



Maternal Health and HIV

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Panel 1: Millennium Development Goals

- 1 Reduce extreme poverty and hunger by half relative to 1990
- 2 Achieve universal primary education
- 3 Promote gender equality and empowerment of women
- 4 Reduce child mortality by two-thirds relative to 1990
- 5 Improve maternal health, including reducing maternal mortality by three-quarters relative to 1990
- 6 Prevent the spread of HIV/AIDS, malaria, and other diseases
- 7 Ensure environmental sustainability
- 8 Develop a global partnership for development

Panel 2: UN Millennium Project task forces

- 1 Poverty and economic development
- 2 Hunger
- 3 Education and gender equality
- 4 Child and maternal health
- 5 HIV/AIDS, malaria, tuberculosis, and access to essential medicines
- 6 Environmental sustainability
- 7 Water and sanitation
- 8 Improving the lives of slum dwellers
- 9 Trade
- 10 Science, technology, and innovation

<http://www.childsurvivalcountdown.com/>



Saving Mother's Report

- Triennium 2005-2007 there has been a 20.1% increase in the number of deaths compared to 2002-2004
- Major cause of death: AIDS (43.7%), HT (15%), Haemorrhage (12.4%) Pregnancy related sepsis (9%), Pre-existing disease (6%)

4th Report on Confidential Enquiries into Maternal Death in South Africa; 2009



Table 7. Comparison of institutional Maternal Mortality Ratios per disease category

Primary Obstetric Cause	2002-2004	2005-2007	p
Direct	77.99	69.95	
Hypertension	27.72	23.92	<0.01; OR 0.86
Postpartum haemorrhage	13.82	14.73	NS
Antepartum haemorrhage	5.69	4.15	NS
Ectopic pregnancy	2.07	2.12	NS
Abortion	5.03	5.23	NS
Pregnancy Related Sepsis	12.09	8.58	<0.0001; OR 0.80
Anaesthetic related	4.02	4.11	NS
Embolism	2.82	2.19	NS
Acute collapse	4.72	4.92	NS
Indirect	63.12	75.61	
Non pregnancy related Infections	55.00	66.49	<0.000: OR 1.21
AIDS	29.22	35.19	
Pre-existing Maternal Disease	8.12	9.11	NS
Unknown	4.37	6.69	
Total	145.48	152.25	NS

4th Report on Confidential Enquiries into Maternal Death in South Africa; 2009



Table 10. Distribution of causes of non pregnancy related infections in relation to their HIV status

Sub categories	HIV +	HIV -	Unk	Total
- Pneumonia	224	21	148	393
- AIDS	891	1	23	915
- TB	138	20	71	229
- Endocarditis	0	0	1	1
- UTI	1	0	2	3
- Appendicitis	0	0	0	0
- Malaria	3	2	11	16
- Meningitis	56	6	44	106
- Other	34	5	27	66
Total	1347	55	327	1729

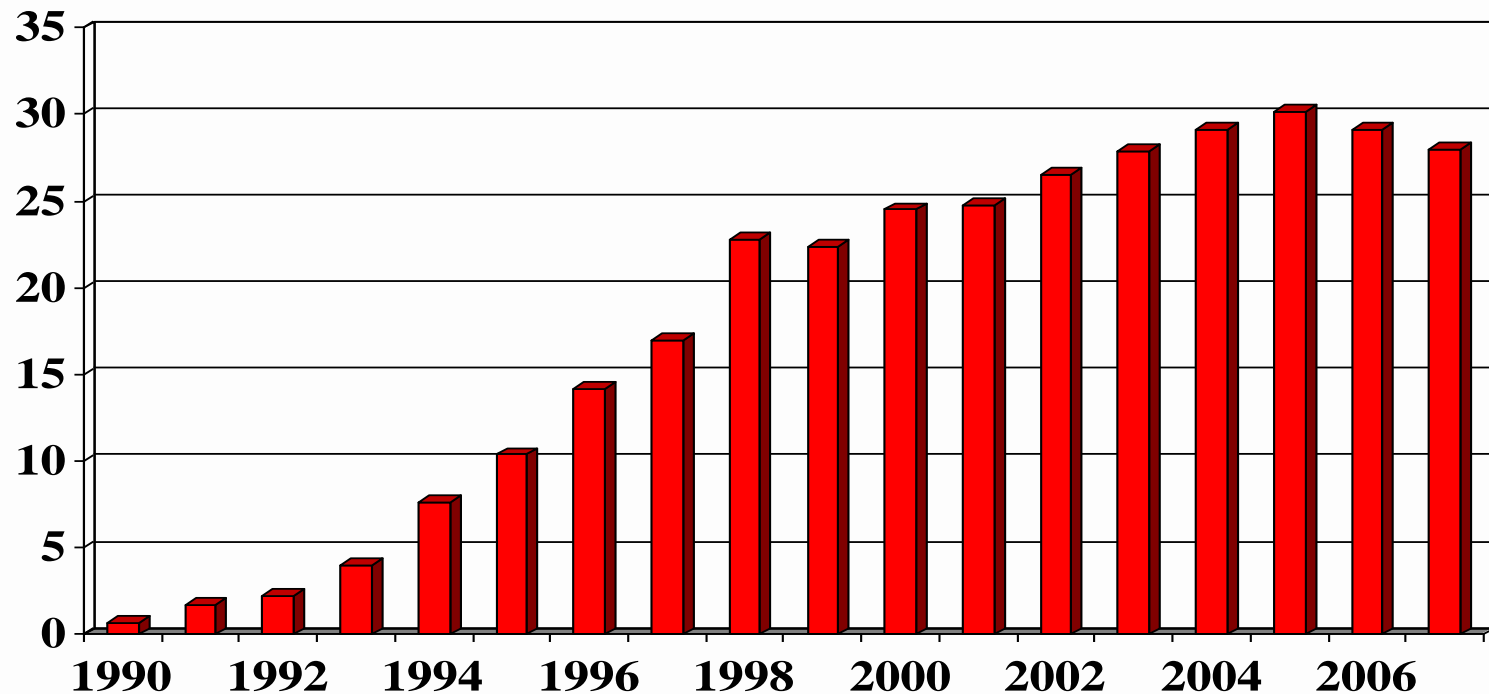
4th Report on Confidential Enquiries into Maternal Death in South Africa; 2009



Scale of the problem



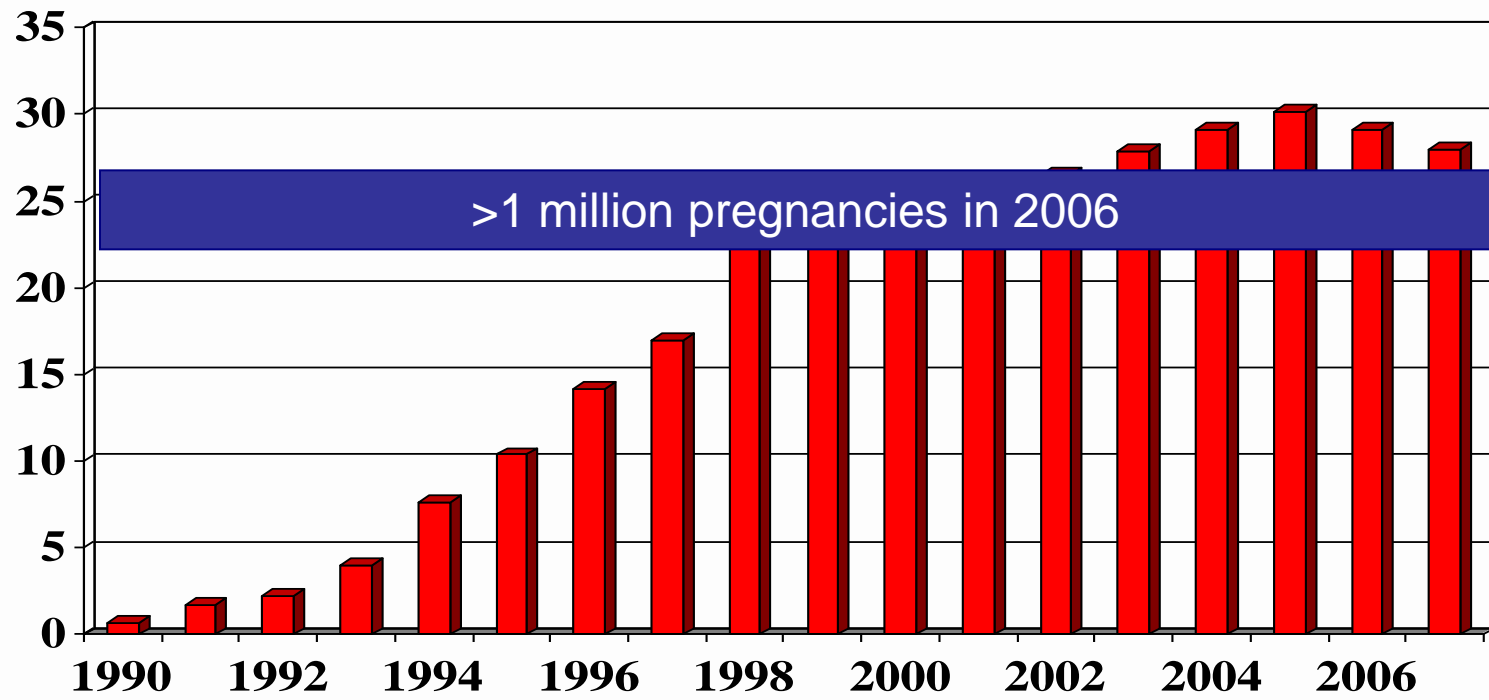
Antenatal HIV prevalence surveys South Africa 1990-2007



www.doh.gov.za/docs/reports/hivreport.html



Antenatal HIV prevalence surveys South Africa 1990-2007



Actuarial Society of SA, UNAIDS,
National DoH



Question of Scale

Number of HIV infected pregnant women / year

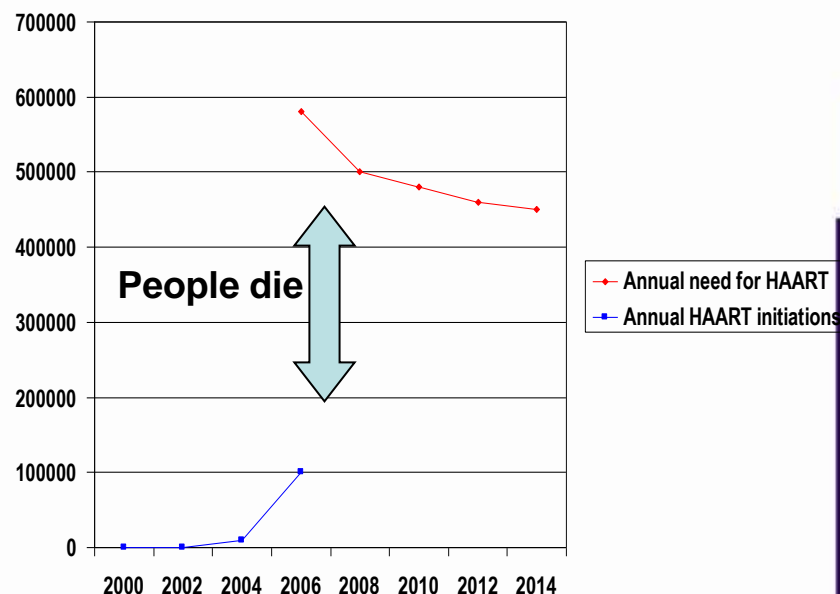


Adapted from McIntyre



HIV Epidemic

- 5.5/47 million HIV infected
- Majority in reproductive age group.
- >50% women.
- Most unaware they are HIV positive!
- Only test when sick
- Treatment gap




Opportunity of Antenatal Services



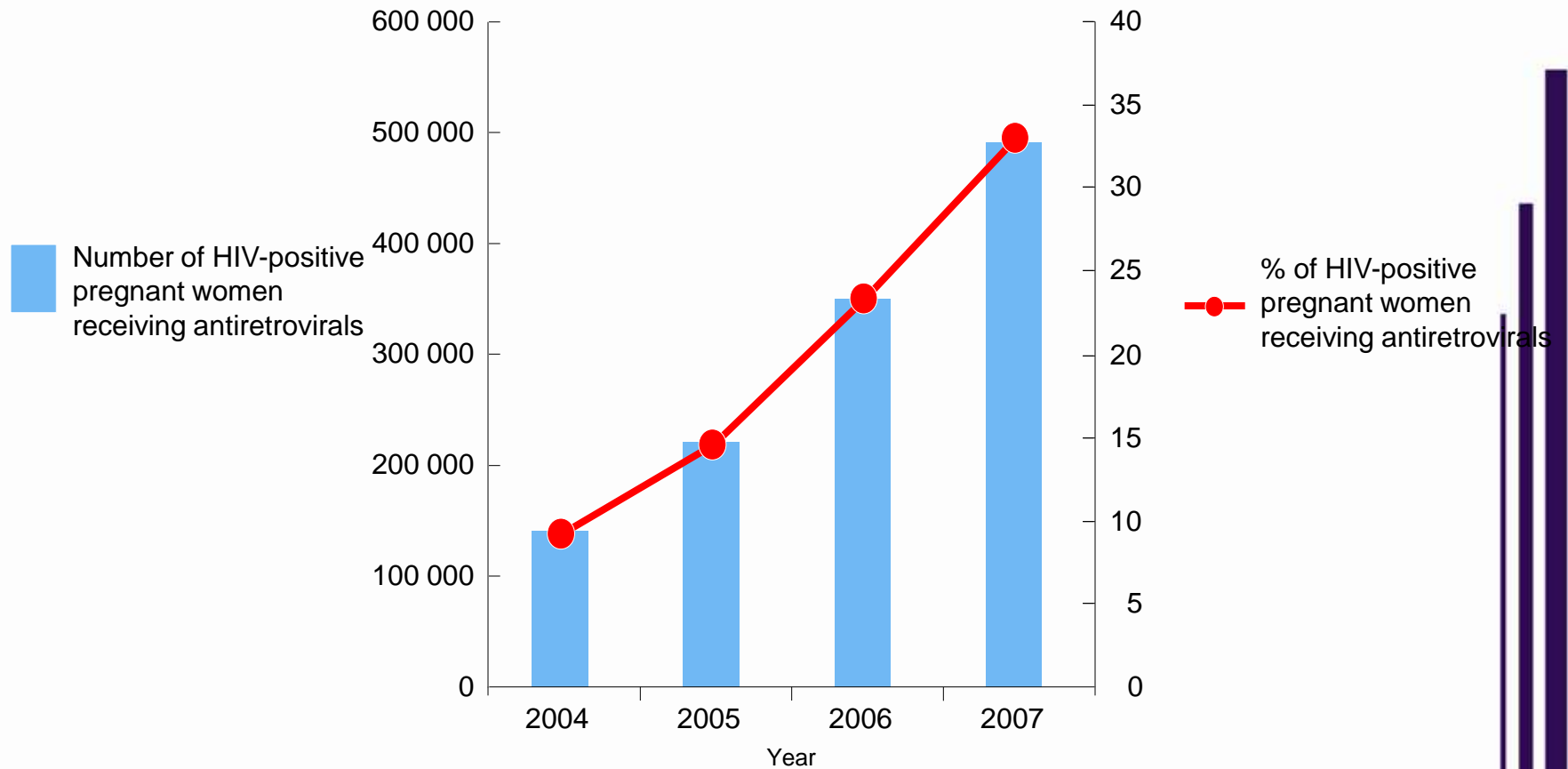
Using ANC to fight against HIV

- 94% of pregnant women attend ANC care
- Find healthy HIV infected women
 - stage HIV infected pregnant women;

initiate them on HAART  Within the Antenatal Clinic
Improve Referral systems

- Find partners, other children infected with HIV

HIV-infected pregnant women receiving antiretroviral prophylaxis, 2004–2007



Managing Pregnant Women on HAART

- What CD4 cell count should we initiate pregnant women onto HAART?
- What regimen should we use?
- What strategy for initiation is best?
- What are the effects of HAART on pregnancy?
- What are the effects on transmission?
- What impacts transmission when HAART is used?
- Does this have an impact on infant / maternal mortality?
- If HAART is used for PMTCT is there a risk to mother?



What CD4 cell count should we initiate women on HAART?



Numerous guidelines advocate HAART for all pregnant women regardless of the CD4 cell count.

However: Over 80% of maternal deaths, and over 80% of perinatal transmissions in pregnant women with CD4 counts $< 350 \text{ cell/mm}^3$

Over 50% of maternal deaths in women with CD4 counts $< 200 \text{ cells/mm}^3$



What regimen should we use?



Don't use single dose Nevirapine

Octane Study

- 7 African countries
- 241 HIV+ women, history of sdNVP at least 6 months earlier randomized to receive either:
 - **NVP+TDF+FTC** (n = 121) or
 - **LPV/r+TDF+FTC** (n = 120)
- Primary endpoint **virologic failure or death:**

(Lockman S et al. 16th CROI, Montreal, 2009. Abs 94LB)



OCTANE cont...

- Virologic failure :

Time since sdNVP	NVP arm	LPV/r arm
6 to < 12 months	37%	3%
12 to < 24 months	26%	12%
> 24 months	12%	10%

Difference between the 2 arms decreased with time since last sdNVP

(Lockman S et al. 16th CROI, Montreal, 2009)



Risk of Congenital Abnormality

- Evidence from trials, cohorts and surveillance studies of ART use in pregnancy – estimated 2-3% prevalence of birth defects
- Similar to that seen in the general population
- No pattern of birth defects suggestive of a common aetiology seen

(Drug Saf. 2007;30(3):203-13; AIDS. 2008;22(13):1633-40; Curr HIV/AIDS Rep 2009;6(2):68-76)



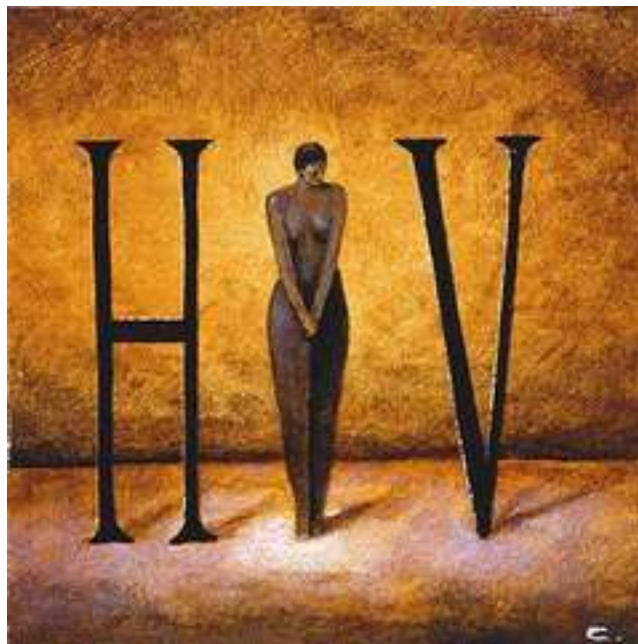
Antiretroviral Registry Update

- 10 405 pregnancies evaluated
- No increase in the prevalence of birth defects following **first trimester** ARV exposure compared to general population
- Sufficient numbers of first trimester exposure to confirm no increased birth defects from the following drugs:
 - Lamivudine, Zidovudine, Abacavir, Stavudine, Tenofovir Emtricitabine
 - Nevirapine, Efavirenz
 - Lopinavir/ritonavir, Ritonavir,
 - Nelfinavir Indinavir Atazanavir

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What strategy for initiation is best?



Access to HAART among pregnant women

3 service models
evaluated

- ANC + ARV services >1 km apart
- ANC + ARV same premise – different building
- Same facility, dedicated day



Stinson, K *et al.* 2008

Access to HAART among pregnant women

Among 516 HAART-eligible pregnant women,

- 51% successfully initiated treatment before delivery.
- 27% received of PMTCT prophylaxis
- **22% of women who were HAART-eligible had no record of receiving any antenatal intervention.**
- No difference between referral models

Stinson, K *et al.* 2008



Integrating HAART into Antenatal Clinics

Established a HAART clinic
in an antenatal clinic
(ANC ARV) in late 2004.

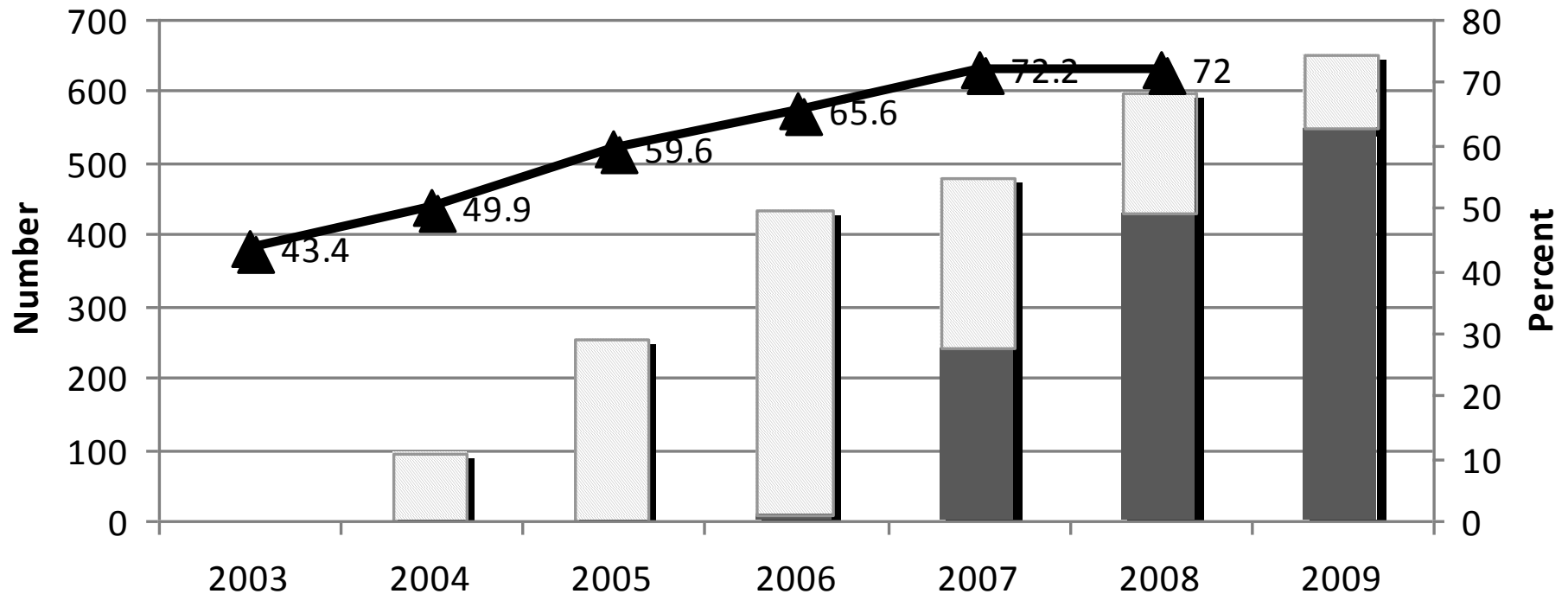
Expanded programme to
Secondary and Primary
Health Care Facilities

Rapid initiation of pregnant
women with
AIDS/advanced HIV onto
ART including close
monitoring & support.



Number of Women Accessing HAART in Antenatal Clinics in the Inner City and Proportion of Known HIV Status at Delivery

Estimated need: 807 women /yr



Number initiated onto ART at Charlotte Maxeke Johannesburg Hospital

Number initiated onto ART at Primary Health Clinics

Percent women of known HIV status

Outcome of integrated services

- Within the ANC ARV programme, initiating pregnant women on HAART was feasible, safe, and effective.
- Advanced gestational stage at treatment initiation, and loss to follow-up emerge as important challenges in this population.
- Strategies are needed to facilitate earlier treatment of HIV-infected pregnant women with advanced disease.



What are the effects of HAART on pregnancy?



Reassuring data

- 400 HIV infected women receiving antiretroviral therapy, adverse events are uncommon (<5%)
Am J Obstet Gynecol 2004
Feb;190(2):506-16

ANC ARV, treated over 1200 pregnant women with ARVs. Feasible, safe & effective

CROI 2008



Pregnancy outcomes on ART

European multicentered study HAART

Prematurity increased (OR 2.6) with PIs (OR 1.8) with non PIs

AIDS 2000;14:2913

American multicentered study with HAART

Increased LBW with PIs (OR 3.6)

No increase in prematurity

N Eng J Med 2002;346:1863

American WITS

Small increase maternal complications including:

- anaemia
- gestational diabetes
- preterm deliver

J Acquir Immune Defic Syndr 2005;38:449



Meta-analysis was performed

14 studies were included (1998-2006)

ART during pregnancy did not increase the risk of premature delivery overall.

Treatment initiated prior to conception or in the 1st trimester were associated with a slightly increased risk of prematurity.

But....

AIDS 2007 Mar 12;21(5):607-15



- Study done in Brazil; 1996 to 2006
- N = 696 HIV+ pregnant women

	Preconception HAART	Post conception HAART	P-value
LBW	33.3%	16.5%	p<0.001
PTD	26.3%	17.7%	p=0.09

(Machado ES, Sex Transm Infect. 2009;85(2):82-87)



Infant outcomes in women with advanced HIV disease exposed and unexposed to HAART Johannesburg

1397 on HAART vs. 233 no HAART

HAART exposure to any regimen was associated with **pre term birth (34-37 weeks)**

More marked for HAART-exposure before 28 weeks gestation.

Low Birth Weight was not associated with HAART-exposure

Van der Merwe K et al IAS 2009



What are the effects on transmission?

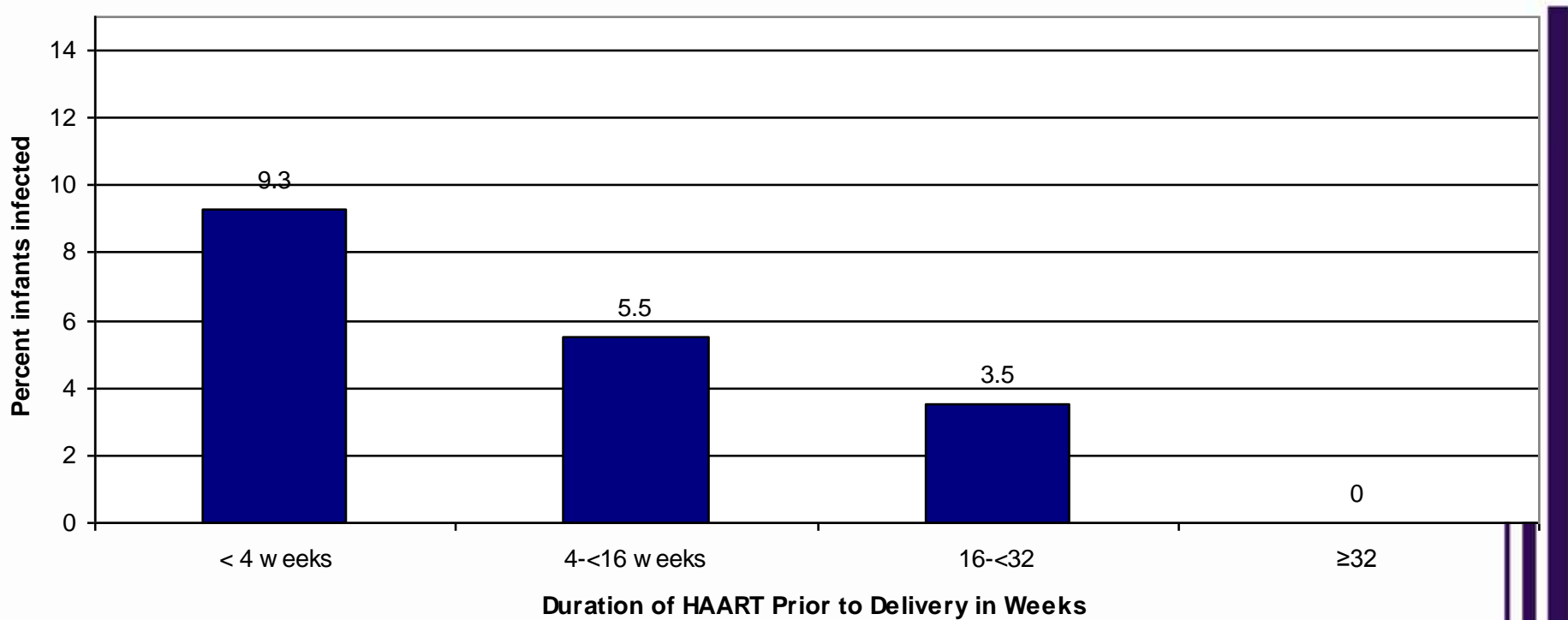


Transmission among women on / not on HAART

Category	Number	Transmission rate
Conceived on ART	1/140	0.7%
ART initiated in Pregnancy	42/734	5.7%
CD4 >250 with sdNVP	121/1534	7.4%
No ART	4/23	17.4%



Maternal HAART Duration is Predictive of Infant HIV Infection N= 734

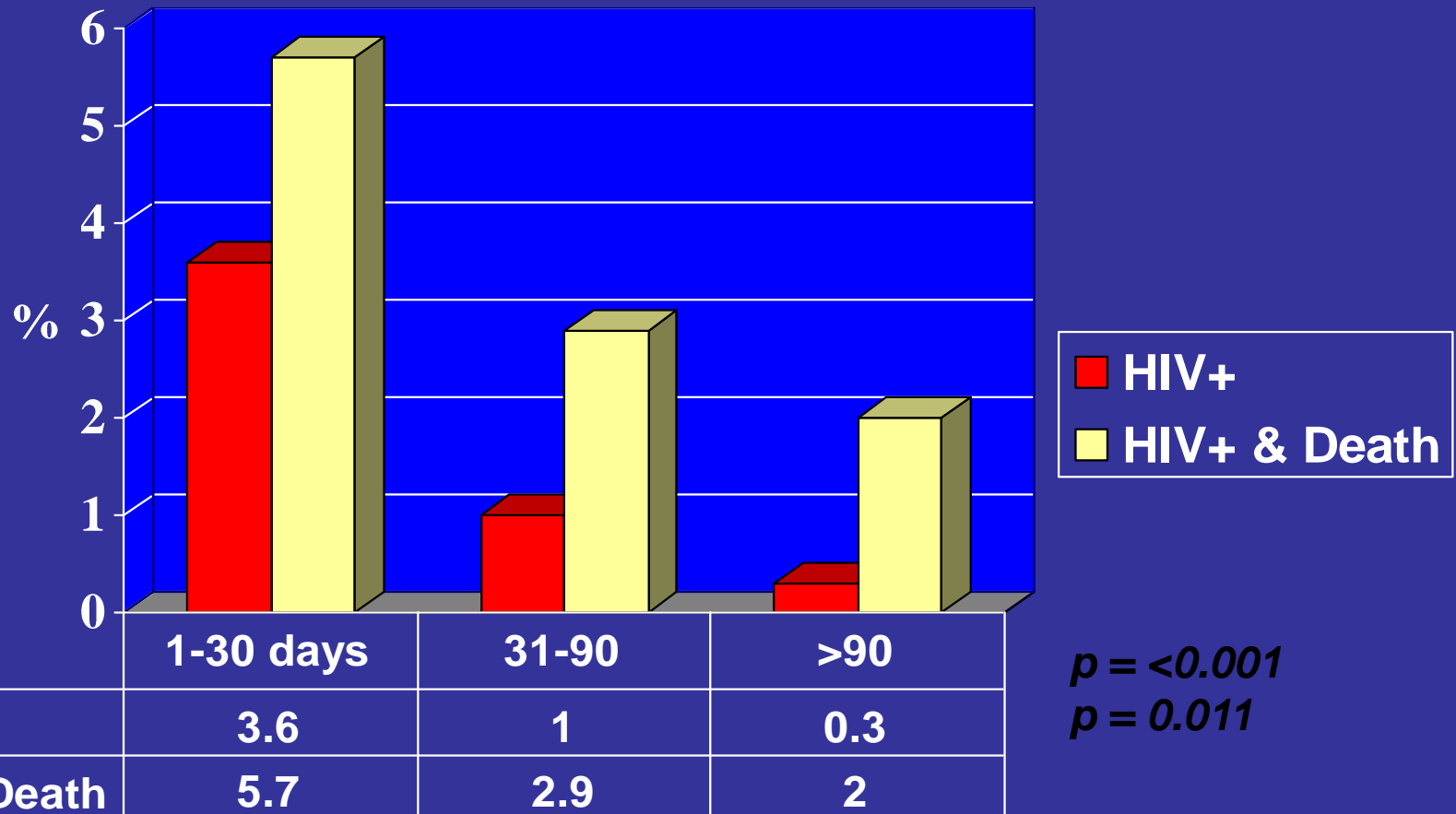


Hoffman, Black et al IAS 2009



HIV transmission and/ or deaths between 1 to 6 months according to pre-delivery length of HAART

n= 2,161 infants



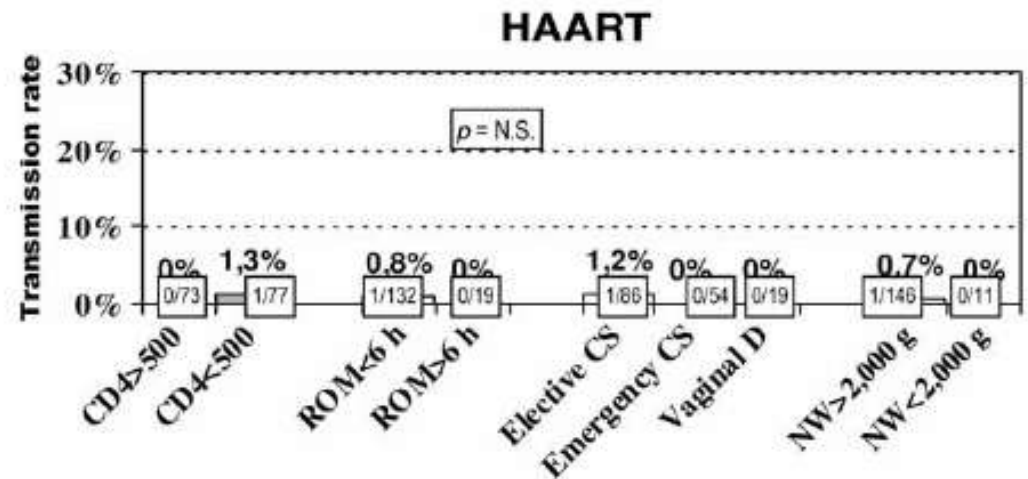
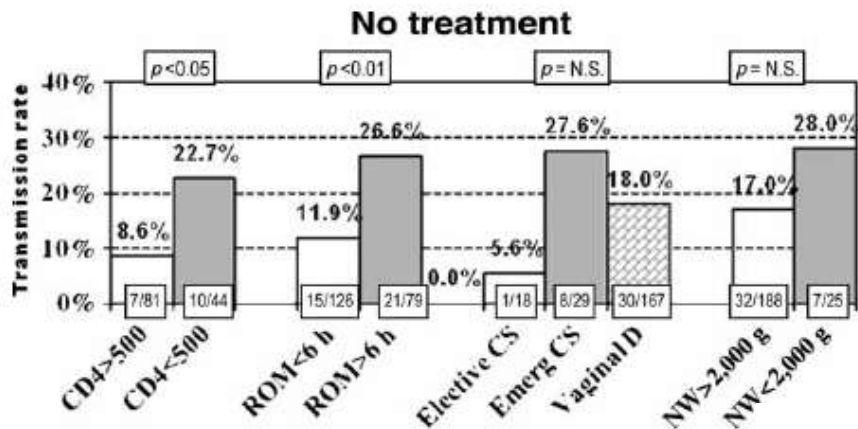
Rates of MTCT

Regimen	Conceived on ART	ART initiated in Pregnancy
Lop/Rit (401)	4% (1/25)	5.3% (20/376)
NVP (356)	0% (0/40)	6.3% (20/316)
EFV (117)	0% (0/75)	4.8% (2/42)
Total MTCT (874)	0.7% (1/140)	5.7% (42/734)
CI	0.02-3.8	4.2-7.7



Influence of HAART on risk factors for vertical HIV transmission

HAART impact in HIV vertical transmission 885



Male partner

Kenya study, 1999 – 2003

465 HIV+ pregnant women, and infants followed up until 12 months postpartum

After adjusting for maternal VL and breast milk exposure, male partner attendance also associated with:

- ~ 50% reduction in HIV transmission risk at 1yr postpartum
- ~ 60% greater infant HIV-free survival, and
- 2.5-fold higher survival in HIV-uninfected children

(Aluisio A et al. IAS, Cape Town 2009, Abs TUAC105)

Does HAART in pregnancy have an impact on maternal/infant mortality?



DREAM cohort

- Malawi and Mozambique; July 2005 to December 2008
- 3 273 HIV+ pregnant women initiated on HAART
- NVP-based HAART from 14 weeks if eligible for own health - CD4 < 350
- Or from 25 weeks until 6 months postpartum if CD4 > 350

- Assessed infant HIV transmission and death at 1 month, and maternal mortality based on duration of prenatal HAART

(Marazzi MC et al. 5th IAS, Cape Town July 2009)



DREAM cohort results

- Infant HIV infection and death at 1 month:

Baseline CD4	Pre delivery HAART	%
< 350	<= 30 days	4.0
	> 30 days	1.4
	Total	1.7
>= 350	<= 30days	1.1
	> 30 days	0.6
	Total	0.7



(Marazzi MC et al. 5th IAS, Cape Town July 2009)

DREAM cohort results

- Maternal mortality increased with shorter duration of HAART, especially with CD4 count < 200 cells/mm³
- Overall, 3.2% vs. 0.7% if CD4 < 200, p<0.001

No. of days of prenatal HAART	none	0-30	31-90	> 90	p-value
Maternal mortality	7.4	2.7	1.2	0.7	p<0.001

(Marazzi MC et al. 5th IAS, Cape Town July 2009)



Facility based Maternal Mortality CMJAH 2003-2007

There were 106 maternal deaths (excl 2 incidental)

No change in maternal mortality over time

Among 76 (72%) women tested, 78% were HIV infected.

The median CD4 cell count was 72cells/mm³
(IQR=29-194 cells/mm³)

BUT

Only 60% of HIV positive women (30/50)

Only two women with AIDS had initiated HAART.



If HAART is used for PMTCT is there a risk to the mother?



HAART for PMTCT

- HAART for PMTCT standard in resource-rich countries
- Practice is to stop Rx post-delivery – concern expressed about viral rebound syndrome
- Rx restarted when indicated for own health – concern about later response to Rx reinitiation



HAART for PMTCT

- Brazil, 2000 to 2005
- N = 75
- Median baseline CD4 count 573
- Prophylaxis started after 26.6 weeks of gestation in 75% of cases
- 24.5% CD4 increase over baseline with prophylaxis

(Palacios R et al. HIV Medicine. 2009;10(3):157-162)



HAART for PMTCT

- Postnatal withdrawal of Rx not associated with immediate significant viral rebound or drop in CD4 count
- Mean time for CD4 count to drop below 300 was 3.5 yrs
- **Reinitiation of HAART not associated with an increased risk of virologic failure**

(Palacios R et al. HIV Medicine. 2009;10(3):157-162)



Challenges in managing pregnant women with HAART



The PEARL study

- To assess PMTCT coverage
- April 2007 to October 2008
- 43 sites in Cameroon, Cote d'Ivoire, South Africa and Zambia
- All sites used sdNVP, with or without ZDV, or NVP-based HAART
- N (cord blood specimens) = 29 095
- **1° outcome – PMTCT coverage = detectable NVP in HIV+ specimens, and recorded infant NVP ingestion**

(Coetzee D et al. IAS, Cape Town, July 2009)

The PEARL study

- 448 seropositive deliveries in the Western Cape
- **26% had no drugs detected**

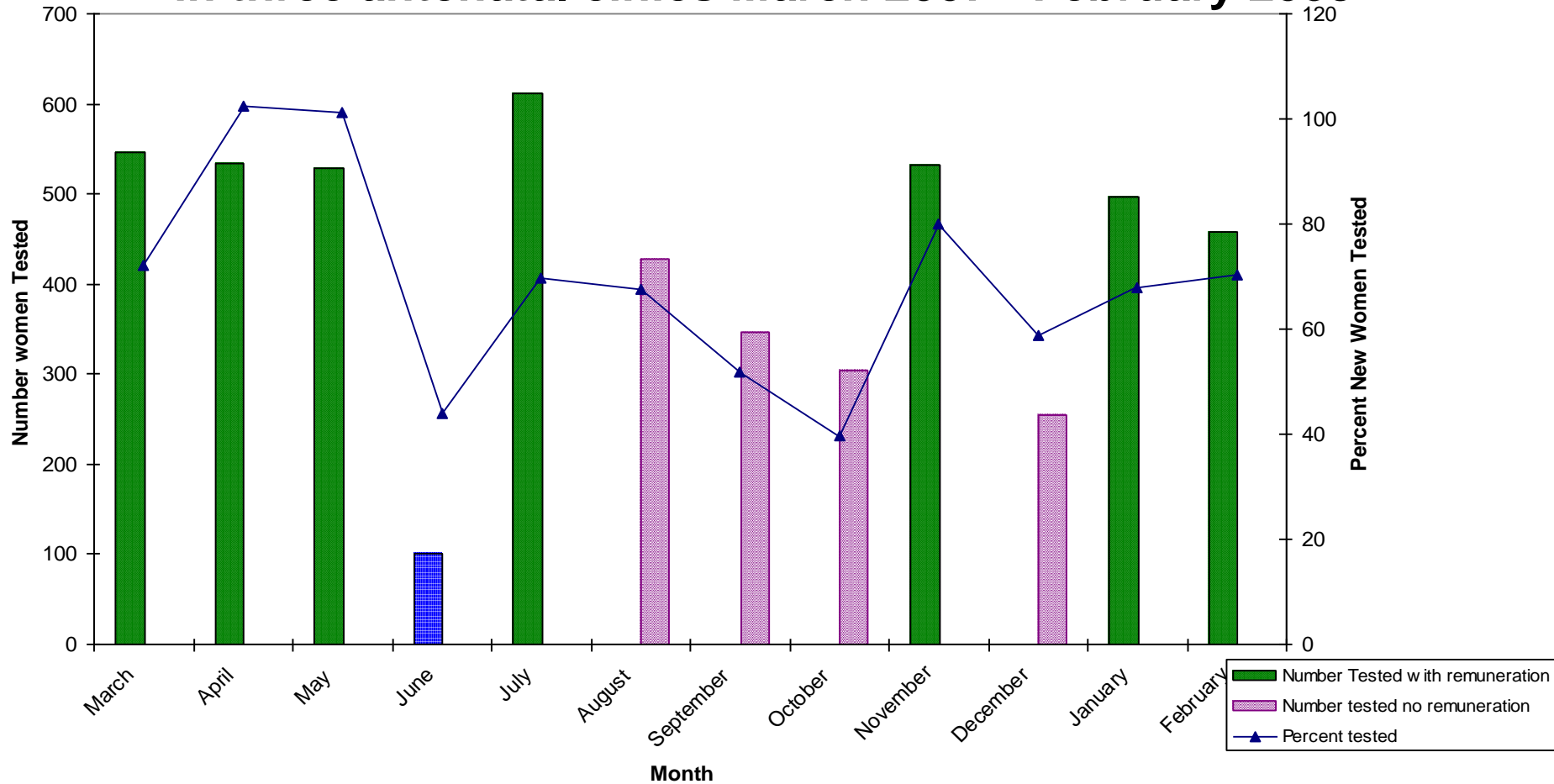
Reasons for no coverage

HIV test not offered	Testing declined	HIV+ results not given	NVP not dispensed	Mother non adherent	Infant not dosed
16%	6%	13%	7%	27%	15%

(Coetzee D et al. IAS, Cape Town, July 2009)



Number and proportion of new pregnant women who had an HIV tests in relation to counsellor remuneration in three antenatal clinics March 2007 - February 2008



Rapid HIV test performance

Category	First Response	<i>Standard diagnostic</i>	<i>Pareekshak</i>
Number	271	42	313
Positive	69	7	74
False negative	4	0	7
Sensitivity	94.5 (CI:85.8-98.2)	87.5 (CI:46.7-99.3)	90.2 (CI:81.2-95.4)
Specificity	100 (CI:97.6-100)	100 (CI:87.7-100)	100 (CI:98-100)

Something else to consider...



Fertility and HIV:

HIV infected women are getting pregnant

- Survey reported that 80% of HIV affected couples (US) who had previously conceived had engaged in unprotected intercourse to achieve pregnancy
- Three studies of unintended pregnancies in HIV infected women in sSA
 - 84% among PMTCT clients in South Africa
 - 51% among women in Cote d'Ivoire
 - 99% among women in an ART program in Uganda

Klein J Obstet Gynecol 2003

Rochat et al; JAMA2006

Desgrées-du-Louê et al., Int J STD AIDS 2002

Smart, T. Aidsmap. 2006.

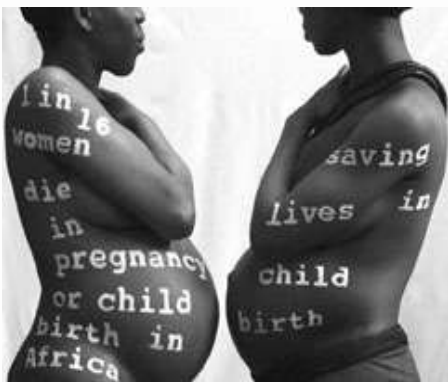
HIV infected “couples” want children

- Studies above show benefit of early HAART
- Low risk of transmission to infant
- High risk of transmission if they do not engage with health sector...



Women's vulnerability to infection: Pregnancy

Pregnant women



Pregnancy and HIV acquisition

- Rakai: 2188 HIV –ve pregnant women, compared to 8473 non-pregnant women.
Adjusted incidence rate ratio of HIV acquisition 2.16 (95%CI 1.39–3.37) during pregnancy
Gray R 2005
- Zimbabwe & Uganda, 4439 women 18-35 years old, 211 HIV infections: pregnancy and lactation not associated with HIV risk *Morrison C 2007*
- Johannesburg: 25% reported multiple partners during pregnancy *Macphail C personal communication 2007*
- Universally, condom use decreases in pregnancy

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