

Is eradication of paediatric HIV an attainable goal?

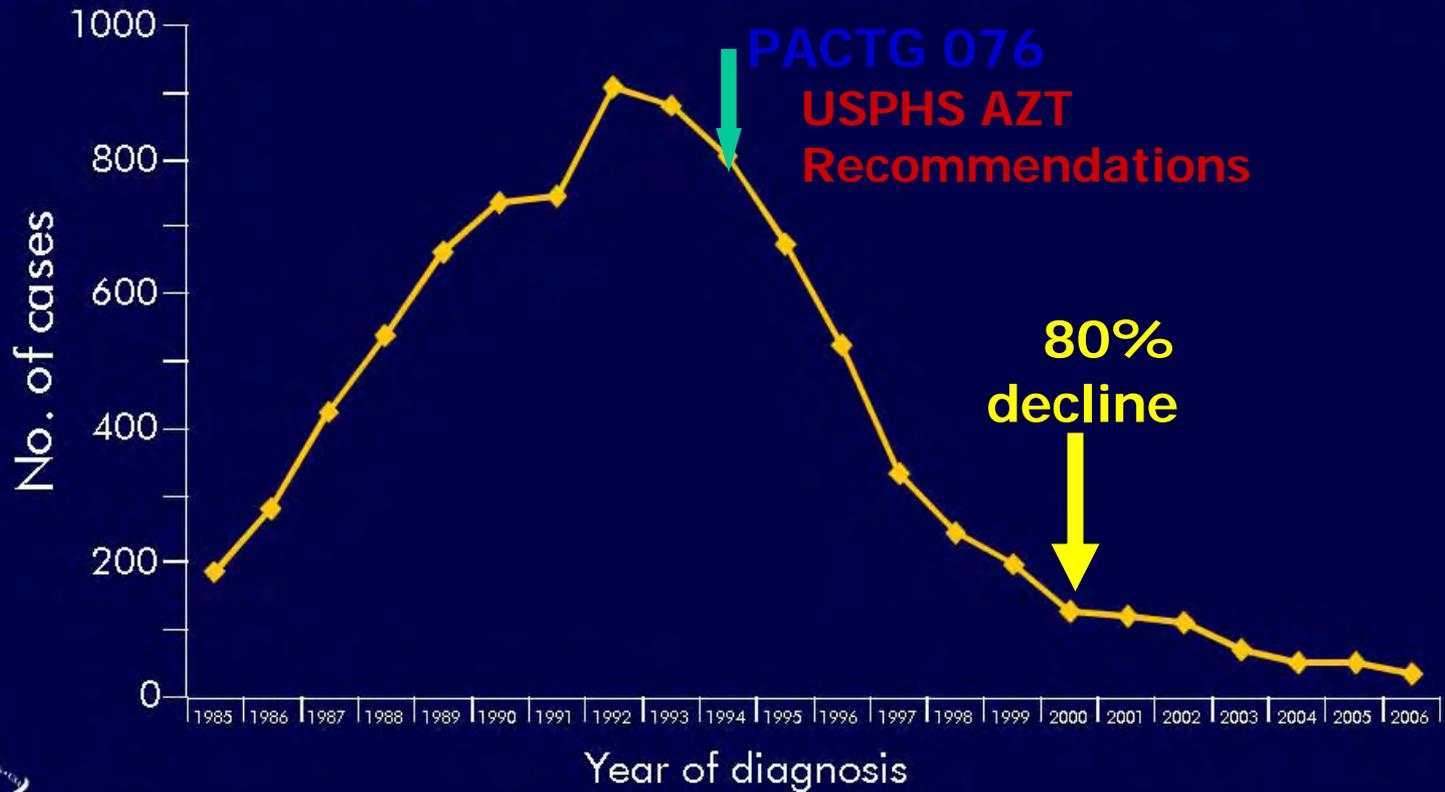
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University of the Witwatersrand
Chris Hani Baragwanath Hospital
Johannesburg, South Africa*



PMTCT: An astounding success.....



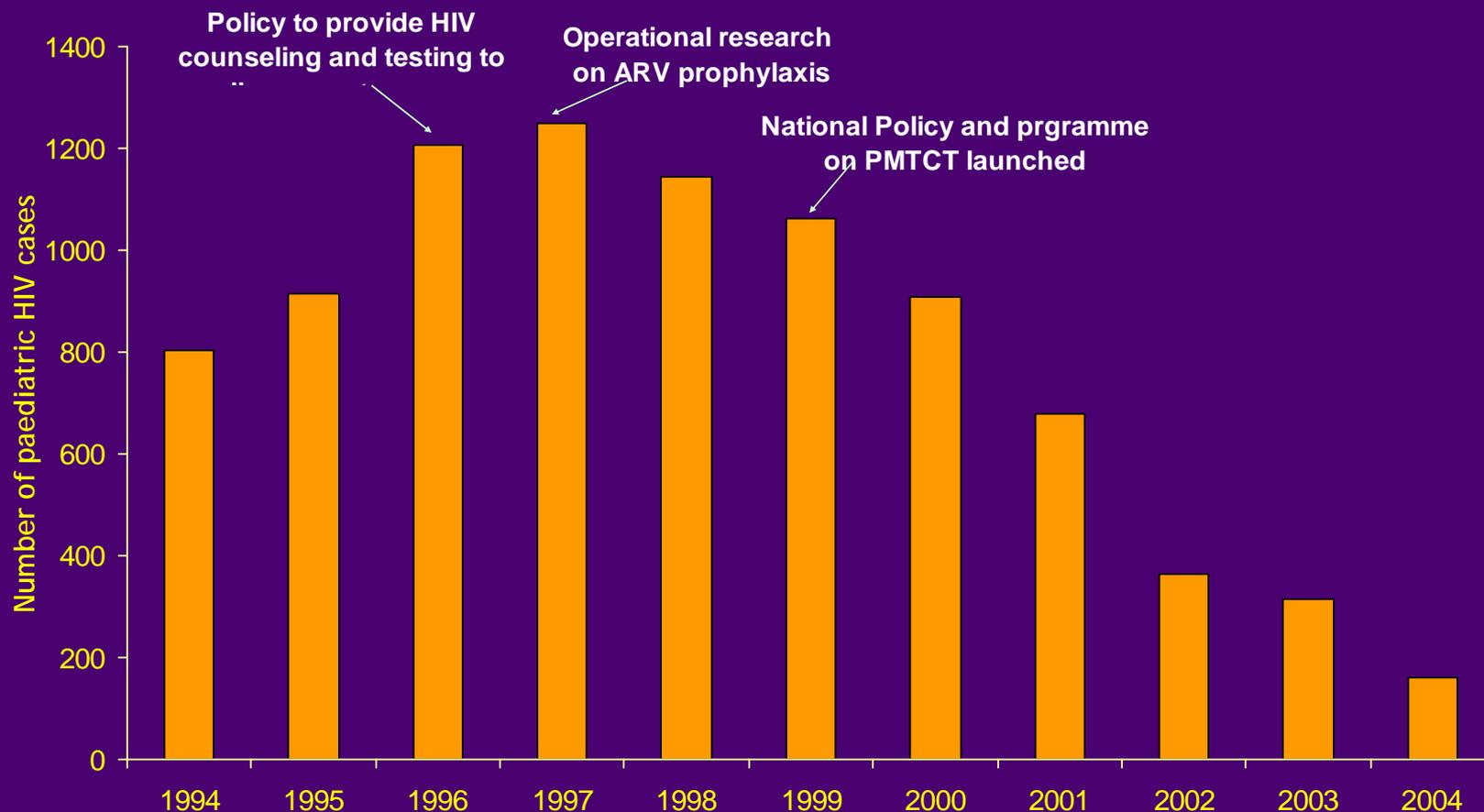
Estimated Number of Perinatally Acquired AIDS Cases, by Year of Diagnosis, 1985–2006—United States and Dependent Areas



Note. Data have been adjusted for reporting delays and cases without risk factor information were proportionally redistributed.

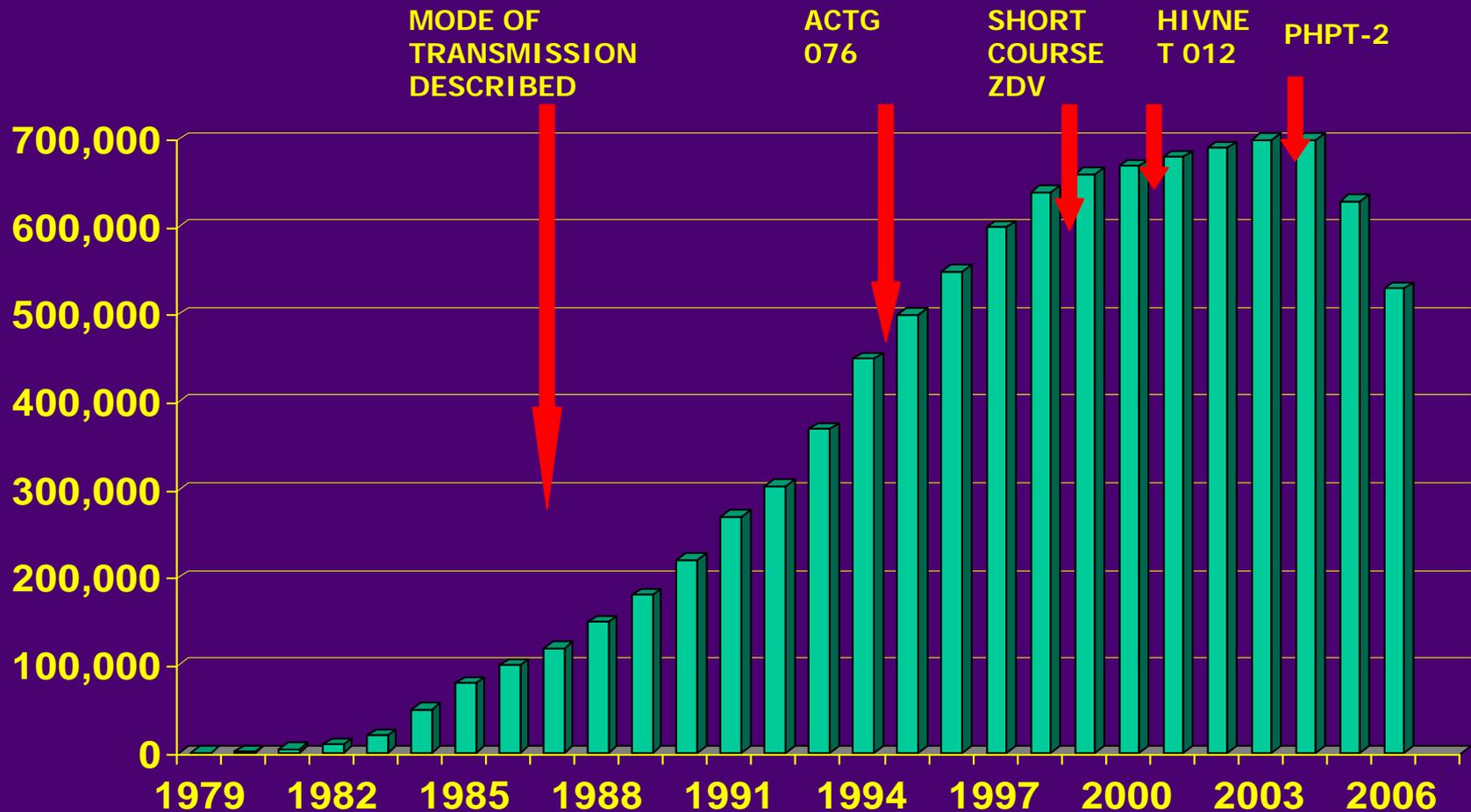


Decrease in paediatric HIV infections after implementation of prevention of mother-to-child transmission programme in Thailand, 1994-2004



Siripon Kanshana, 2007

Mother-to-Child Transmission (MTCT) of HIV Estimated Children Newly Infected in World



UNAIDS estimates

Looking beyond PMTCT in the era of universal access

- PMTCT services have a dual responsibility: care for the mother and care for the child
- As antiretroviral treatment becomes more accessible, there will be increased need to tailor MTCT strategies to fit with appropriate treatment for mothers
- PMTCT must be more than an intervention for a day or a month of a woman or baby's life



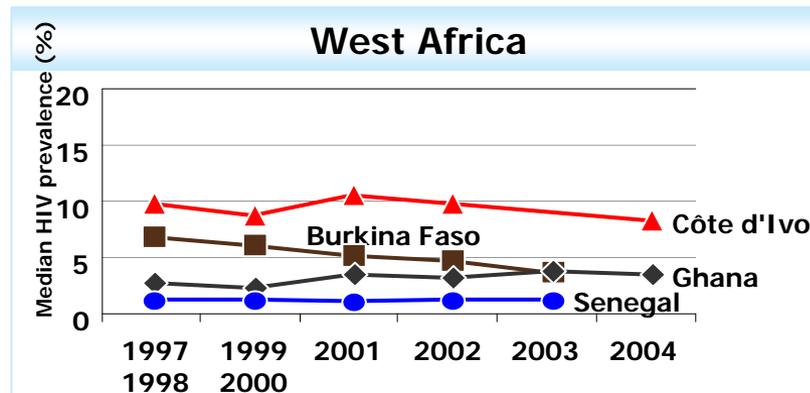
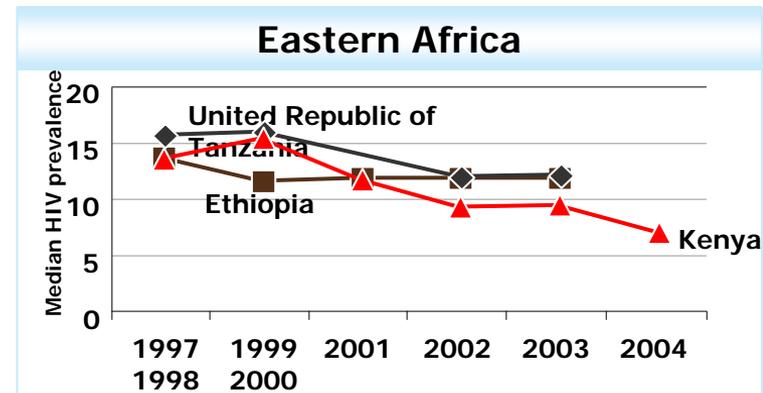
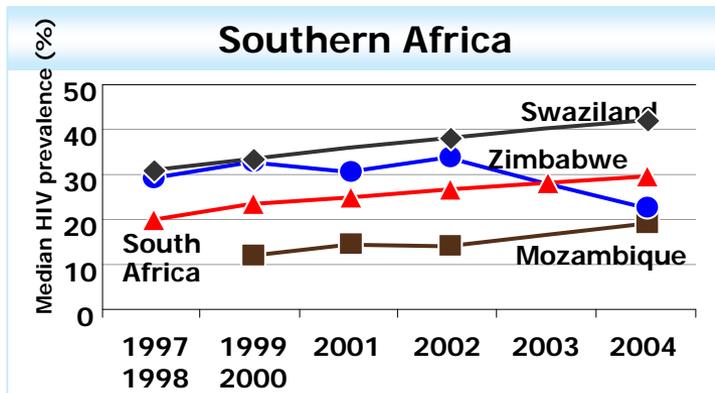
PMTCT: The four-pronged strategy



- Primary prevention of HIV in parents-to-be
- Prevention of unwanted pregnancies
- Prevention of transmission from HIV-infected mother to infant
- Appropriate treatment and care

Primary prevention to prevent HIV transmission is a key component for decreasing paediatric HIV

HIV prevalence (%) among pregnant women attending antenatal clinics in sub-Saharan Africa, 1997/98 – 2004

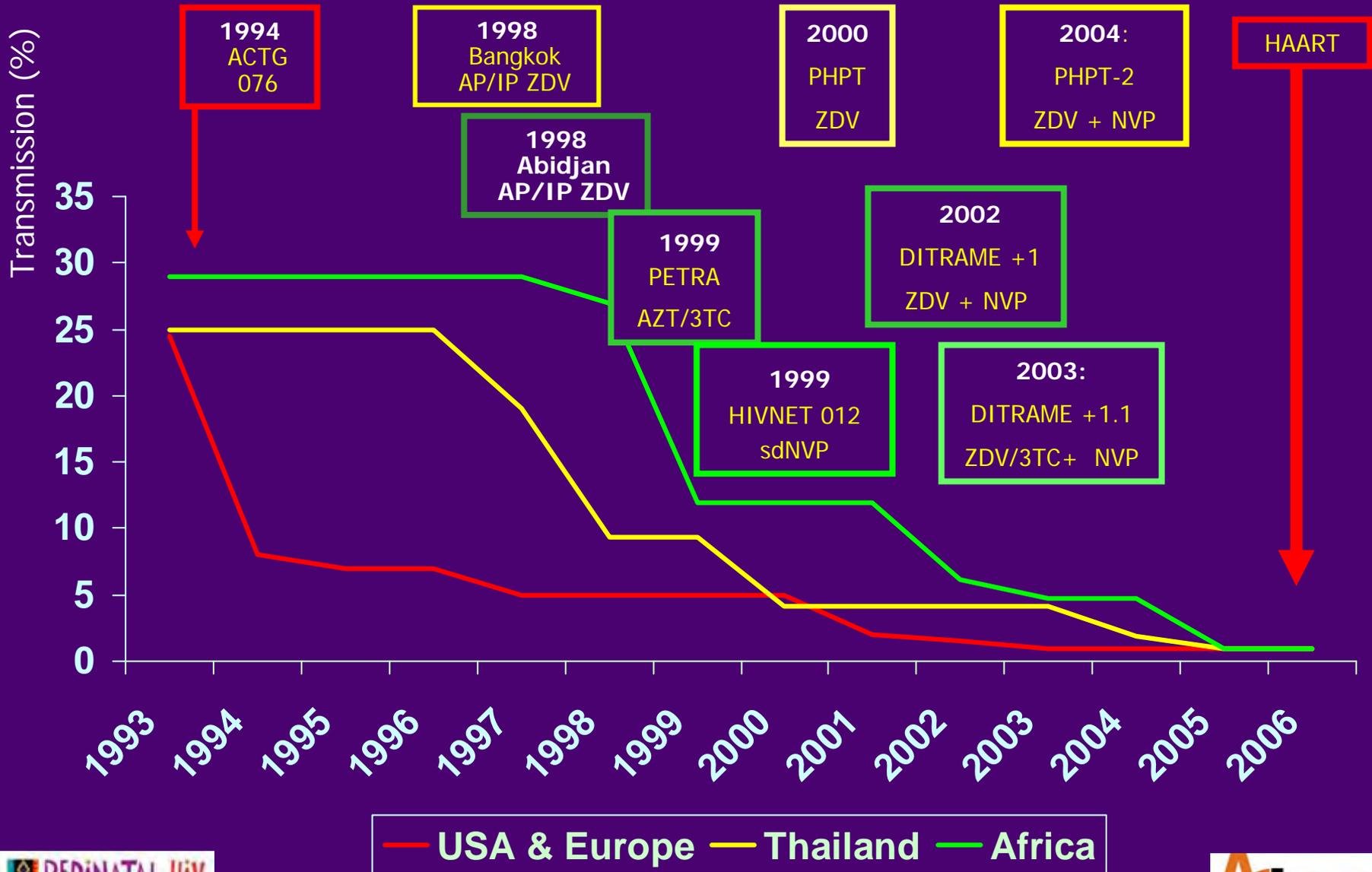


Note: Analysis restricted to consistent surveillance sites for all countries except South Africa (by province) and Swaziland (by region)

Advances in preventing mother-to-child transmission of HIV



Trends in reduction of MTCT: study results over time

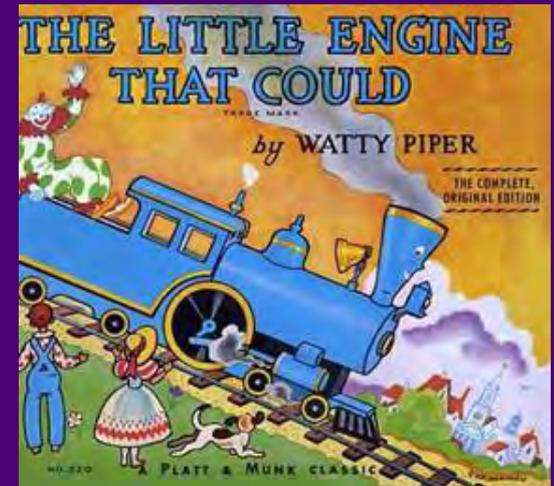


“The little engine that could”

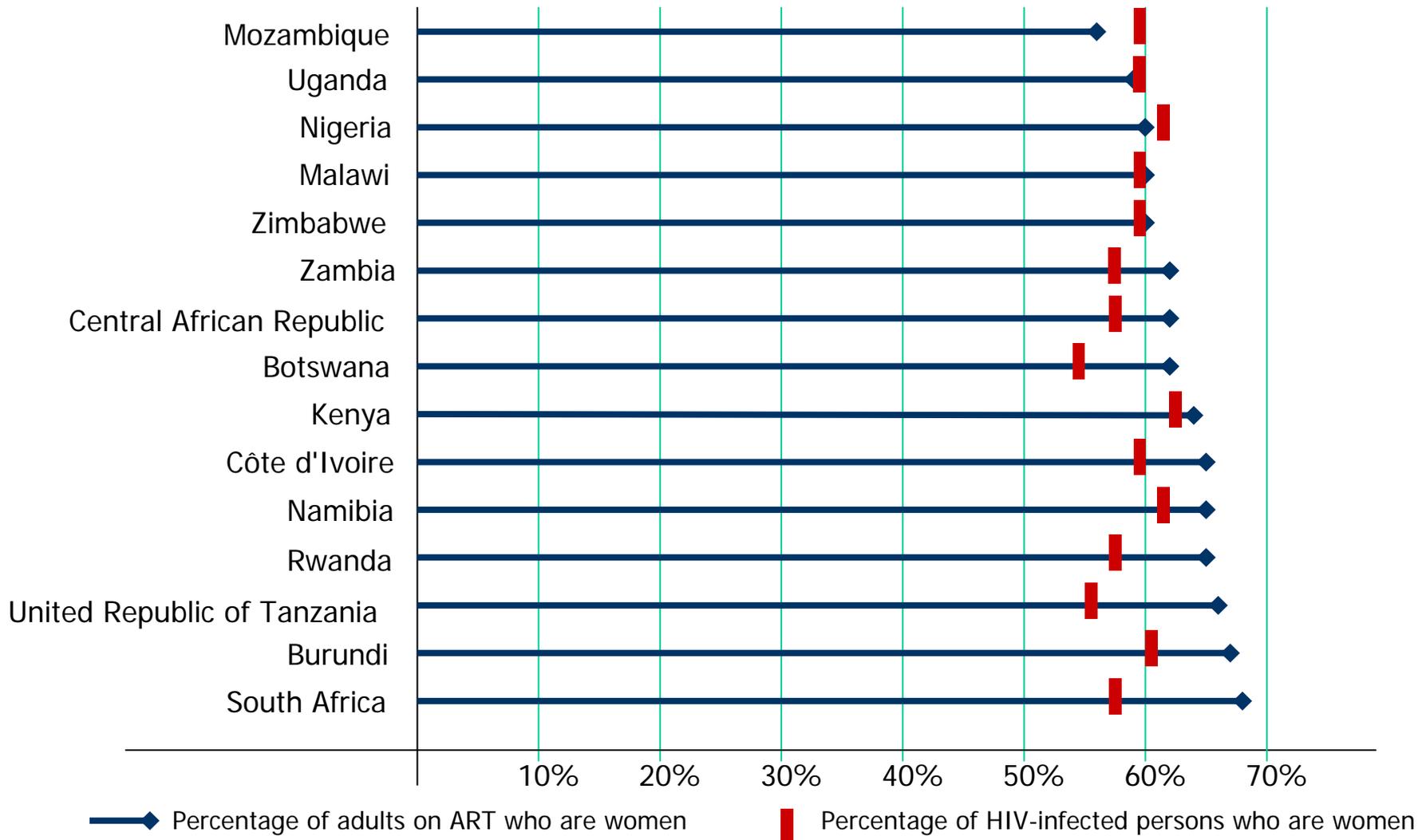
The single dose nevirapine regimen has provided the momentum to start PMTCT programs in many developing countries.

By 2006, the manufacturer’s PMTCT donation programme had distributed over a million doses

These services have provided the experience and the foundation for more complex PMTCT programmes and ARV treatment access programs



Women's access to HIV treatment, June 2006



Public Health Service Task Force

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States

November 2, 2007



World Health
Organization



HIV/AIDS Programme

Strengthening health services to fight HIV/AIDS

Antiretroviral Drugs for Treating Pregnant
Women and Preventing HIV Infection in
Infants in Resource-Limited Settings

Recommendations for a Public Health Approach
2006 version

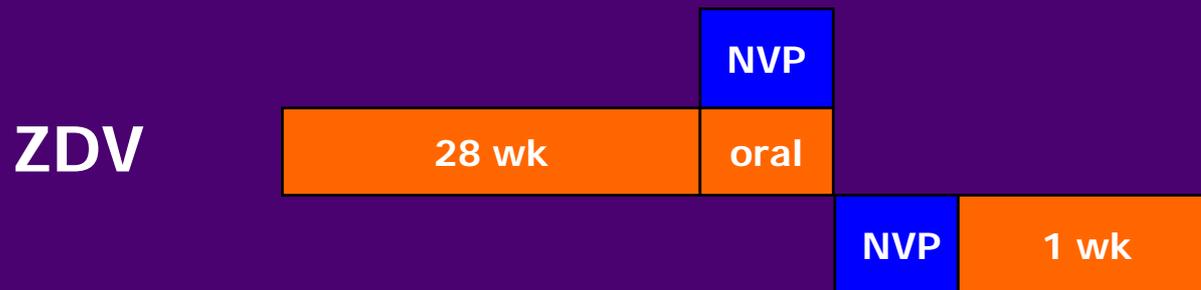
WHO PMTCT guidelines, 2006



- 1] antiretroviral therapy for symptomatic women WHO stage 4) or with CD4 counts below 200/mm³;
- 2] consideration of ARV treatment for women with WHO stage 3 and CD4 counts between 350 and 200/mm³ ;
- 3] a simpler regimen of zidovudine from 28 weeks with NVP added in labour and to the baby, and the addition of a seven day zidovudine/lamivudine postpartum cover to reduce resistance; and
- 4] the retention of the simplest NVP regimen for emergency settings or where nothing else is available.

We can do better than single dose nevirapine

PHPT-2 (Thailand)



Transmission rate 2% (non breastfeeding)



Programme experience of “dual therapy” PMTCT interventions

The “PHPT-2” regimen has now been used in a number of PMTCT programmes, with reported transmission rates of 3 – 5%, including those in Thailand, Botswana and the Western Cape Province in South Africa



HAART or HAART-less?

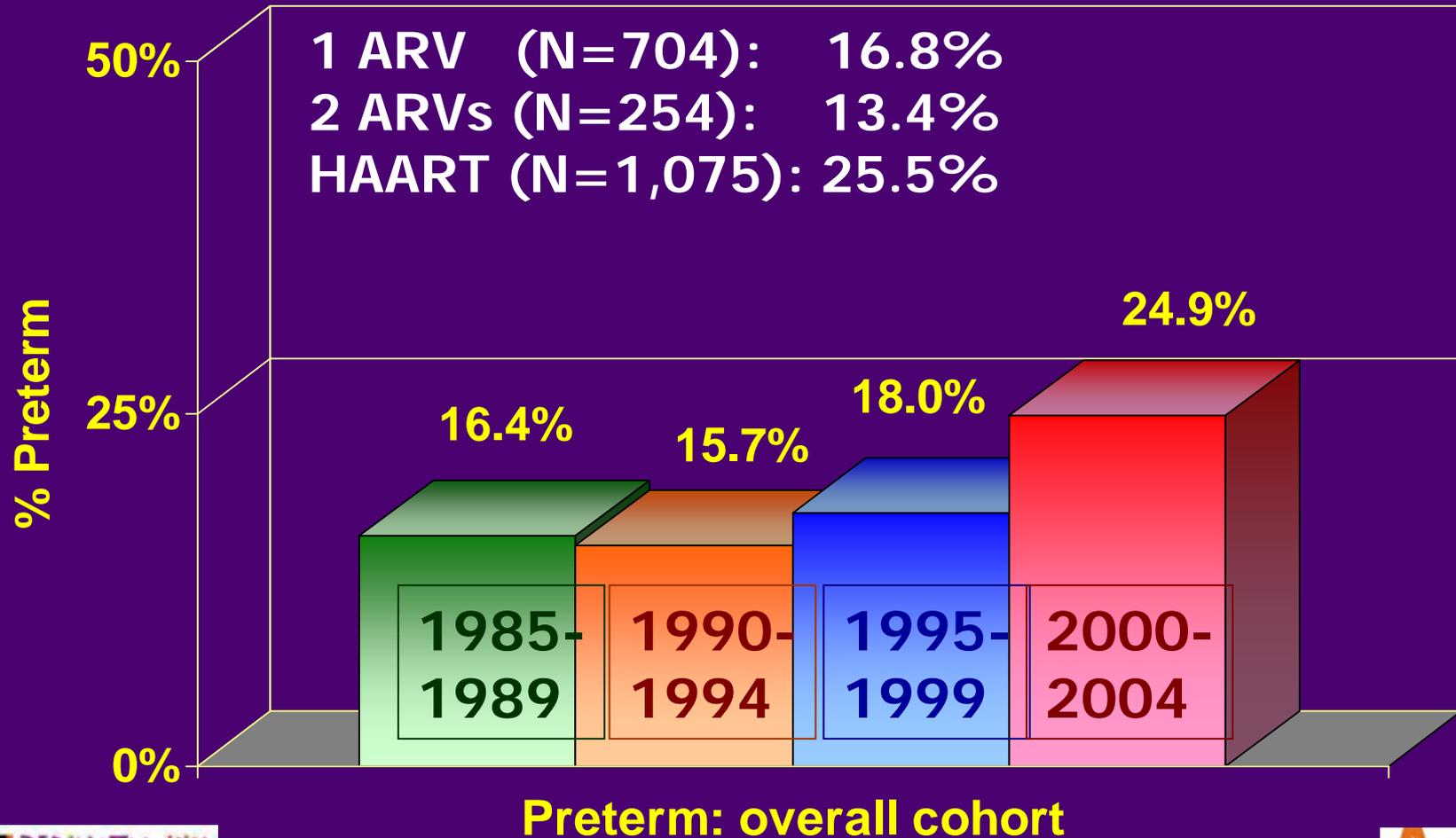


“Treat them all !!”

- Use of HAART in pregnancy only for the indication of PMTCT is the standard of care in many resource-rich settings
- Some reports about safety and efficacy of HAART in pregnancy for PMTCT : DREAM, Mozambique, KIBS Kisumu
- Concerns remain about HAART regimens for PMTCT in resource poor settings with less than optimal monitoring, especially where nevirapine is a standard part of first line regimens

Increase in Prematurity (GA <37 Weeks) in HIV-Infected Women Over Time

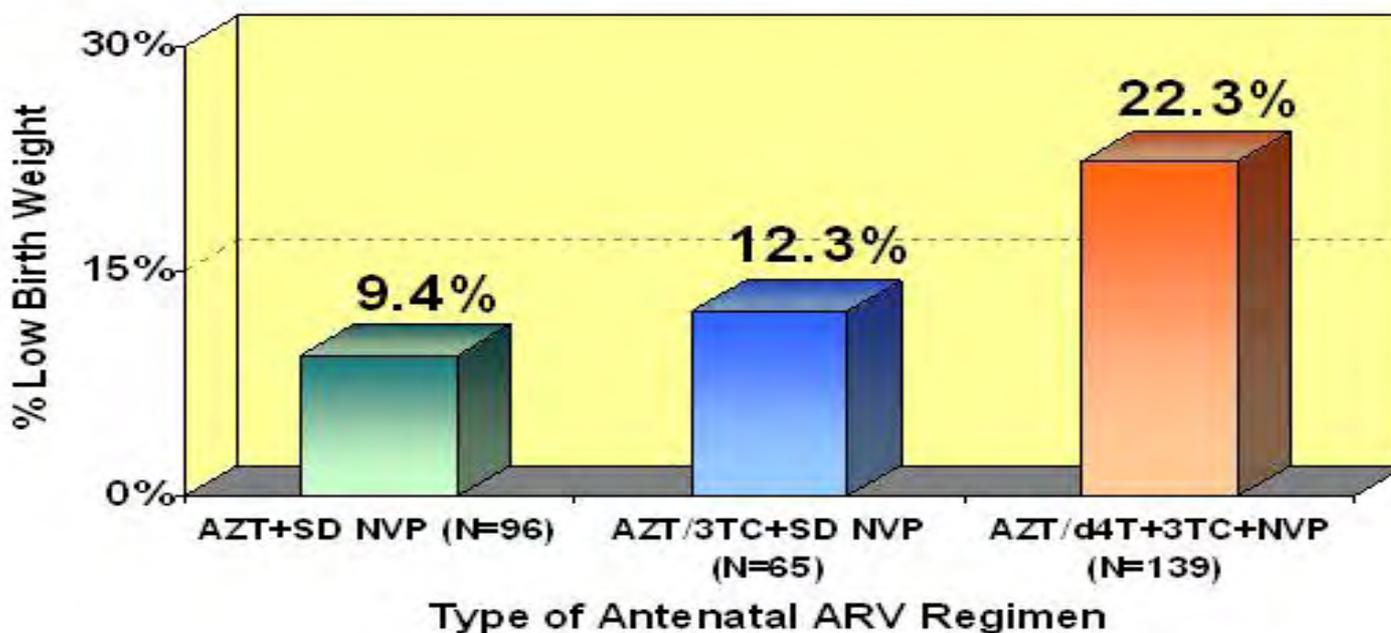
European Collaborative Study. AIDS 2004;18:2337-9



HAART in pregnancy and low birth weight

Low Birth Weight and ARV Regimen Used During Pregnancy: Cote d'Ivoire

Ekouevi D et al. 15th CROI, Boston, MA, 2008 Abs. 641



Reality Check

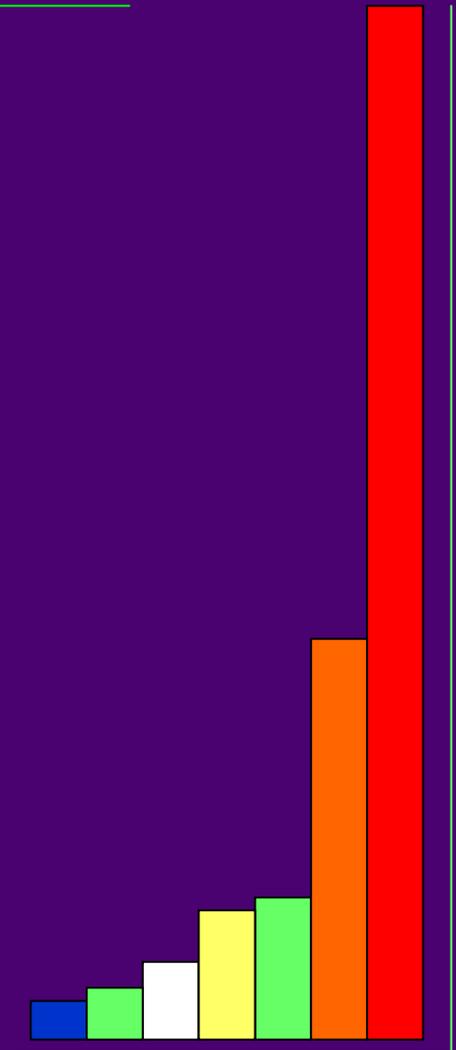
- CD4 counts need to be available for HIV positive pregnant women in order to decide on appropriate treatment options, and few PMTCT services have moved to include CD4 at all health service levels
- Provision of more complex ART requires more laboratory and toxicity monitoring, additional procurement infrastructure, and more intensive follow up
- Most PMTCT services (based on antenatal care) do not yet have the capacity to deliver ART



Reality Check: a question of scale

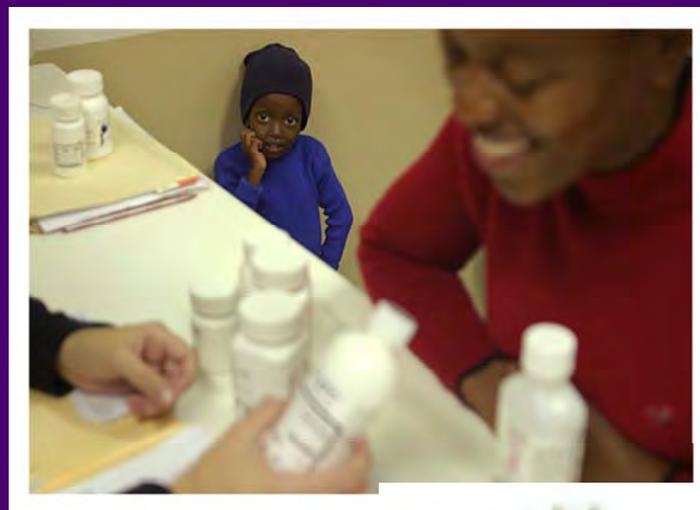
Annual pregnancies in HIV positive women:

	United States	< 7,000
	Rwanda	8,600
	Botswana	14,000
	Europe	15,000
	Kenya	100,000
	South Africa	250,000
	Soweto	9,000



Setting priorities for implementing ART in pregnancy

- Access to CD4 counts for pregnant HIV-positive women is the key to moving forward
- First priority should be to get women with low CD4 counts onto HAART – starting in pregnancy and continuing
- Moving to more effective triple therapy PMTCT regimens will be increasingly possible as treatment programmes mature



What are the implications of HAART for PMTCT?

HÄGAR the Horrible

®

By Dik Browne

YOU SHOULD TRUST
DOCTORS MORE...
OUR FIRST RULE IS:
"DO NO
HARM"

12-29

CHRIS BROWNE

IT WORRIES ME THAT
THEY'D NEED A RULE
TO FIGURE THAT OUT

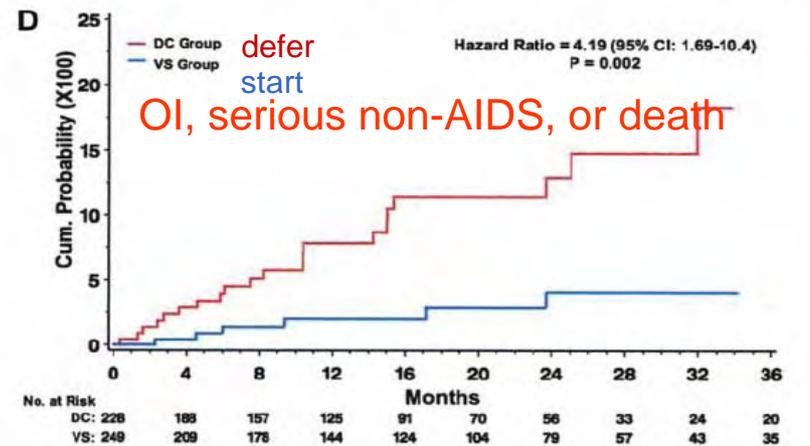
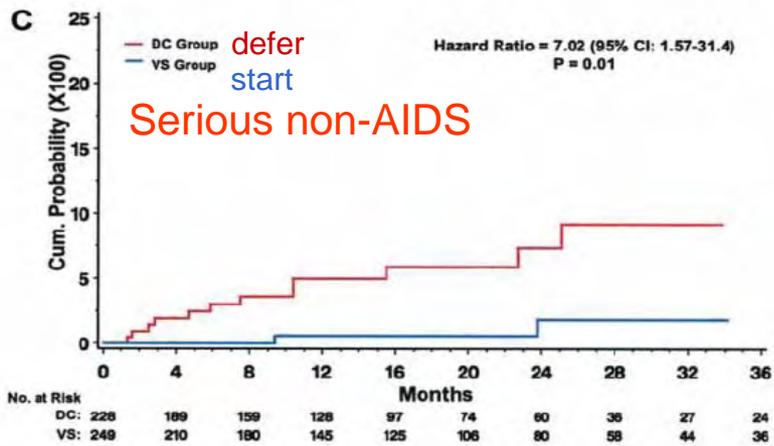
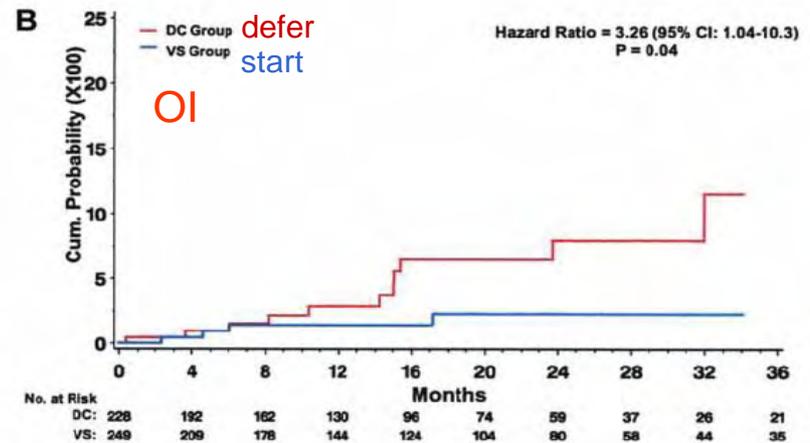
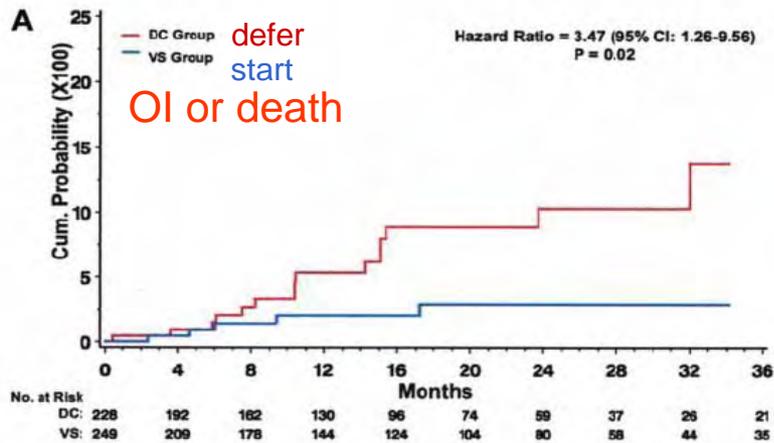
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Short course triple therapy in pregnancy: possible problems

- A critical issue in HIV management is to determine how interventions using ART for PMTCT impact on maternal health in the short and long-term.
- Current PMTCT standards of care are based on the notion that women with CD4 >350 do not need HAART “for their own health”.
 - How sure are we about this?

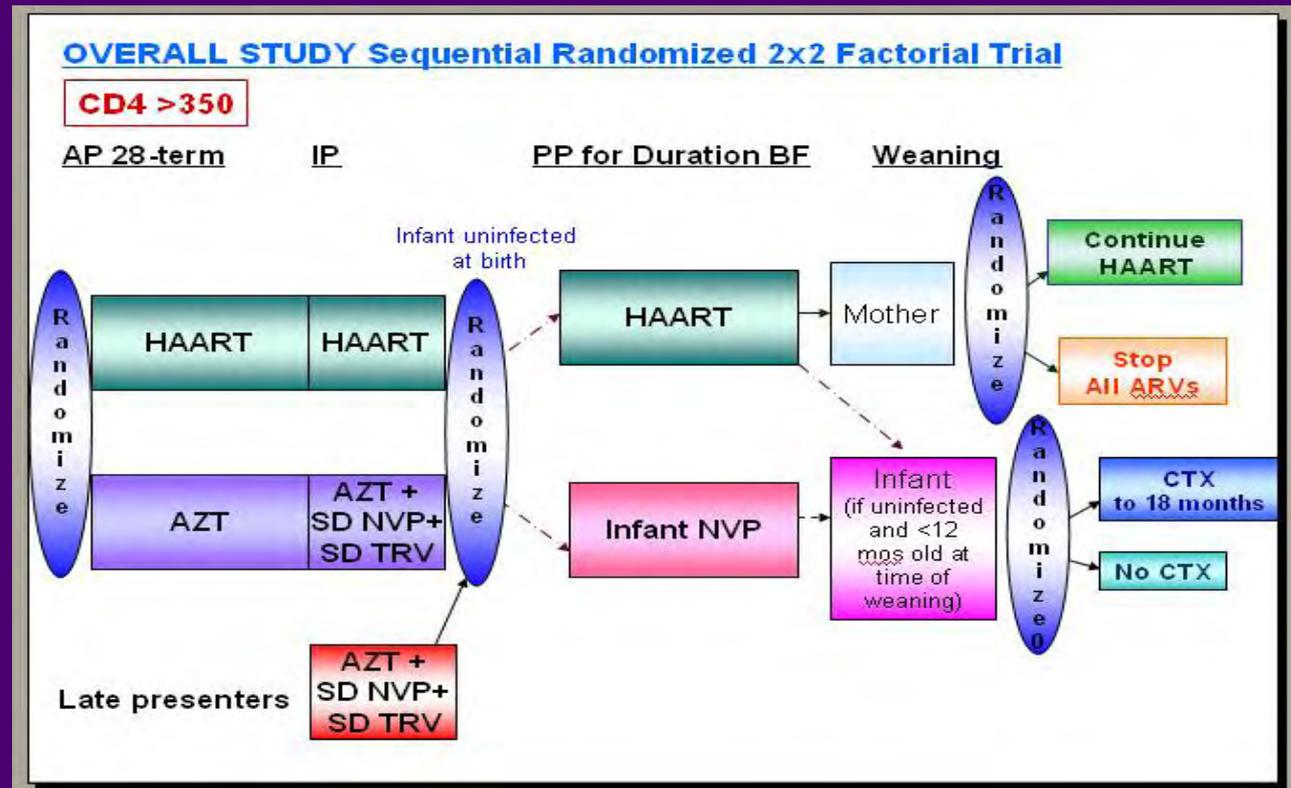
In ARV-Naïve/Off ART Patients in SMART, Deferring ART Had ↑ Risk of Morbidity/Mortality Compared to Starting ART

SMART Study Group. *J Infect Dis* 2008;197:1133-44



What next? IMPAACT PROMISE: Promoting Maternal-Infant Survival Everywhere

The PROMISE study provides the opportunity to integrate high priority questions about the use of ART and the prevention of MTCT.



Will we ever have a vaccine for PMTCT?



PMTCT: A resounding failure.....



The need for effective PMTCT Regimens for Resource-Poor Countries

WHO Paediatric HIV/AIDS in 2005	Global Estimate	Sub-Saharan Africa	Resource-Rich Countries
Children Living with HIV/AIDS	2.3 million	2.0 million	14,000
New Infant HIV Infections	700,000	630,000	700
Deaths in Children with HIV/AIDS	570,000	480,000	200

MTCT has been reduced to <2% in countries which bear 0.6% of the global paediatric HIV burden

The need for effective PMTCT Regimens for Resource-Poor Countries

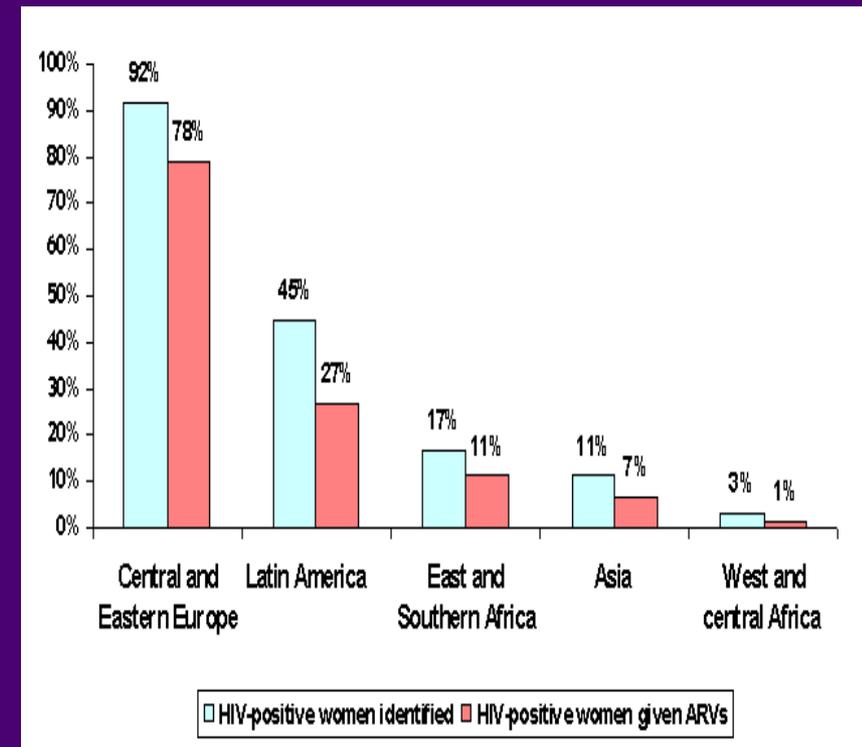
- 1,500 new infections in children each day –
- Approximately:
 - 1 per day in Europe
 - < 1 per day in the United States
 - 100 per day in Asia and the Pacific
 - 1,400 per day in Africa



www.worldmapper.com

Reality check: Global inequities in PMTCT

- More than 95% of paediatric HIV infection occurs in resource-limited settings
- 100 countries globally have started PMTCT programmes but only 7 have achieved coverage of more 40% of pregnant women receiving ARV for PMTCT.

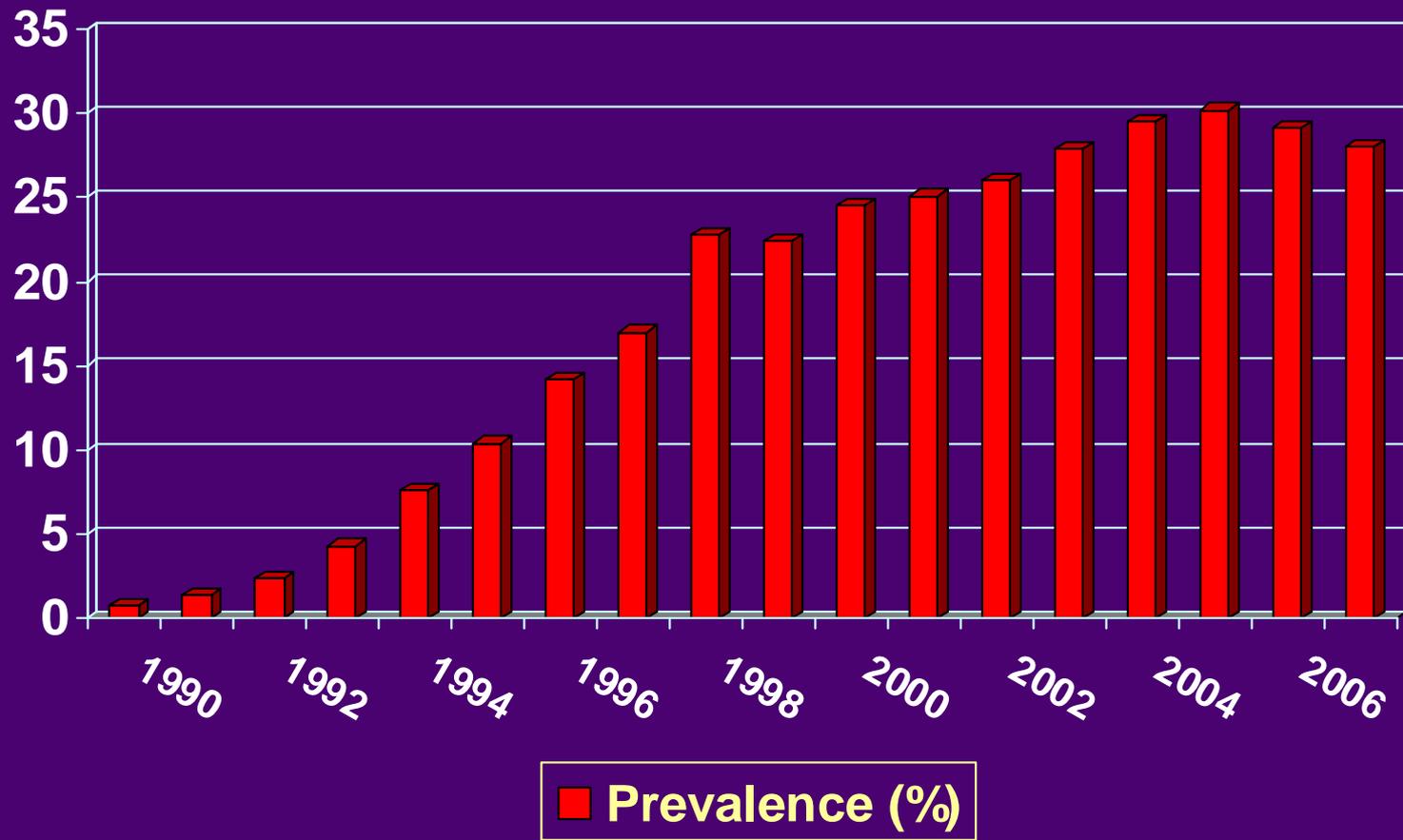


WHO 2006

Reality check: Global inequities in PMTCT

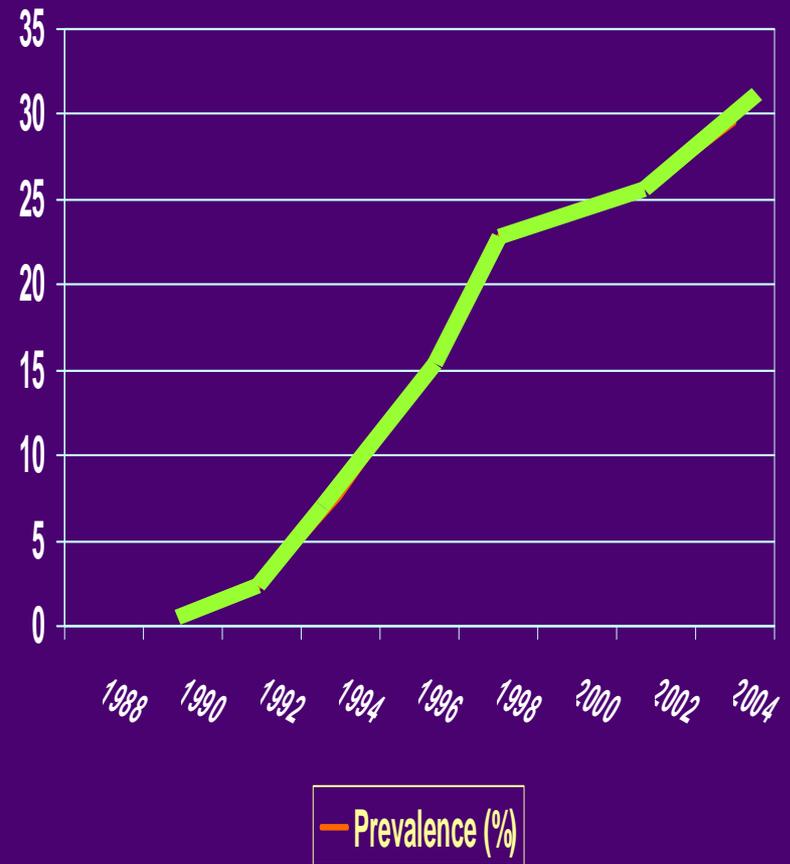
- Low coverage and uptake in resource-limited settings:
 - Less than 15% of pregnant women tested for HIV
 - Less than 12% (8%–16%) of positive pregnant women are offered ARV prophylaxis
 - Less than 5% of pregnant HIV-infected women in need of treatment are offered ART

HIV prevalence among ANC attendees in South Africa, 1990 to 2007



HIV prevalence among ANC attendees in South Africa, 1988 to 2005

100 fold
increase:
from
1 in 300
to 1 in 3



PMTCT services in South Africa

- 78% antenatal sites offer PMTCT services
- <50% mothers take up testing
- ~30% of HIV-infected women receive nevirapine



Meyers 2006

Access to PMTCT interventions

WHO/UNAIDS estimates for South Africa, Jan 07 – Dec 07

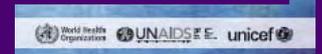
HIV +ve women in need of ARV for PMTCT:

220 000 (180 000 – 260 000)

HIV+ve women receiving PMTCT intervention:

127 164

Coverage: 57% (49% - 69%)



Paarl

Western Cape



Well-run site

Most women
choose to formula
feed

84.0% of babies
alive and
HIV-negative after
9 months

Umlazi

KwaZulu Natal



Well-run site

Most women
choose to
breastfeed

73.4% of babies
alive and
HIV-negative after
9 months

Reitvlei

Eastern Cape



Women given the
option to use
formula but supplies
often run short

64.3% of babies
alive and
HIV-negative after
9 months

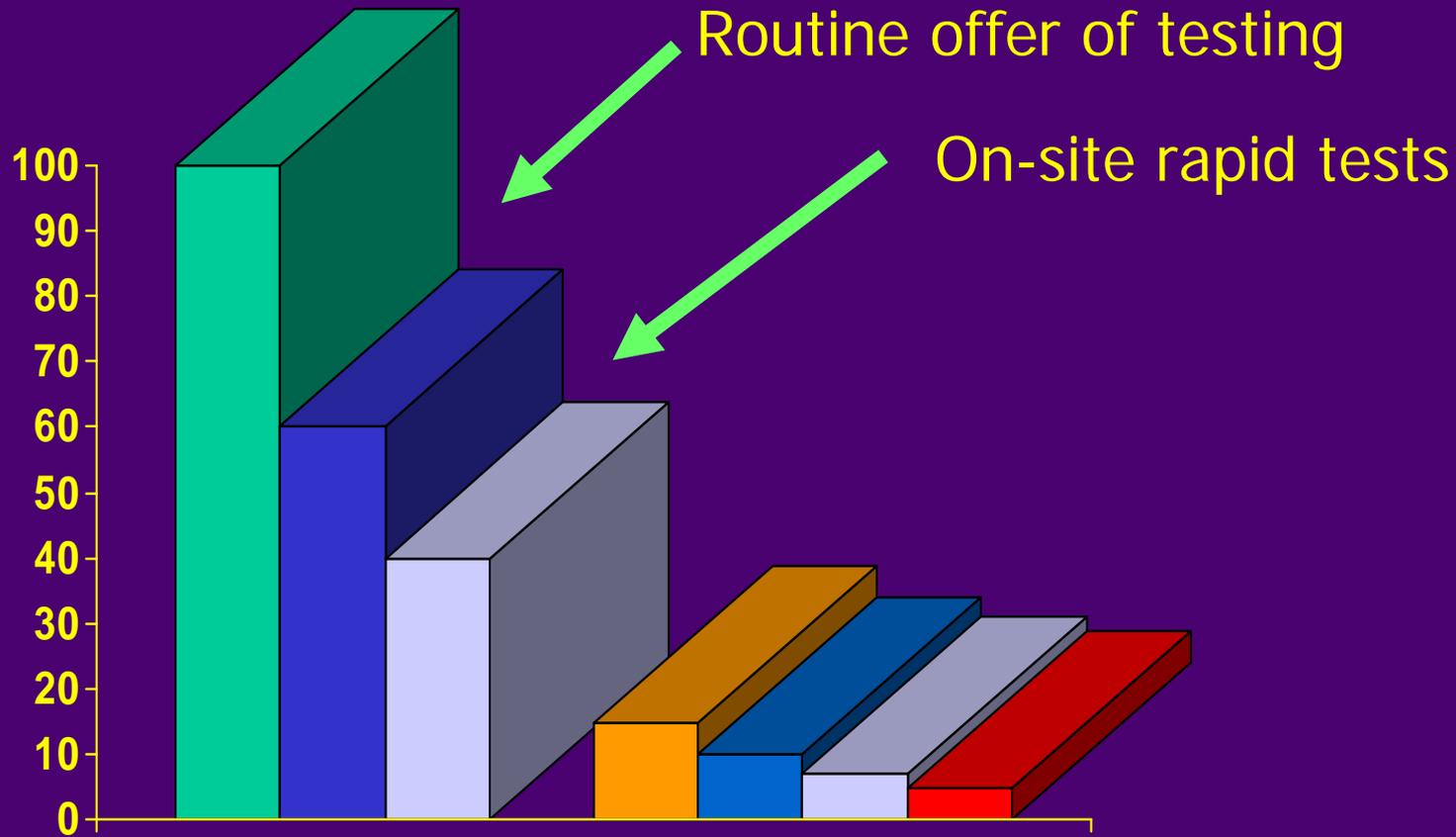
Who:

“It is a human rights issue that babies continue to be infected by their HIV positive mothers because the clinic sister has not bothered to tell the pregnant mother about how she could reduce the risk of her baby being infected”



Nozizwe Madlala-Routledge
Former Deputy Minister of Health, South Africa
27 October 2006

The uptake of PMTCT programmes

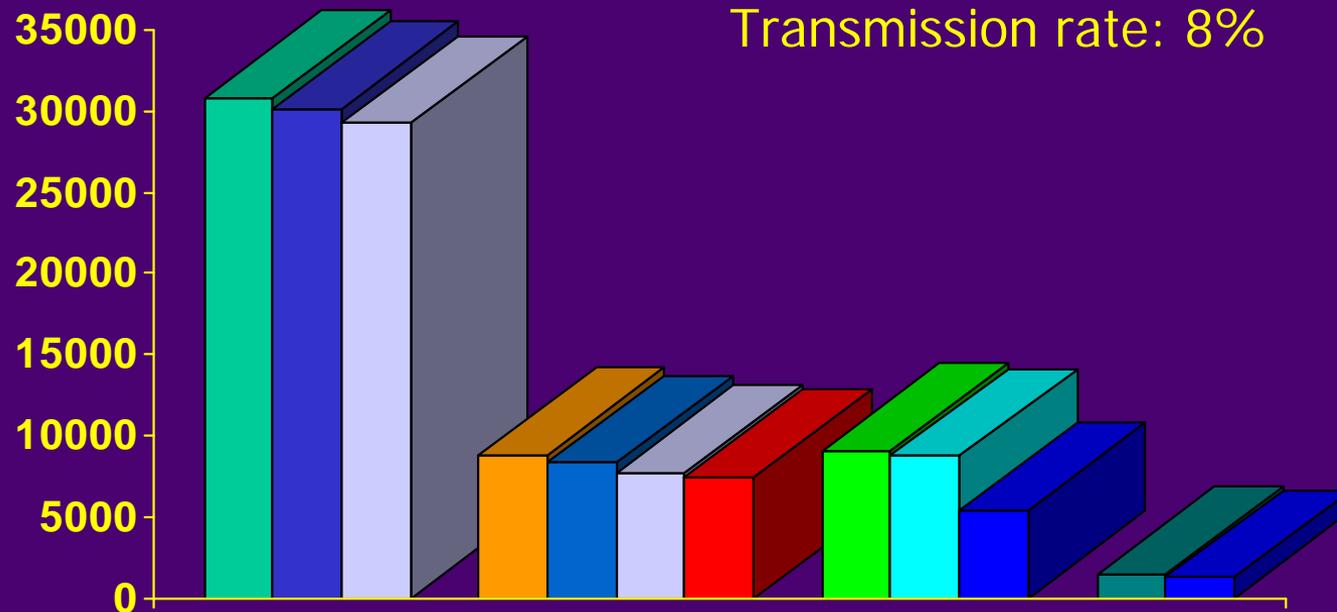


- ANC clinic visits
- Accepting VCT
- Receive results
- HIV-positive
- Post-test counselled
- NVP Mom
- NVP baby

Soweto PMTCT Programme 2006

30,739 pregnant women – 98% tested – 8,872 (29.4%) positive

14.9% of positives with CD4 < 200 – Most women formula feed



The Soweto PMTCT programme started in late 2000, in partnership with the Gauteng Department of Health, and is currently operating in all 13 public sector ANC sites

- ANC clinic visits
- Accepting VCT
- Post-test counselling
- HIV-positive
- Post-test counselled
- NVP Mom
- NVP baby
- Referred for CD4 test
- CD4 test done
- Received results
- CD4 < 200
- Received results

A failure to prevent?



“Keeping negative women negative.....”

Missed opportunities for HIV prevention?



HIV incidence in pregnancy

- HIV incidence in pregnancy reported between 2% and 5% in East and Southern African studies – new infections in women with a documented negative test in that pregnancy
- New infections in women may be a major source of MTCT, where effective interventions have reduced transmission in identified women
- Counseling in PMTCT services tends to focus more on the urgent issues of explaining MTCT risk and urgent initiation of PMTCT regimens or HAART for pregnant women, and much less on reinforcing risk reduction counseling for negatives

The impact of infections during pregnancy

Women who acquire HIV while pregnant or breastfeeding are at high risk of infecting their infants, and are not usually identified by PMTCT programs.

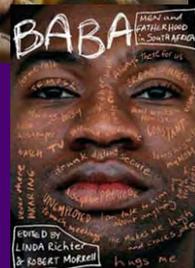
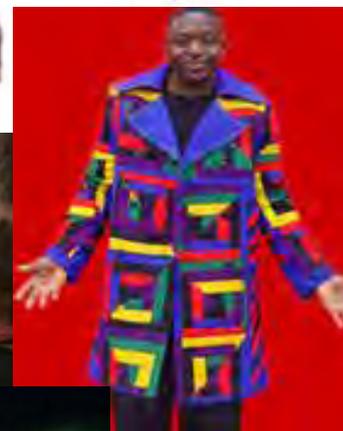
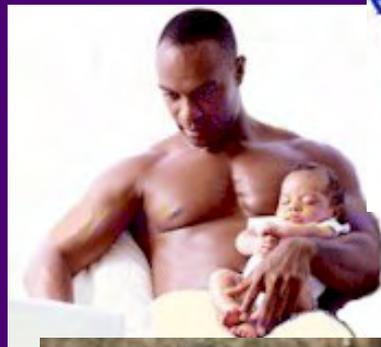
MTCT rates of 70% among women with incident HIV during pregnancy, and 36% during breastfeeding, have been reported

The impact of infections during pregnancy

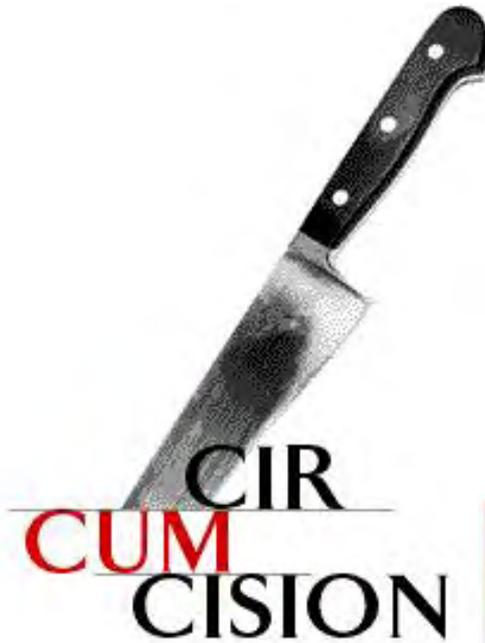
- A Botswana study showed that 1.3% of women who had tested negative in early pregnancy became infected in the 17 weeks prior to delivery, and 1.8% in the first postpartum year.
- Extrapolating these findings to the national Botswana figures, the researchers estimate that 950 women acquired HIV during pregnancy or the first postpartum year, and infected 470 infants.
- PMTCT program and infant testing data show an overall MTCT rate of 4.7% among women known to be HIV-infected during pregnancy, with 13,900 women infecting an estimated 620 infants.
- Incident HIV is thus estimated to account for 470/1090 (43%) of infant infections in 2007

What about men?

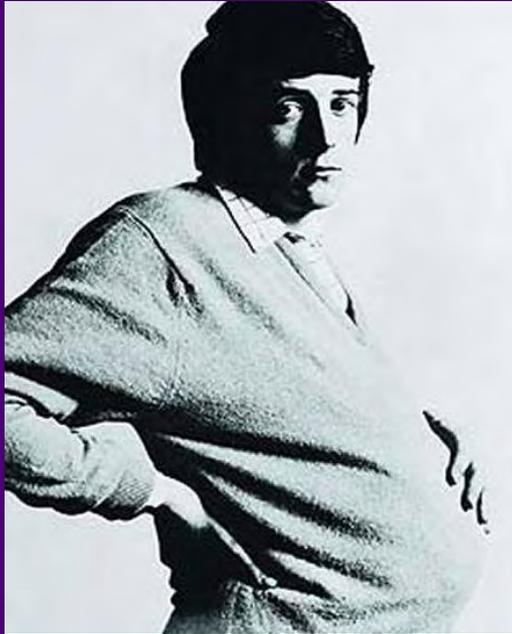
- Men have been “left behind” in PMTCT programmes
- PMTCT programmes often miss the opportunity to provide testing and counseling for male partners, or to prioritize their access to care
- Should “preventing new infections in men be seen as part of “PMTCT”?”



Is circumcision going to really protect against HIV?



Rare sightings.....

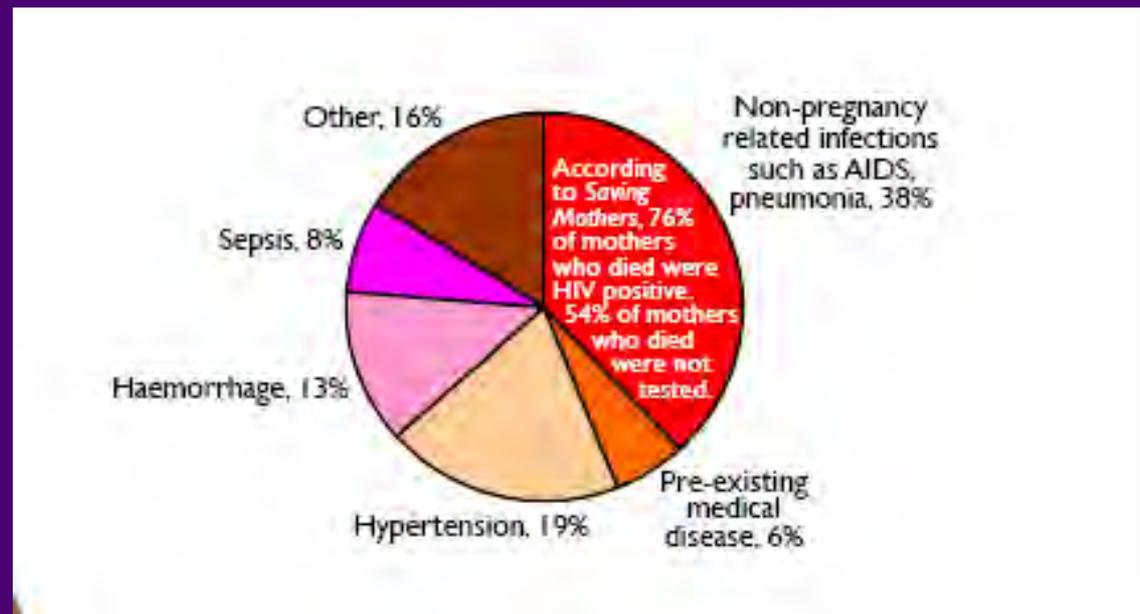


A failure to care?

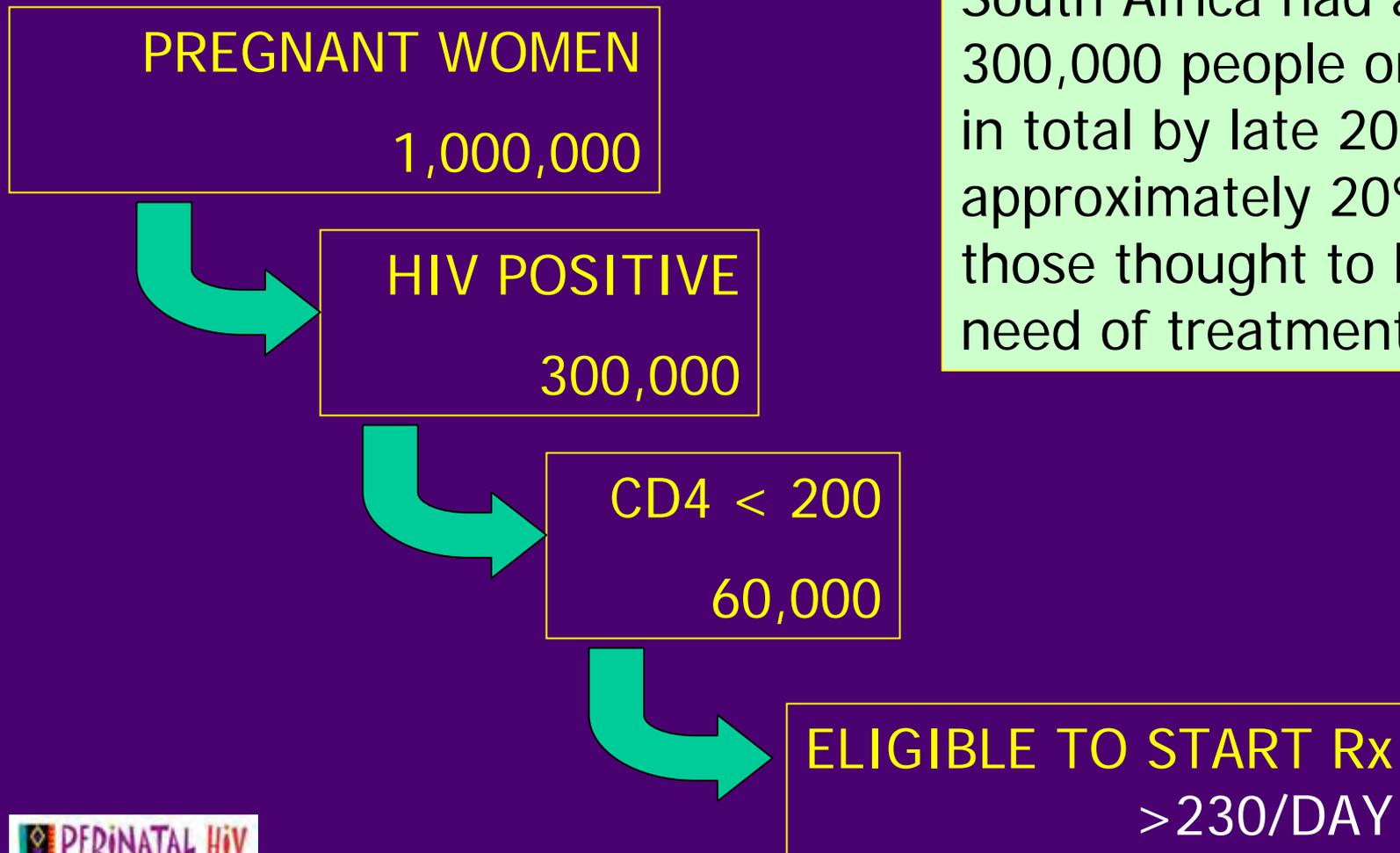


The Report on the Confidential Enquiry into Maternal Deaths (CEMD) in South Africa – 2002 - 2004

- Non-pregnancy related infections were the most common cause of death, responsible for 37.8% of deaths.
- AIDS was the single biggest cause of death at 20.1% of all deaths, higher than any direct obstetric cause.



SOUTH AFRICA: HIV POSITIVE PREGNANT WOMEN: IMPLICATIONS FOR TREATMENT NEEDS



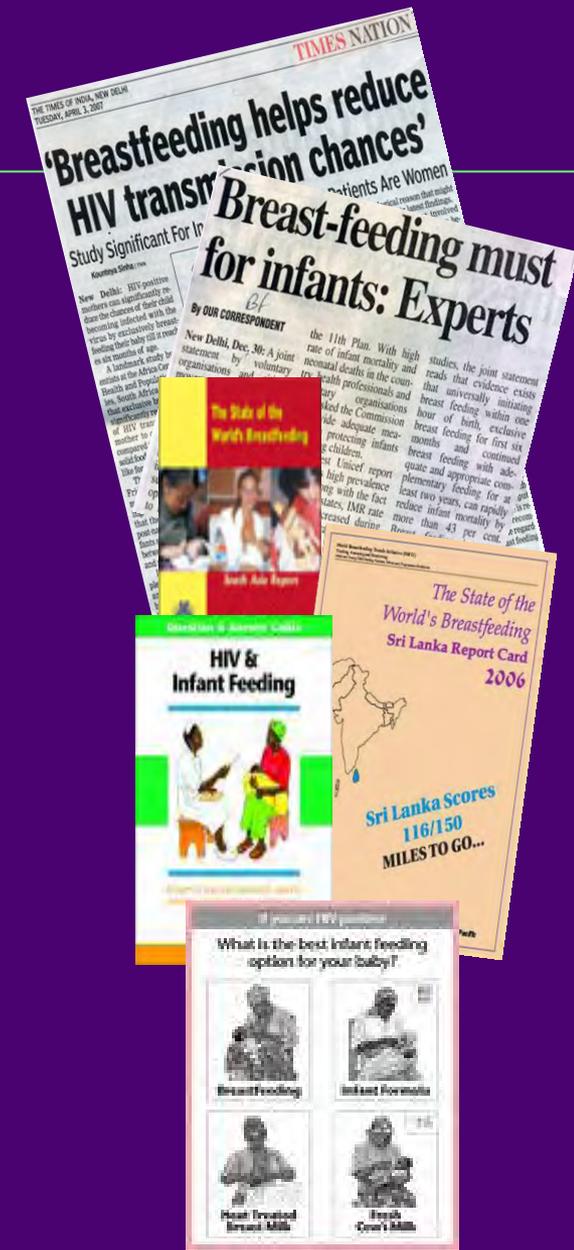
South Africa had about 300,000 people on ART in total by late 2007, approximately 20% of those thought to be in need of treatment

Eradicating paediatric AIDS: HIV-free infant survival is the new frontier



Infant feeding and HIV

- Infant feeding is one of the most difficult and most emotive issues in HIV management in low-resource settings
- Even with complete coverage of an effective peripartum ART intervention, an estimated 300,000 children will acquire infection through breastfeeding each year
- HIV transmission during this period remains a challenge in places where infant formula cannot be safely provided



A new postpartum transmission ABC.....?

Abstain

Avoid breastmilk

Be Faithful

Breastmilk only

Condomise

Cover with ARV

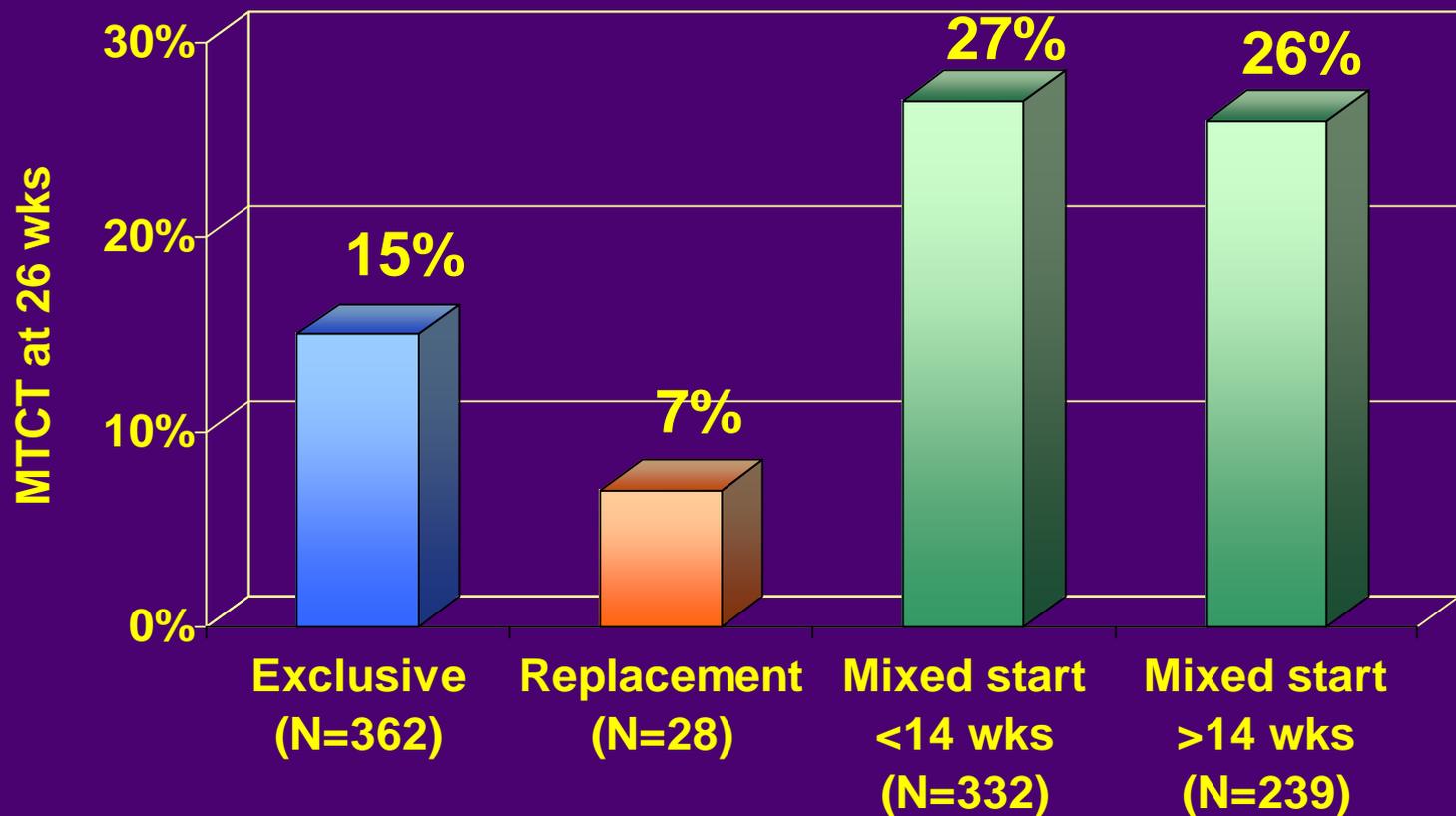
New evidence on HIV and Infant Feeding

- Exclusive breastfeeding associated with decreased risk of HIV transmission compared to non-exclusive breastfeeding
- Early cessation of breastfeeding associated with diarrhoea and mortality in HIV-exposed children
- Breastfeeding of HIV-infected infants beyond 6 months associated with improved survival compared to stopping breastfeeding



HIV Infection Rate at Age 26 Weeks by Mode of Infant Feeding at 26 Weeks

Coovadia H et al. Lancet 2007;369:1107-16



HIV and Infant Feeding Technical Consultation

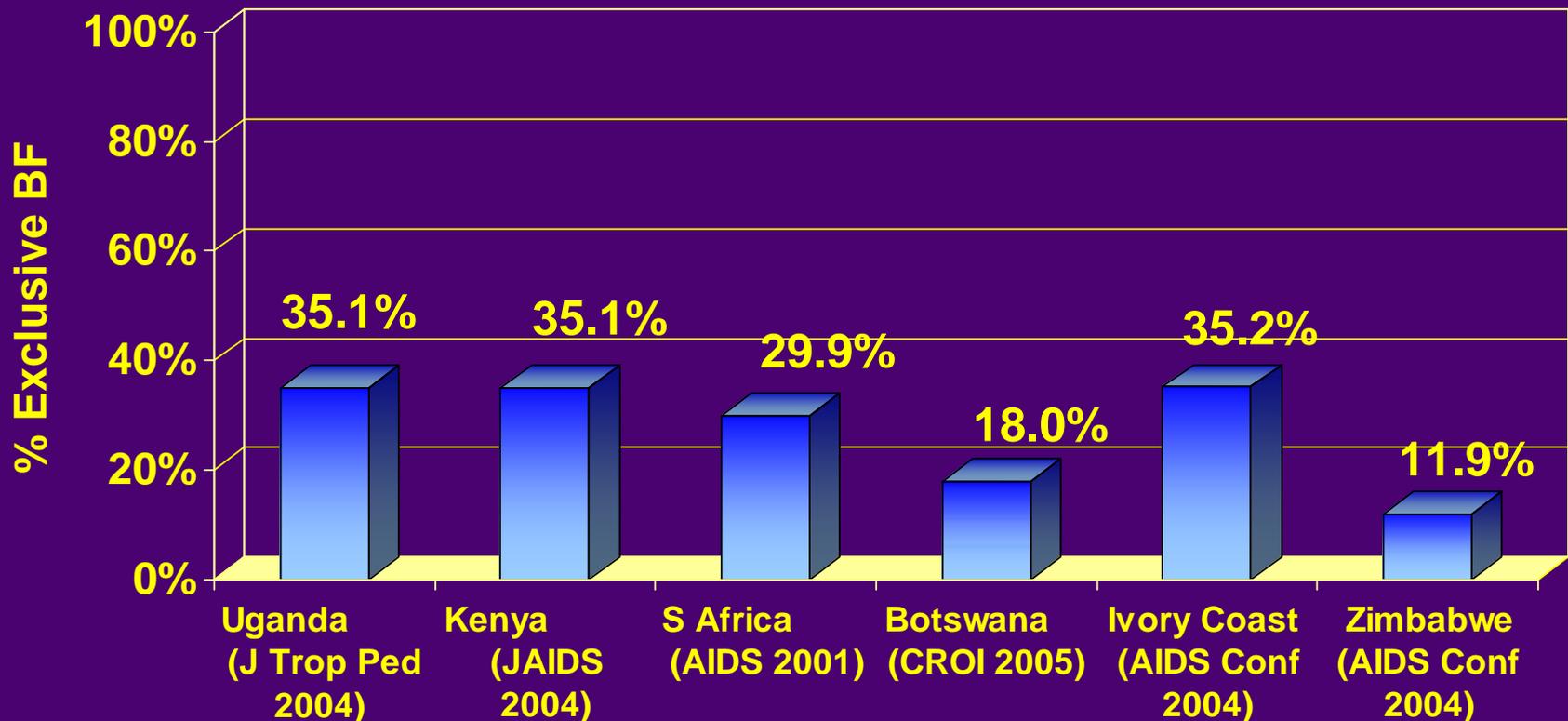
Geneva, October 25-27, 2006

CONSENSUS STATEMENT



- The most appropriate infant feeding option for an HIV-infected mother should continue to depend on her individual circumstances, including her health status and the local situation, but should take greater consideration of the health services available and the counselling and support she is likely to receive.
- Exclusive breastfeeding is recommended for HIV-infected women for the first 6 months of life unless replacement feeding is acceptable, feasible, affordable, sustainable and safe for them and their infants before that time.
- When replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected women is recommended.

Rates of Exclusive Breastfeeding in HIV-Infected Women are Low in Resource-Poor Countries Even in Setting of a Clinical Trial



Requirements for safe replacement feeding

- **A** cceptable
- **F** easible
- **A** ffordable
- **S**ustainable *and*
- **S**afe

for the mother and baby

Assessment should also include:

- Health service accessibility
- Counselling and support available



Henderson, WHO, 2006

The range of formula feeding and early weaning outcome data

- Different results in different sites:
 - Data from Malawi, Uganda, Botswana , Zambia: Excess morbidity and mortality with formula feeding and early weaning
 - Data from Ivory Coast, Rwanda, Western Cape & Soweto, South Africa: Do not see excess morbidity or mortality with formula feeding or early weaning
- What makes formula feeding and early weaning safe in some settings and not others?

Operationalizing “choice” of infant feeding

In the South African “Good Start” study of 635 women across three sites:

Three criteria were found to be associated with improved infant HIV-free survival amongst women choosing to formula feed:

- piped water
- electricity, gas or paraffin for fuel
- disclosing HIV status.

Doherty et al, AIDS 2007

Antiretroviral drugs for preventing HIV postnatal transmission through breastfeeding

- The use of ARV drugs in the mother and/or infant solely to prevent MTCT through breastfeeding may prove to be a valuable option
- Encouraging data from a number of observational and randomised trials looking at role of infant prophylaxis, and observational studies of maternal ART treatment through breastfeeding.

Infant Antiretroviral Prophylaxis of Breast Milk HIV Transmission

- **SWEN study: SD NVP vs 6 weeks infant NVP**
 - 46% decrease in postnatal MTCT at 6 weeks, but diminished effect at 6 months (20%↓).
- **PEPI Malawi: SD NVP/1 week AZT vs adding 14 weeks NVP or 14 weeks NVP+AZT**
 - 67% decrease in postnatal MTCT at 6 weeks, 60% decrease at 6 months, 51% at 9 months (no difference NVP vs NVP+AZT).
- **HPTN 046 (ongoing): 6 weeks vs 6 months of infant NVP, with weaning at 6 months.**



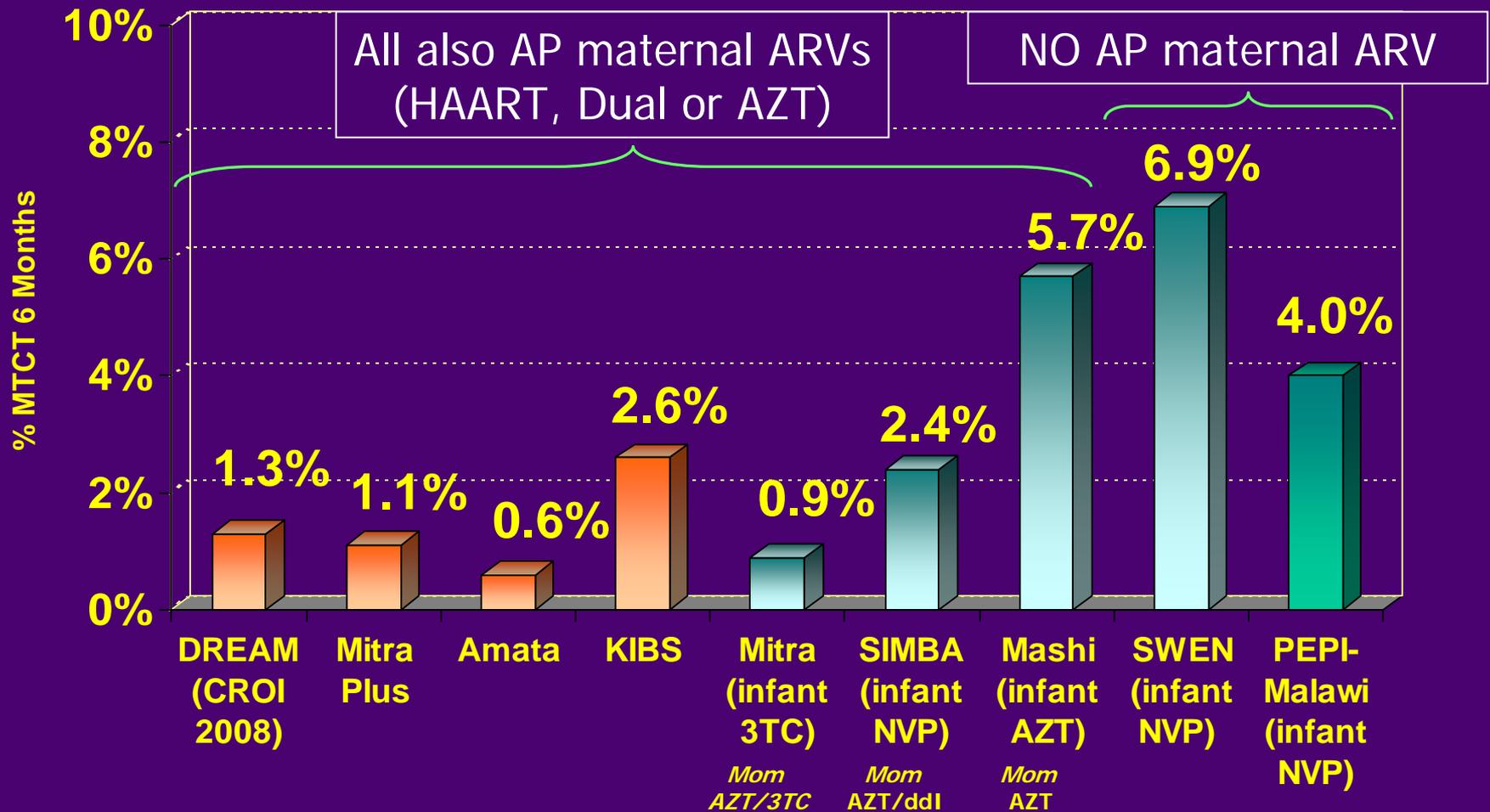
Maternal HAART Prophylaxis of Breast Milk HIV Transmission

Observational studies suggest maternal HAART may reduce postnatal transmission.

- **KISUMU (KIBS) Phase II Trial:**
HAART starting 34 weeks to 6 months postpartum
 - Overall MTCT at 6 months 5.0%
 - Postnatal MTCT at 6 months 2.6%
- **MITRA PLUS:**
HAART starting 36 weeks to 6 months postpartum
 - Overall MTCT at 6 months 5.0%
 - Postnatal MTCT at 6 months 0.9%



ARV Prophylaxis: 6 Month Transmission Rates in Breastfeeding Populations

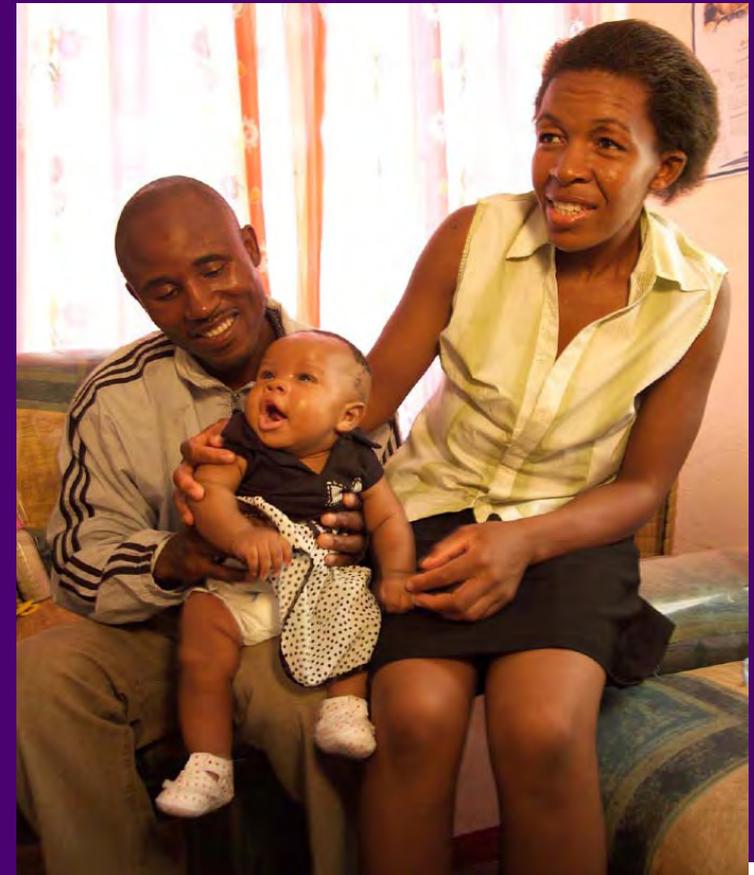


Maternal PP HAART

Infant PP ARV

Eradicating paediatric AIDS :

Early diagnosis and treatment saves children's lives



Early diagnosis and care are essential to improve child survival

- Early PCR diagnosis is an important part of care for HIV-exposed children
- Waiting for clinical signs may be too late
- In a Malawian cohort, at diagnosis:
 - 73% of children were undernourished,
 - 33% were acutely ill
 - 20% hospitalised within two weeks of diagnosis.



Early diagnosis and treatment saves children's lives: Children with HIV Early Antiretroviral Therapy (CHER) Study

ART initiated before 12 weeks reduces early mortality in young HIV-infected infants by 75% in first year

HIV-infected children <12 weeks with CD4 >25% randomised to start ART immediately (n=125) or following standard CD4 and clinical criteria during follow up (n = 250)

Survival in first year:

Immediate treatment :	96%
Deferred treatment:	84%

CIPRA-SA



Violari et al, IAS 2007

Towards eradication of paediatric AIDS:

- A concerted global effort is needed to accelerate the scale-up of comprehensive PMTCT interventions
- Comprehensive PMTCT services are lacking in most low- and middle-income countries.
- The available guidance and know-how on PMTCT should now be translated into action



WHO Access Report 2007

"Shall I repeat garlic, shall I talk about beetroot, shall I talk about lemon... these delay the development of HIV to Aids-defining conditions, and that's the truth."

**Health Minister Manto Tshabalala Msimang,
7 June 2006**



"I would thoroughly endorse the role-out of anti-retrovirals and any way we can accelerate that, the better"

**Health Minister Barbara Hogan,
26 September 2008**

Towards eradication of MTCT in low resource settings

6 A's

- Access
- Acceptance of testing
- ART for those in need
- Appropriate PMTCT regimen
- Attitude of staff and community
- Advocacy

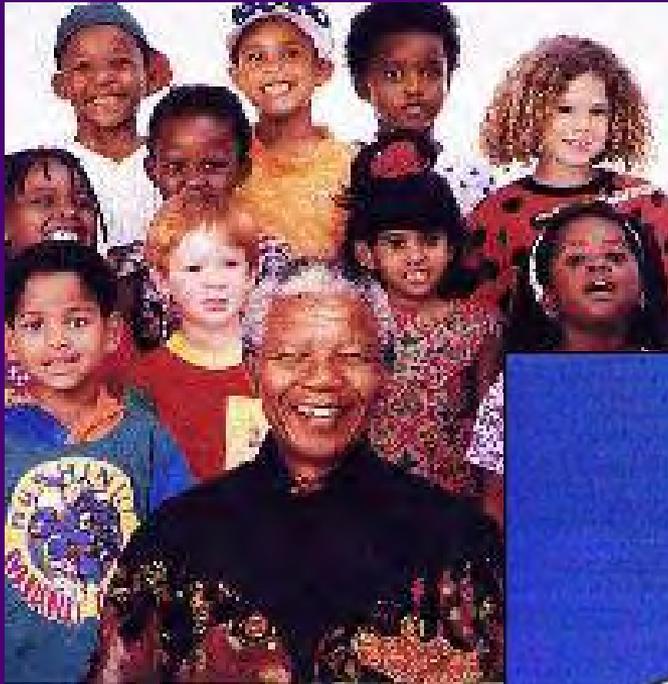
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- Peggy Henderson
- Rene Ekpini
- Francois Dabis
- Glenda Gray
- Siripon Kanshana
- Tracey Creek



for use of their data and slides.



“Give a child love, laughter and peace, not AIDS”

Nelson Mandela

December 1 2000