 cells per μ L
 - Intra-partum (early) HIV infection

Estimated unadjusted overall mortality of infected and uninfected children



Children at risk	1 day	7 days	28 days	365 days	730 days
Overall	3330	3269	3212	2063	297
p (death)	0.002	0.006	0.008	0.110	0.174
Infected	693	691	681	299	54
p (death)	0.0015	0.003	0.008	0.352	0.525
Uninfected	2127	2114	2078	1364	211
p (death)	0.0005	0.003	0.006	0.049	0.076

Higher 2 Year Child mortality in HIV-exposed Uninfected Infants than Infants whose Mothers are HIV-Negative



NE: HIV-negative (n 9510)
NI: HIV-exposed uninfected (n 3135)
PN: Postnatal infection (n 258)
IP: Intrapartum infection(n 508)
IU: Infected in-utero (n 381)

HIV infected children are 'high risk' children

- If no intervention-
 - High morbidity and mortality
 - Infants less than 1 year most vulnerable
- The mother's health is the key to the child's health and survival

'Taking stock: HIV in children'

- Worldwide about 10%, and in sub-Saharan Africa about 6% of pregnant woman are currently offered pMTCT services
- Only 4% of children receives prophylactic co-trimoxazole to prevent opportunistic infections
- Tools for diagnosing HIV in infants tend to be unaffordable or absent
- Only 10% of children requiring HAART receives it

(WHO Report, 2006)

ART coverage for children has lagged behind

- Lack of trained physicians/ HCW
- Unaffordable diagnostic and monitoring (viral load) assays
- Need for paediatric drug formulations
- Poorly developed drug procurement systems
- **Fragmentation of health systems** (McCoy et al, Global Health Concerns 2005)

Obstacles (Sutcliffe et al, Lancet 2008)

- Non-standard monitoring and assessment systems
- Older age and advanced levels of immune suppression at treatment start
- High malnutrition at treatment initiation
- Suboptimum antiretroviral regimens available for use

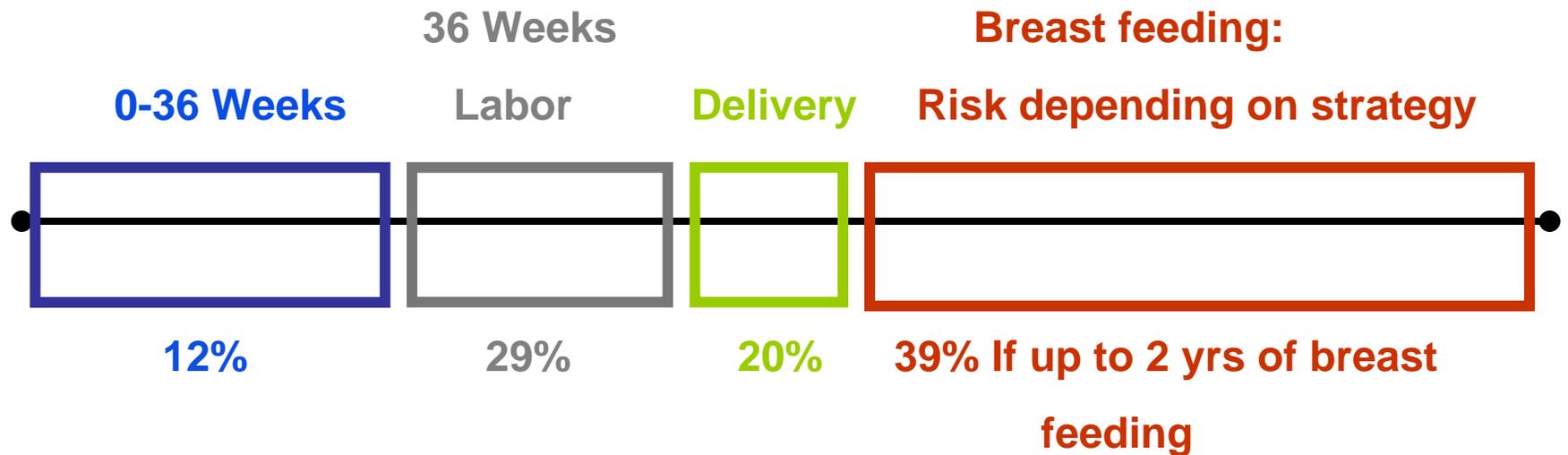
PMTCT the key

- Paediatric HIV can be prevented by effective PMTCT interventions
 - > 95% of paediatric infections are the result of MTCT
 - Women of childbearing age have very high rates of HIV infection
 - 50% of adults living with HIV are women (60% in sub-Saharan Africa)
 - 45% of all new infections occur in young adults (15-24 years of age), F:M = 2:1
 - 40% of exposed breast feeding infants will become infected in absence of intervention
- Paediatric HIV/AIDS morbidity and mortality can be decreased by timely ART access
 - Probability of survival 1 year after the start of HAART ranges from 84-97% (Sutcliffe et al, Lancet 2008)

WHO Approach to Prevention of HIV infection in Children

Opportunity	Intervention
Prevent HIV in women of childbearing age	Delay sexual debut, VCT and education (ABC)
Prevent pregnancy in HIV-infected woman	Education and family planning
Prevent infection in HIV-exposed infants	Good antenatal care, prophylaxis with short course ART or treatment with HAART if required/available, safe obstetric practices, educate on infant feeding and infant follow-up

Timing of MTCT of HIV



Key Risk Factors for HIV Transmission

Maternal Factors	High plasma viral load Low CD4 Advanced HIV Disease
Obstetric Factors	Rupture of Membranes > 4 hours Vaginal delivery Assisted delivery
Infant Factors	Prematurity < 37 weeks Low birth weight
Breast-feeding	Acute maternal HIV infection Advanced maternal disease (High HIV RNA, low CD4+) Early mixed feeding Oral thrush in infant The presence of breast abscesses, nipple fissures, or mastitis Duration of breastfeeding

Program Elements of PMTCT

- 1. Offer VCT for HIV to all pregnant women**
- 2. Enroll all HIV positive women into pMTCT programs**
 - Test other family and household members and enroll them into care and treatment
- 3. Provide comprehensive care to the mother**
 - Assess maintain the mother's health - CD4 and staging
 - Initiate HAART if she needs it
 - Ensure a safe delivery
 - Prepare the mother to care for her HIV-exposed baby
- 4. Close follow up of the Exposed Infant**
 - Counsel the mother on infant feeding and care
 - Ensure ongoing support for breastfeeding and adequate formula supply for replacement feeding
 - Provide cotrimoxazole prophylaxis for the exposed baby
 - Monitor growth, development, and health of child
 - Determine the HIV status of the infant
 - Referral of infected infants for ART

ART Regimens for PMTCT

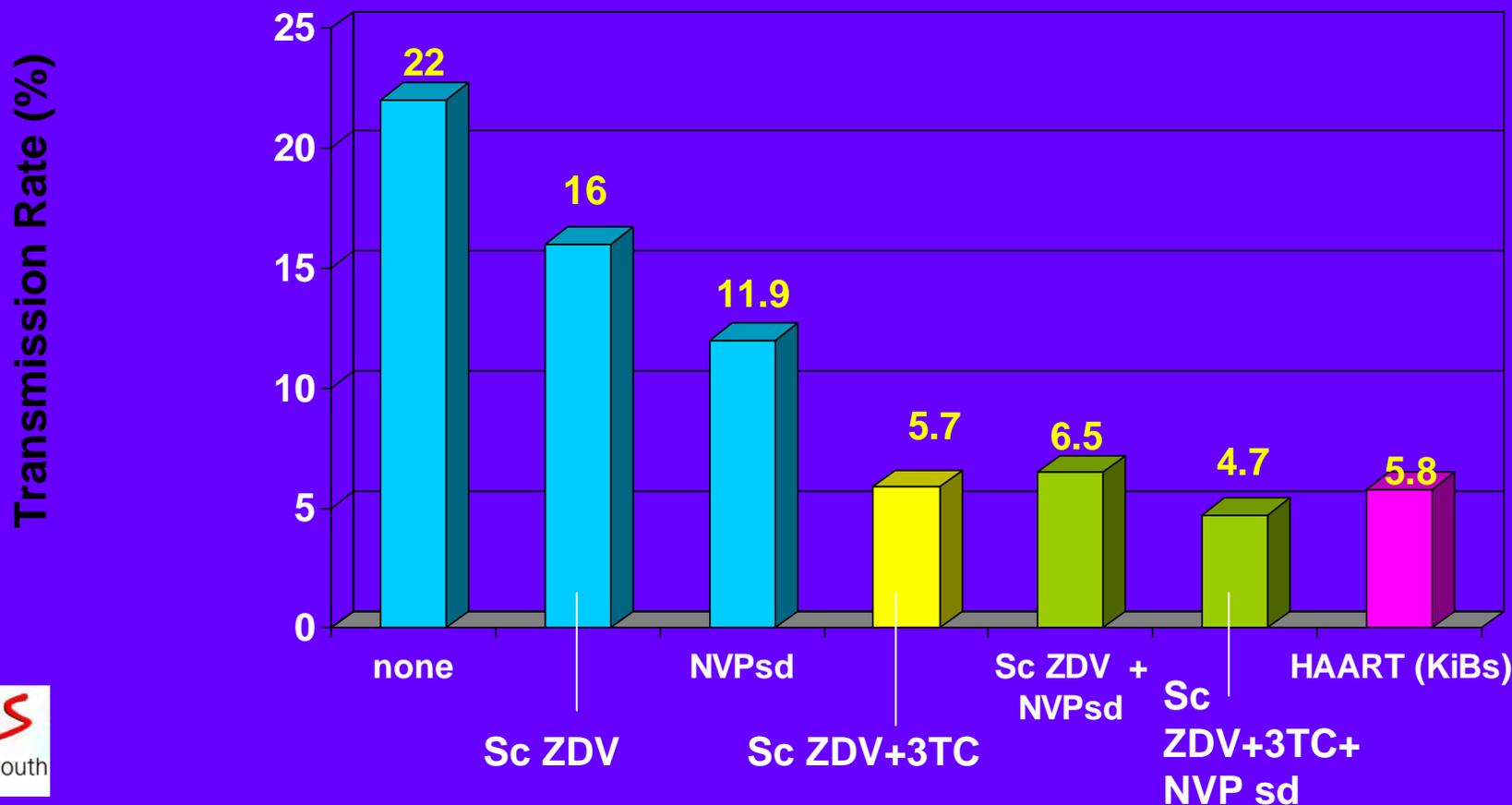
- Single dose-NVP
- Short course regimens
- Highly Active Antiretroviral Therapy (HAART)

Short-Course ART for pMTCT: AZT or AZT+3TC and SD-NVP

- Efficacy generally increases with longer duration of prenatal treatment
- Efficacy of short-course regimens (AZT or AZT+3TC) generally increases with addition of SD-NVP
- Long courses of dual therapy to mothers associated with risk of 3TC resistance and subsequent treatment failure

Summary of Maternal ARVs and Early 6 week Transmission Rates in BF Africa sites

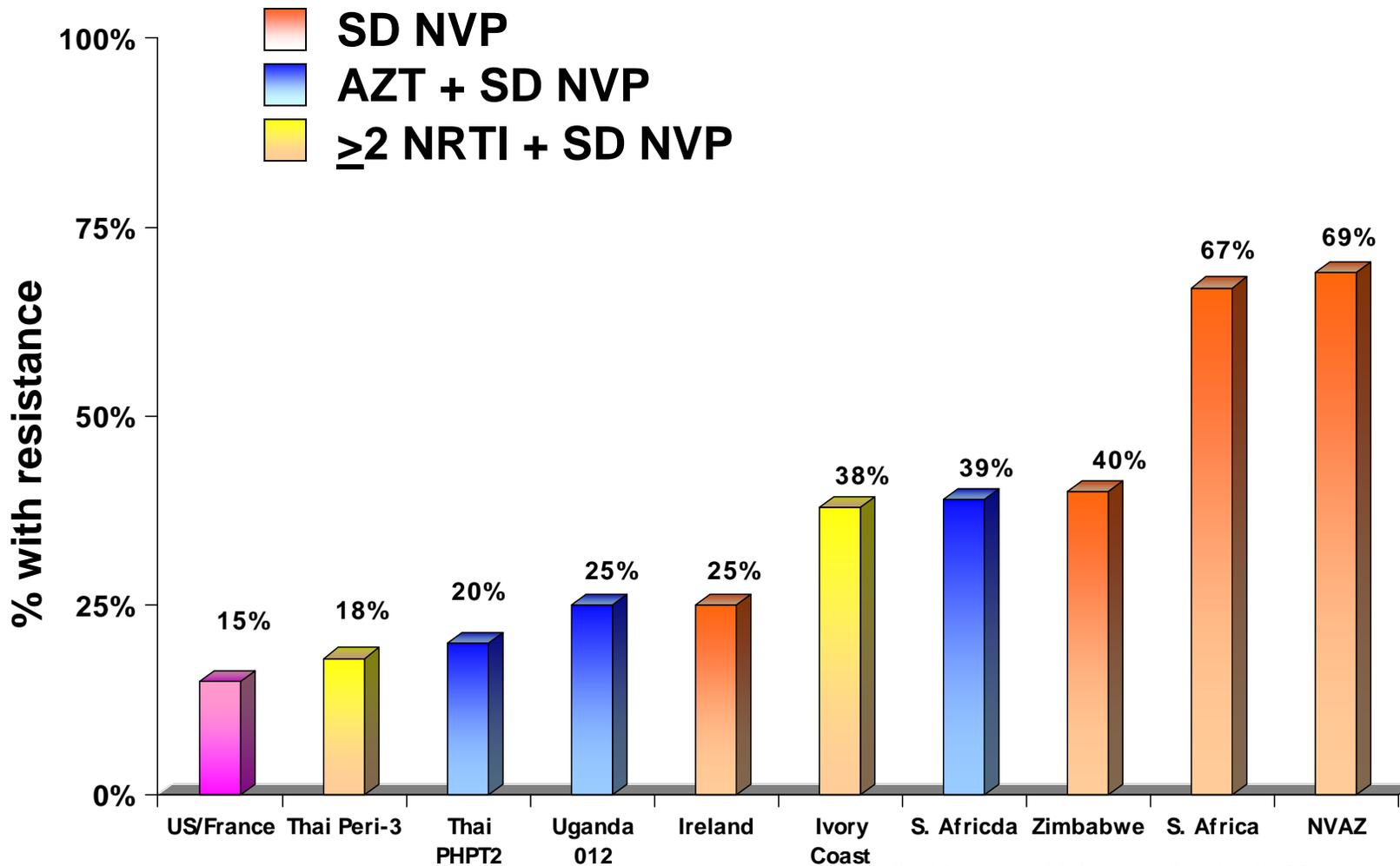
Data suggests benefit of combining SD NVP with Short Course Antenatal ARVs



Why Is a Single Dose of Nevirapine So Effective?

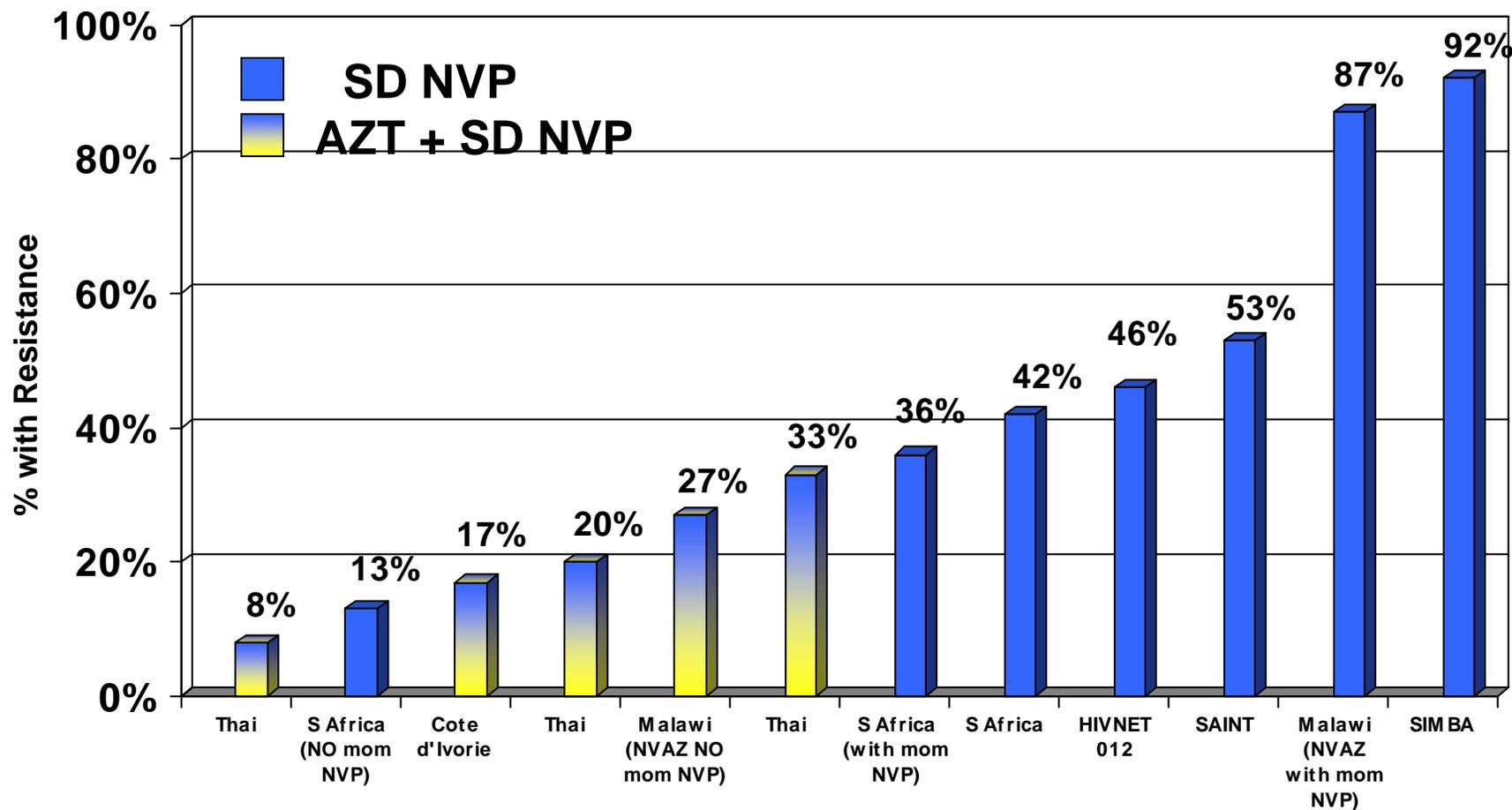
- Highly potent: rapidly diminishes VL
- Crosses the placenta: provides prophylaxis to the infant
- Long half-life: levels are detectable in maternal plasma for up to three weeks
- Inexpensive and easy to administer

Reported Rates of NNRTI Resistance in Women who Received SD- NVP



Compiled from multiples studies by L. Mofenson, NICHD

NNRTI Resistance in Infants Failing SD-NVP Prophylaxis



Impact of Acquired NNRTI Resistance on Response to ART

- In mothers
 - If treatment initiated with nevirapine containing regimen within the first 6 months post partum 40% of women fail within 6 months
- In infants
 - Data in 30 children show increased virological failure

How can we reduce the risk of early treatment failure

- Treat women that need HAART in pregnancy with HAART
- AZT+3TC 4-7 days postpartum has been shown to protect against the development of resistance mutations and can potentially reduce resistance to 10%.
- Delay treatment (only if possible) till 6 months after birth
- Use alternative regimens for women that need HAART within first 6 months post partum if possible,

pMTCT Regimens (WHO)

Scenario	Woman	Infant
CD4 < 200 OR Stage IV OR CD4 < 350 AND Stage III	HAART During pregnancy	<ul style="list-style-type: none"> •SD-NVP as soon as possible- within 72 hours •AZT BD x 7 days
Stage I or II OR Stage III AND CD4 > 350	<ul style="list-style-type: none"> •AZT from 28 weeks •AZT+3TC + SD-NVP at onset of labor • AZT + 3TC x 7 days postpartum 	<ul style="list-style-type: none"> •SD-NVP as soon as possible- within 72 hours •AZT BD x 7 days
Woman receives no ANC care Unknown status at Labor	<ul style="list-style-type: none"> • HIV Test, If positive: •AZT+3TC + SD-NVP at onset of labor • AZT + 3TC x 7 day postpartum 	<ul style="list-style-type: none"> •SD-NVP up to 72 hours after birth •AZT BD x 4 weeks

Breastfeeding- risks

- Breastfeeding continues to pose a substantial risk for MTCT
 - Approximately 30–40% of the overall likelihood of MTCT of HIV can be attributed to breastfeeding
 - 10–15% of children who are not infected at birth acquire infection through breast-feeding by the time they are 2 years old

Exclusive Breastfeeding - Benefits

- **Data from several (although not all) studies suggest that exclusive breastfeeding is associated with a lower risk of MTCT when compared with mixed feeding**
- The **ZVITAMBO sub-study** of a large vitamin A trial in Zimbabwe looking at postnatal transmission
 - Followed 2,060 infants testing PCR-negative at 6 weeks for 18 months
 - Introduction of solid foods or animal milks < 3 months of age was associated with 4x greater risk of postnatal transmission (PNT) at 6 months of life
 - EBF during the first 3 months of life was associated with a 61% reduction in PNT at 18 months, compared with MBF
- Maternal health status was significantly associated with risk of postnatal transmission
 - Women with CD4 count < 200 were 9x more likely to transmit postnatally compared with women with CD4 count > 50

KZN EBF Intervention Study

- Estimate risk per 100 child years of EBF = 10.7; 0.89% per month EBF exposure
- Intensive (expensive, but not complicated = counseling, home visits) intervention to improve EBF: 82% EBF at 6/52, 40% @6/12.
- Mixed feeding with other fluids HR 1.56 (0.66-3.69)
- Mixed feeding with solids HR 10.87 (1.51-78.0)

Risk of transmission with an EBF intervention, according to feeding type and maternal CD4 count

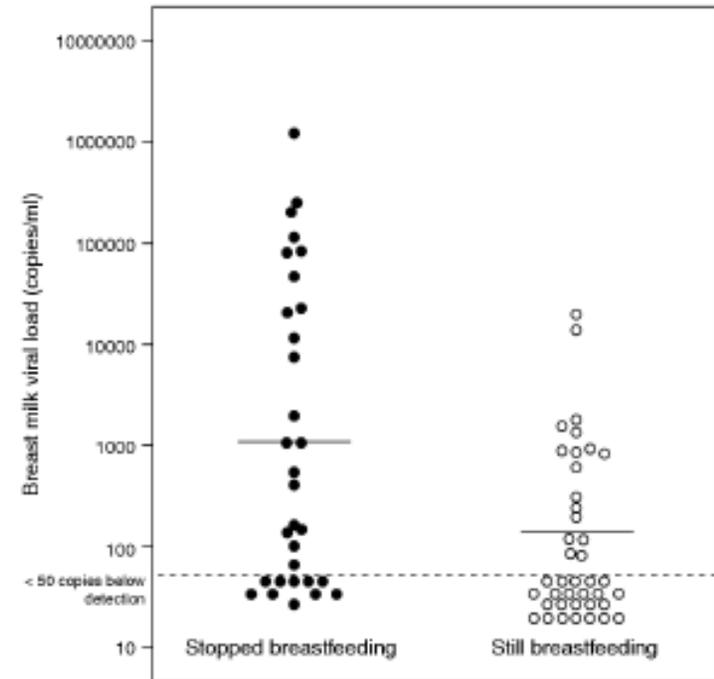
	Maternal antenatal CD4 count by feeding method (cells per μ L)				HIV point prevalence rates
	<200	200-500	>500	Missing	
EBF (n=362)	30 (8%)	162 (45%)	155 (43%)	15 (4%)	55 (15%; 11.7-19.3)
RF (n=28)	10 (36%)	9 (32%)	8 (29%)	1 (4%)	2* (7%; 0.9-23.5)
MBF (starting <14 weeks; n=332)	40 (12%)	159 (48%)	113 (34%)	20 (6%)	89 (27%; 22.1-31.9)
MBF (starting >14 weeks; n=239)	30 (13%)	96 (40%)	101 (42%)	12 (5%)	61 (26%; 20.1-31.5)

Data are number (%) or number (%; 95% CI). EBF=exclusively breastfeeding. RF=replacement feeding. MBF=mixed breastfeeding. * Two children who switched from EBF to RF.

Table 2: Maternal antenatal CD4-cell counts and HIV point prevalence rates at 26 weeks by method of feeding at 26 weeks

EBF with rapid weaning: Risks

- Rapid weaning may be associated with increased risk of transmission
- After weaning may be non HIV related growth faltering and increased hospitalizations for gastroenteritis as with replacement feeding

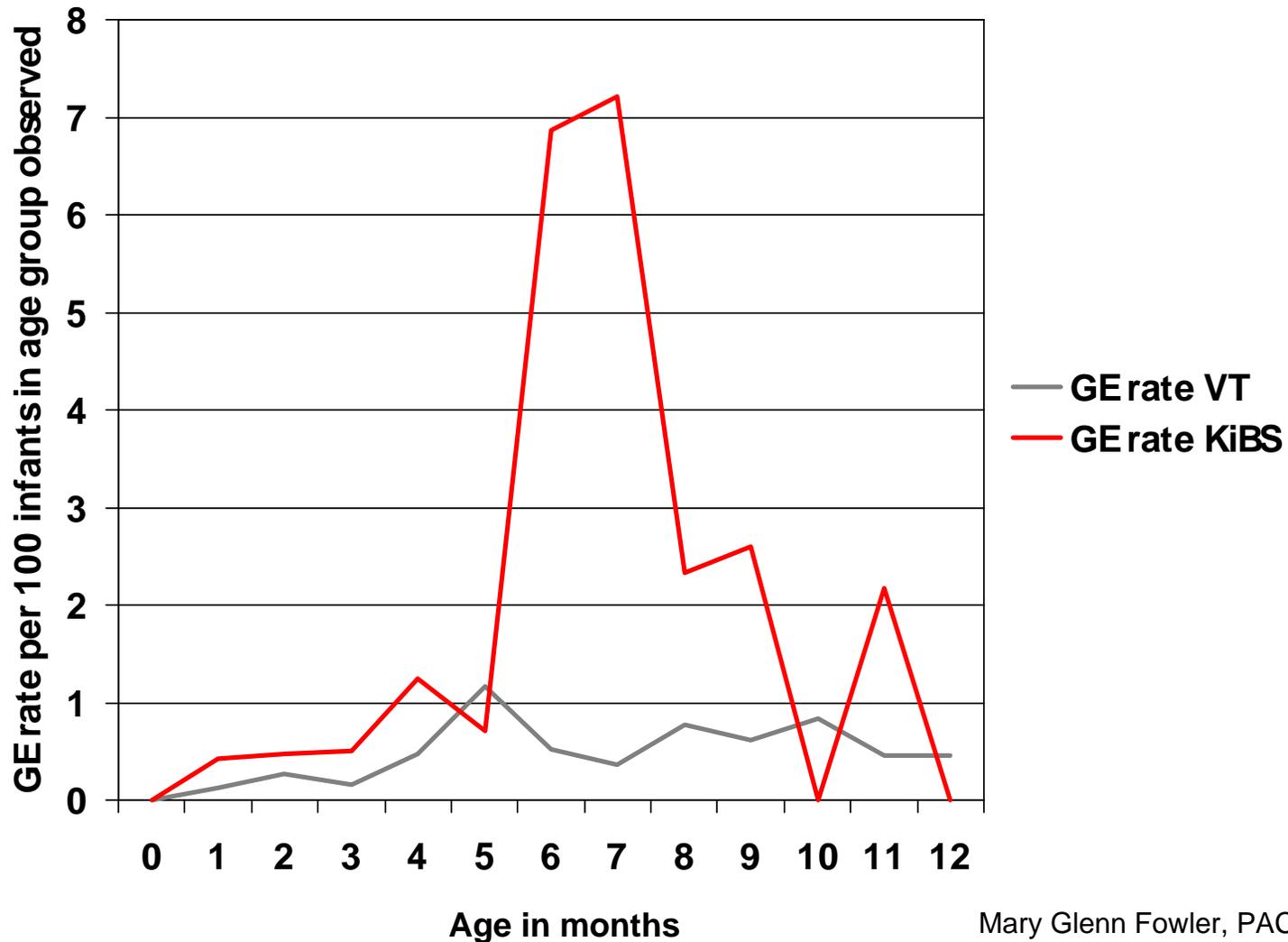


Thea, AIDS 2006

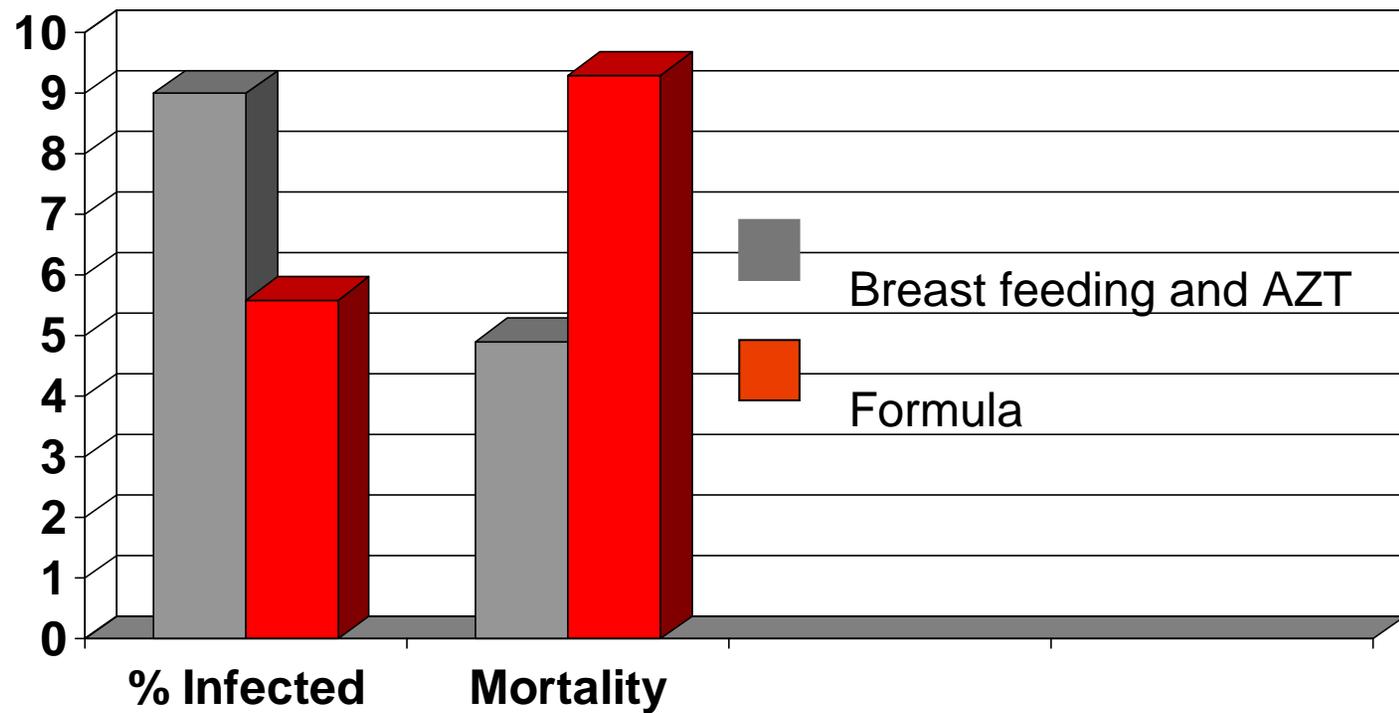
Replacement feeding: Risks

- Risk of diarrhea during outbreak in Botswana 2006: Not breastfeeding AOR = 50 (4.5-100)
- Botswana pMTCT: Long Course AZT +sd NVP, FF 12 months - 80% uptake.
- Of inpatient cohort:
 - 93% FF, 65% moms HIV+, 18% infants infected.
 - 42% developed marasmus, 20% kwashiorkor, 22% mortality (Unrelated to HIV status)
 - Problems: Inadequate supply of formula well documented

Higher Rates of GE Hospitalizations with Early Weaning, Kisumu, Kenya



ARVs to infant during breastfeeding: The Mashi Study at 7 months



Thior et al JAMA. 2006;296:794-805

Recommendations on breast feeding

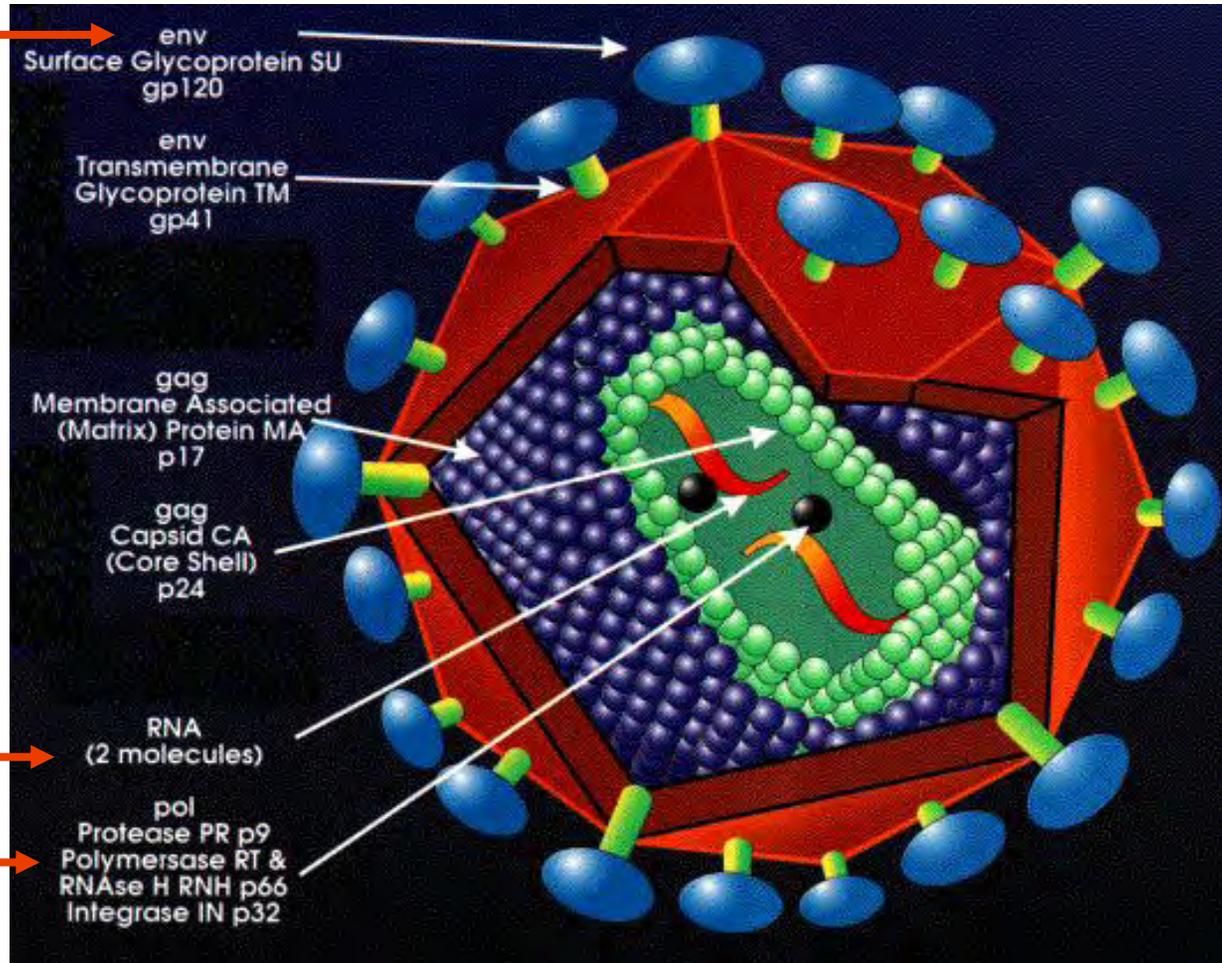
- Exclusive breastfeeding is recommended for the first 6 months of life unless replacement feeding is acceptable, feasible, affordable, sustainable and safe
- At six months, if replacement feeding is still not acceptable, feasible, affordable, sustainable and safe, continuation of breastfeeding with additional complementary foods is recommended
- All breastfeeding should stop once a nutritionally adequate and safe diet without breast milk can be provided.
- In an infants or young child is infected and still breastfeeding strongly encouraged to continue breastfeeding.

Supporting Infant Feeding

- Choosing to breastfeed or replacement feed is complex:
 - Personal preference of woman/family
 - Local community norms
 - Availability of supplies (formula, water)
- Ongoing counseling should be provided regarding the risks and benefits
- Women should be supported in their infant feeding decisions
- Infant feeding should be discussed at each visit for mother and child
 - Assure accurate history of intake
 - Assess problems and concerns

The culprit... HIV structure and function

Binds CD4
Co-receptors
(CCR5,
CXCR4)



Genetic
material

Viral
enzymes

Classification of HIV: Types and Subtypes

Genus *Lentivirus*

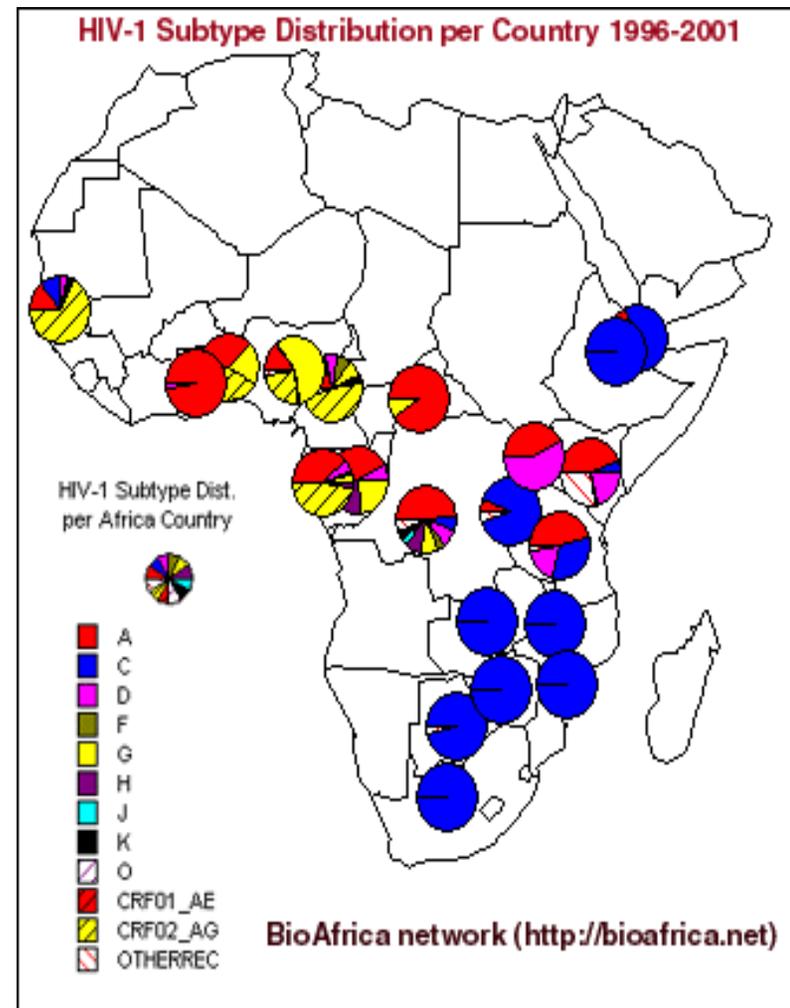
Family *Retroviridae*

Divided in 2 Types

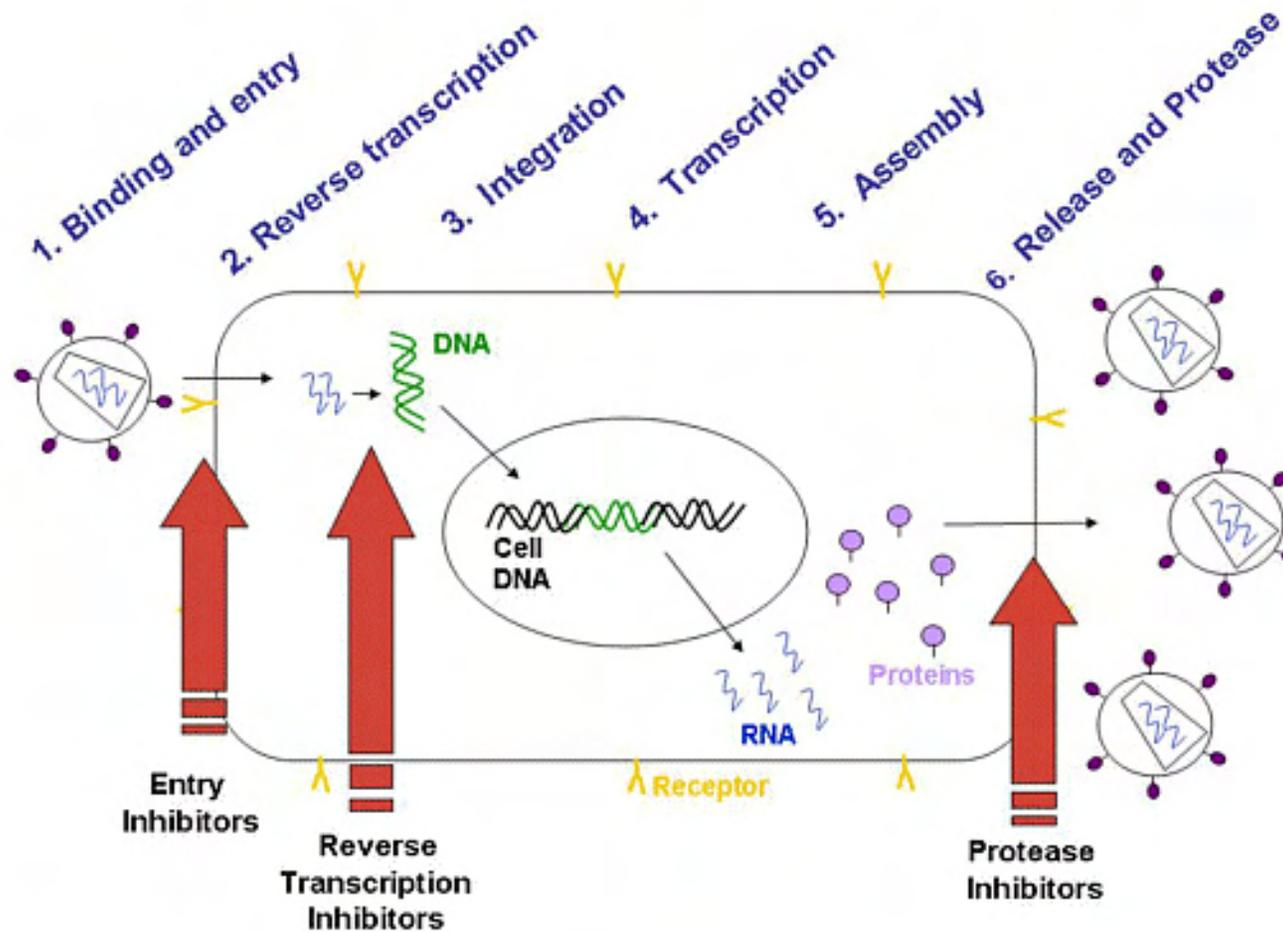
- HIV-1 → global pandemic
- HIV-2 → West Africa, Mozambique, Angola

Subtypes (clades) of HIV-1

- Africa: A, C, D most common
 - Subtype C responsible for >90% of infections in Southern Africa
- Europe and America: B



HIV Life Cycle



ART Regimens used in SA

Regimen	Children \leq 3 years	Children $>$ 3 years old and/or $>$ 10 kg
First Line	<ol style="list-style-type: none"> 1. Stavudine (d4T) 2. Lamivudine (3TC) 3. Lopinavir/Ritonavir (Kaletra©) 	<ol style="list-style-type: none"> 1. Stavudine (d4T) 2. Lamivudine (3TC) 3. Efavirenz (EFV)
Second Line	<ol style="list-style-type: none"> 1. Zidovudine (ZDV) 2. Didanosine (ddI) 3. Nevirapine (NVP)/ Efavirenz (EFV)* 	<ol style="list-style-type: none"> 1. Zidovudine (ZDV) 2. Didanosine (ddI) 3. Lopinavir/Ritonavir (Kaletra©)

Summary

- Effective perinatal prevention is the most certain way to protect and secure the future of children born to women with HIV
- This can be achieved by:
 - Enrolling mothers at all points of entry
 - Ensuring maternal health by providing access to HAART to mothers that need it.
 - Providing a full set of pMTCT interventions: ART and HAART, safe obstetric practices, STI treatment, nutrition counseling
 - Establishing open communication and **strong linkages** between services
 - Ensuring appropriate infant follow-up
 - Providing early infant diagnosis if available
 - Prompt referral of HIV-infected infants

Summary cont.

- Children are at risk for rapid disease progression compared to adults
- Early identification and ART initiation is key to prevention of disease progression
- There are multiple challenges that must be overcome in order to provide sustainable HIV care and treatment for children



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