HIV-associated Maternal Mortality

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Euphoria around survival from HIV

- 1.9 million people in SA now on ART
- New HIV infection rate (15-49) declined from 2.0/100 person-years in 2005, to 1.3/100 py in 2008
  (O Shisana *PLoS ONE 2010*; 5)
- DART study: 5-year survival = 87-90%
  (AS Walker *Lancet 2009;* 6736)
- Khayelitsha ART programme: 80% alive at 5 years
  (A Boulle *AIDS 2010;* 24)
- Near normal life expectancy on ART in US
  (A Hill *AIDS 2010*; 24)
- South Africans have benefited from ART rollout since 2004

Improved survival from HIV

- Infant transmission rate in SA dropped considerably from 10% to 2.7%
  (A Goga DoH *2012)*
- 3-year mortality in SA children on ART = 7.7%
  (IeDEA, *SAMJ 2009*; 99)
- Infant mortality in SA decreased from 57/1000 in 2001 to 38/1000 in 2011
  (SA Stats 2011)

Curb your Enthusiasm for Pregnant Women

HUMAN RIGHTS WATCH

"SA will fail millennium maternity goal"

Human Rights Watch says SA's maternity death ratio quadrupled over the past decade instead of dropping, leaping from 150 to 625 deaths per 100 000 live births, and the country will miss the UN Millennium Development Goals

ROY DOWNING
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Human Rights Watch (HRW) believes SA will miss its target of reducing maternal deaths by 75% under the United Nations Millennium Development Goals.

HIV-related Maternal Deaths *(NCCEMD)*

	1999-2001	2002-2004	2005-2007	2008-2010
Maternal Deaths	2 445	3 296	3 959	4 867
Proportion tested for HIV	28%	46%	59%	79%
HIV-related Deaths	±684	842	1 347	1 720
Percentage of Maternal Deaths	28%	26%	34%	35%

Who were these women?

- Ages 20-39 years
- 61% died in the postpartum period
- 19% had advanced immune suppression – not started on ART
- 80% died from 3 conditions:

TB

Pneumonia (including PCP)

Meningitis (including cryptococcal meningitis)

- Findings consistent across all nine provinces
- Obstetric haemorrhage (14.1%) & hypertension (14.1%) distant $2^{nd}/3^{rd}$ causes

Maternal Mortality by HIV status

MMR per 100 000 LB	2005-2007	2008-2010
HIV negative	34	75
HIV positive	328	430

NCCEMD data
2005-2010

ART-related Deaths

	2008	2009	2010
Number maternal deaths due to complications ARVs	14	17	42
Approx. Number HIV infected pregnant women per year	279798	279650	277216
Maternal deaths due to complications of ARVs/ Number pregnant HIV infected women /100000 births	5.00	6.08	15.15
Number of maternal deaths who were on HAART	214	306	362
% of deaths due to complications of ARVs of all maternal deaths who were on HAART	6.5%	5.6%	11.6%

Possible Reasons

- ***SA PMTCT (2010) guidelines:***
  - promoted NVP use for pregnant women with WHO 3 & 4 regardless of CD4 cell count, hepatitis B, abnormal liver transaminases, or TB co-treatment
  - EFV use "banned" throughout pregnancy in SA (2010)

- Several recently published observational studies = no association between NVP toxicity & CD4 cell count
- WHO 2009 meta-analysis (836 pregnant women)
  RR hepatotoxicity (CD4 ≥250): 1.04 (95% CI 0.22 - 4.93)

Objectives

- To determine whether ART-naïve pregnant women initiating NVP-based ART at higher CD4 counts experience more toxicity vs lower CD4 counts

Methods

- ART-naïve women initiating NVP-based ART during index pregnancy
- NVP-based ART for at least 7 days
- Excluded: ART-experienced pregnant women, abnormal LFT's at baseline
- Toxicity comparison: CD4 <250 versus CD4 ≥250

Methods

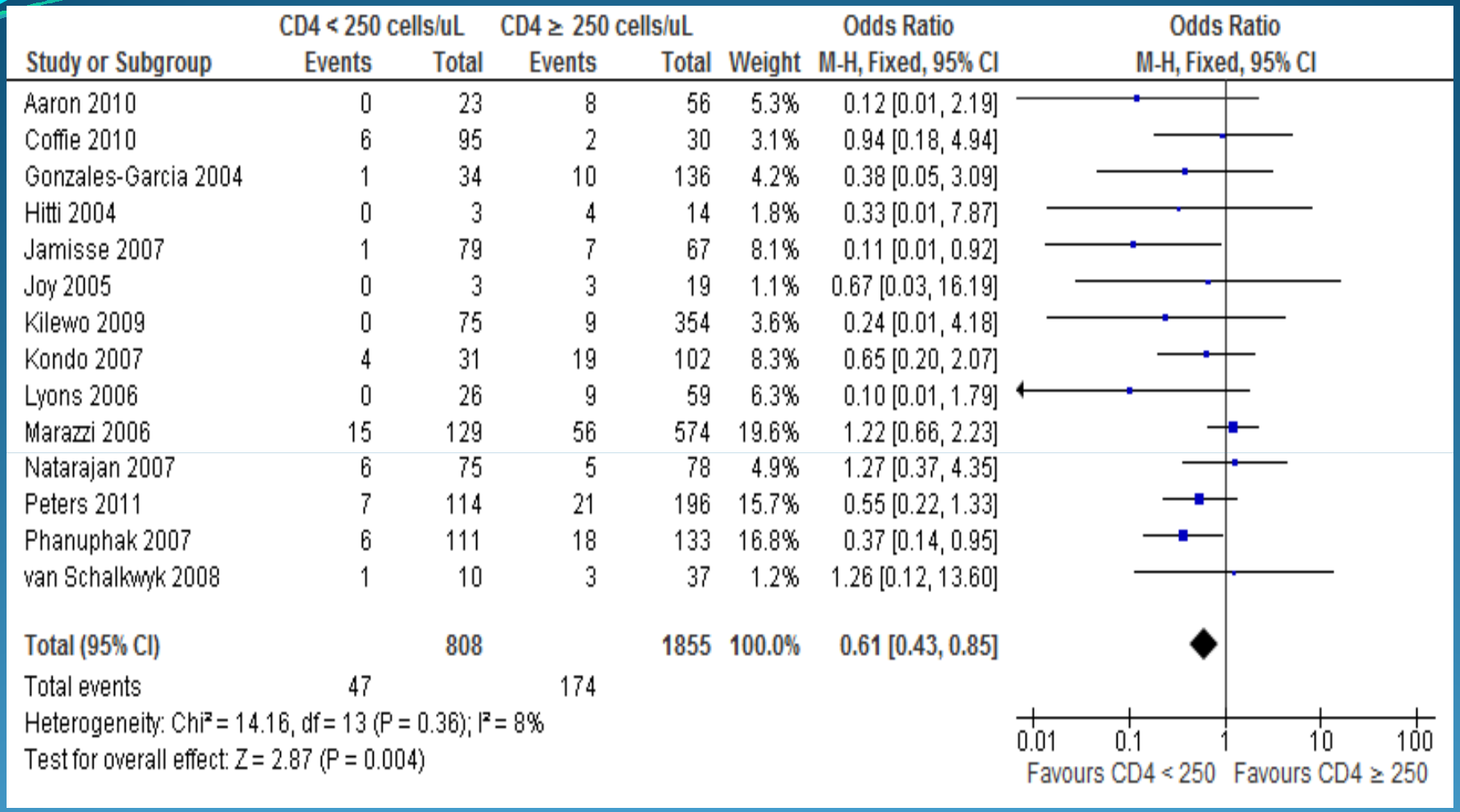
- Overall NVP toxicity = grade 3 or 4 hepatotoxicity PLUS grade 3 or 4 cutaneous reaction *(NIH DAIDS 2004 guidelines)*
- PubMed; SCOPUS; EMBASE; major journals & AIDS conference proceedings to Dec 2011; study authors contacted for additional data
- Independent data extraction (EB & RM)
- Data entry & analysis: RevMan 2011, dichotomous Mantel-Haenzsel, OR, 95% CI, I^2

Included Studies

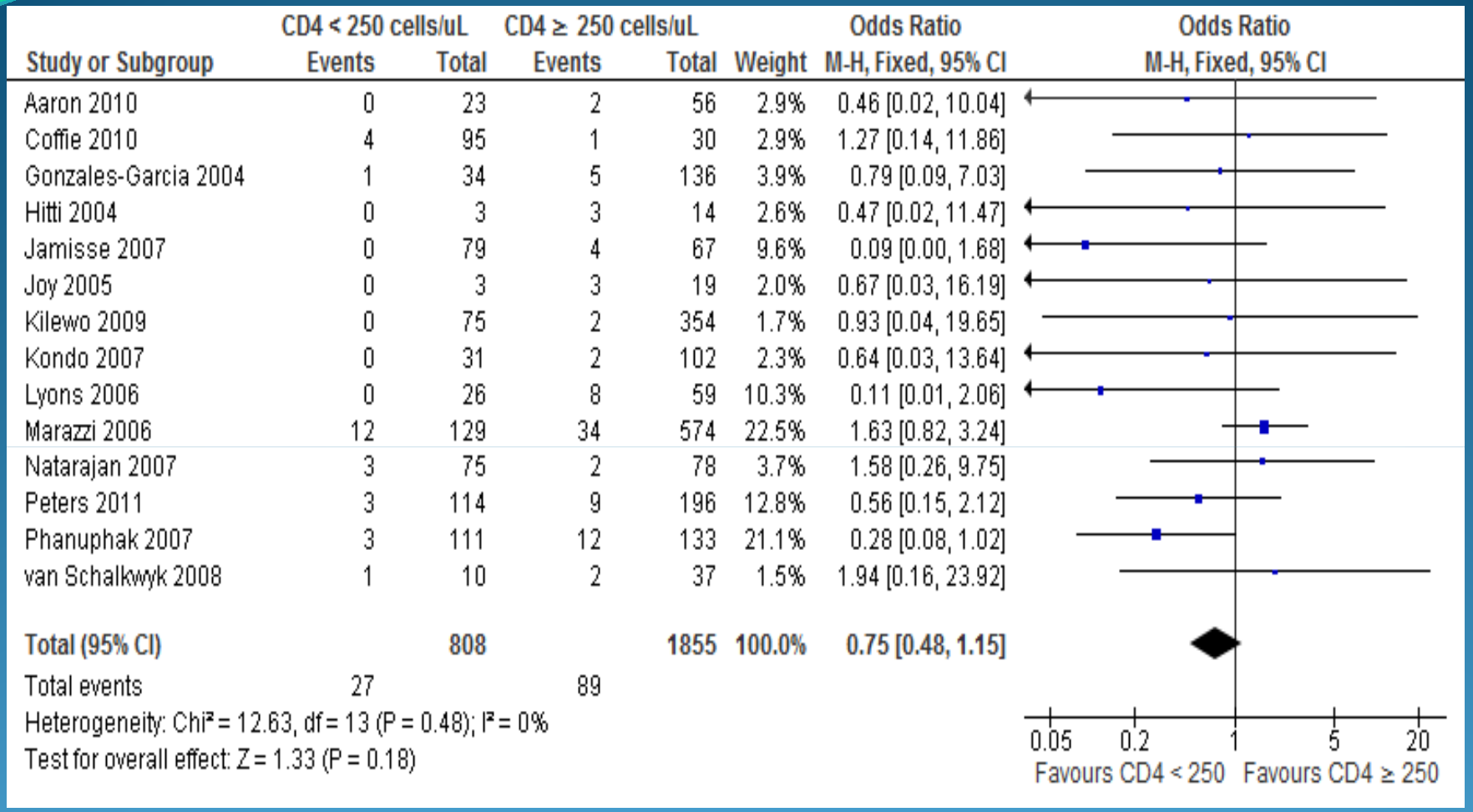
- Included: 14 studies, 2 663 participants
- USA, Africa, UK, Ireland, Thailand, Brazil, Canada
- Predominantly observational studies, one RCT
- Number of participants varied from 17 to 703
- Most studies undertaken between 2001 & 2006
- One of the studies funded by Boehringer Ingelheim

Included Studies

- Age = 28 years
- Mean CD4 count = 113–545 cells/uL
- ART initiation at 27 weeks' gestation
- NVP 200mg daily x 2 weeks in all women
- CD4 cut-off → 250 cells/uL for all studies except one study (200 cells/uL)
- Mean time to toxicity: 27–74 days
- Overall NVP toxicity rate = 8.3%
- 14 maternal deaths, 4 directly attributed to NVP



Forest plot for overall NVP toxicity
All studies

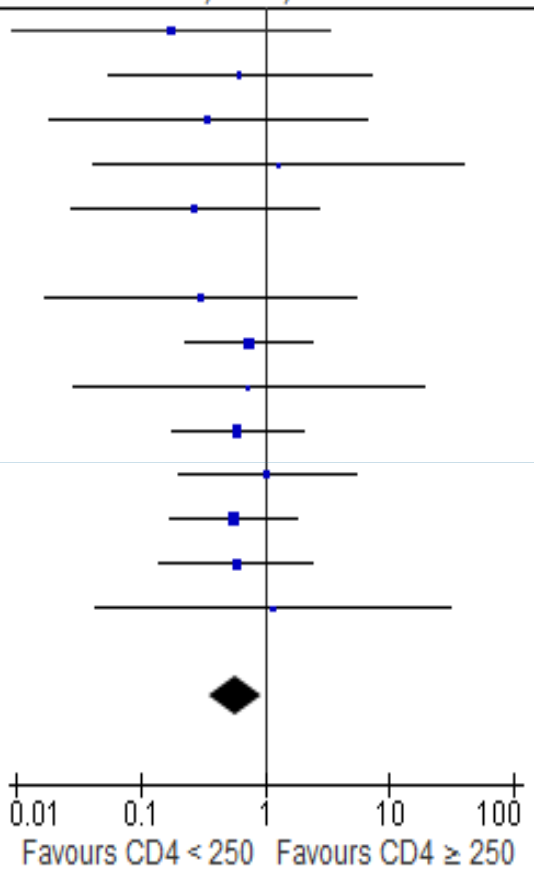


Forest plot for severe hepatotoxicity
All studies

Study or Subgroup	CD4 < 250 cells/uL Events	Total	CD4 ≥ 250 cells/uL Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aaron 2010	0	20	6	53	7.6%	0.18 [0.01, 3.31]
Coffie 2010	2	95	1	30	3.2%	0.62 [0.05, 7.13]
Gonzales-Garcia 2004	0	34	5	136	4.7%	0.35 [0.02, 6.42]
Hitti 2004	0	3	1	14	1.2%	1.29 [0.04, 38.90]
Jamisse 2007	1	79	3	67	6.9%	0.27 [0.03, 2.69]
Joy 2005	0	3	0	19		Not estimable
Kilewo 2009	0	75	7	354	5.6%	0.31 [0.02, 5.43]
Kondo 2007	4	31	17	102	14.8%	0.74 [0.23, 2.39]
Lyons 2006	0	26	1	59	2.0%	0.74 [0.03, 18.66]
Marazzi 2006	3	129	22	574	16.9%	0.60 [0.18, 2.03]
Natarajan 2007	3	75	3	78	6.1%	1.04 [0.20, 5.33]
Peters 2011	4	114	12	196	18.3%	0.56 [0.18, 1.77]
Phanuphak 2007	3	111	6	133	11.4%	0.59 [0.14, 2.41]
van Schalkwyk 2008	0	10	1	37	1.4%	1.16 [0.04, 30.59]
Total (95% CI)		**805**		**1852**	**100.0%**	**0.57 [0.35, 0.94]**
Total events	20		85			

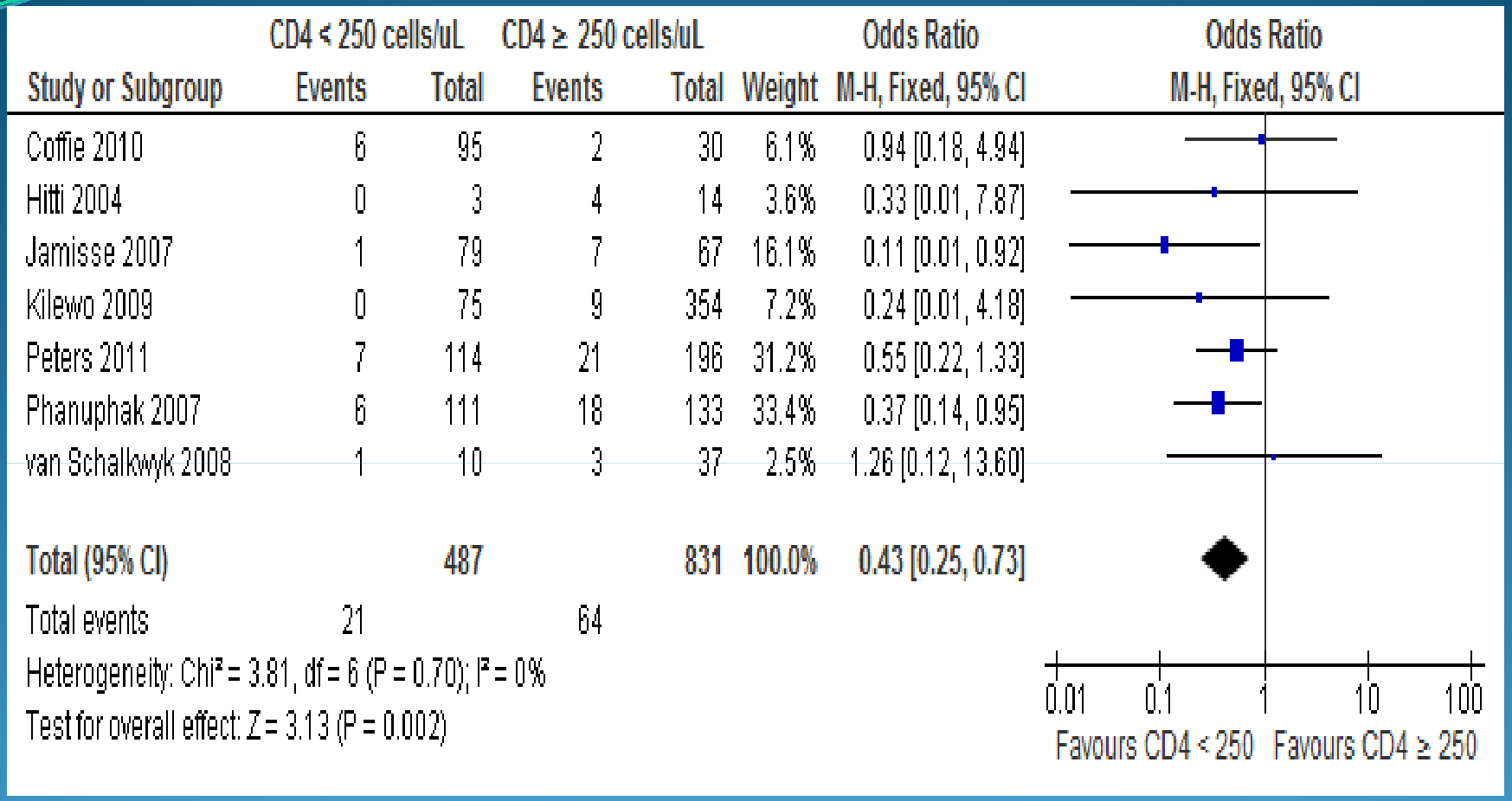
Heterogeneity: $Chi^2 = 2.44$, $df = 12$ ($P = 1.00$); $I^2 = 0\%$

Test for overall effect: $Z = 2.21$ ($P = 0.03$)

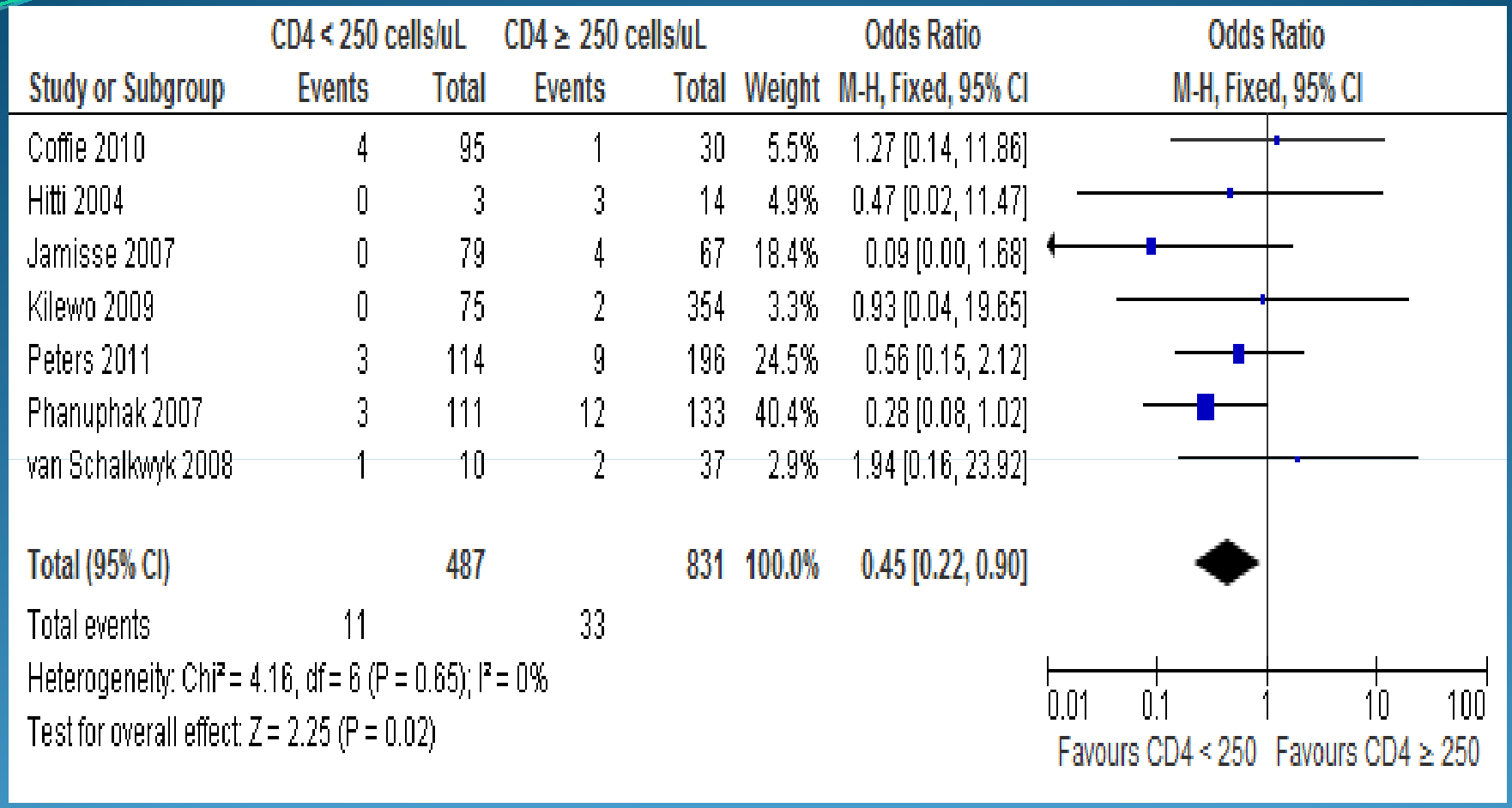


Forest plot for severe cutaneous reaction
All studies

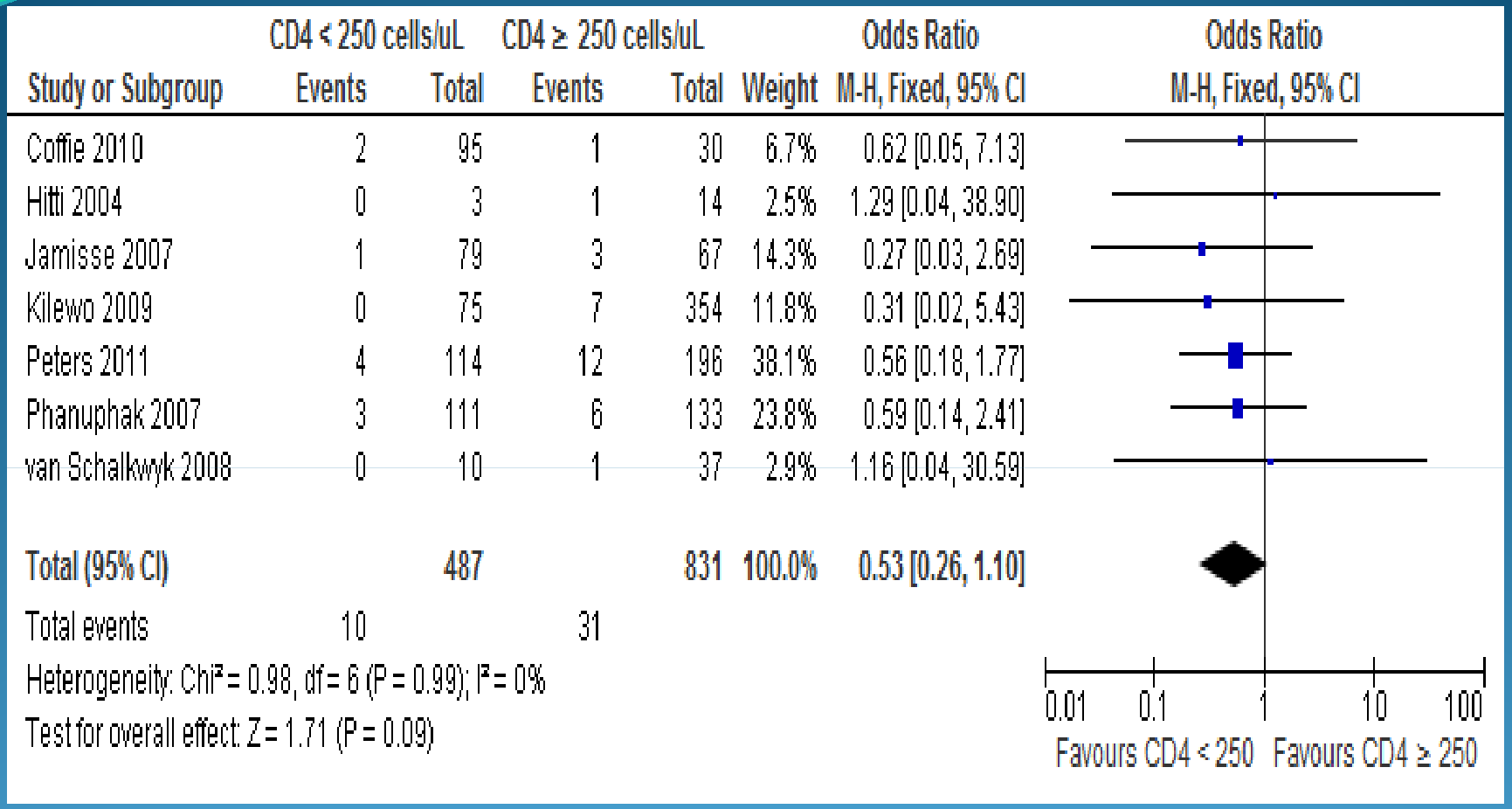
Prospective studies only



Forest plot for overall NVP toxicity
Prospective studies only



Forest plot for severe hepatotoxicity
Prospective studies only



Forest plot for severe cutaneous reaction
Prospective studies only

Comment

- NVP use in pregnant women with CD4 ≥250 cells/uL significantly increases odds of toxicity
- Our findings consistent with previous meta-analysis that informed current FDA recommendation
- Largest dataset, robust methods, most included studies were published after FDA advisory in 2005
- NVP toxicity occurs fairly soon – within 10 weeks of ART initiation
- For every 200 women starting NVP at CD4 ≥250, seven additional women develop SAEs

Other Studies

- Recently published studies included toxicity data of ART-naïve & ART-experienced pregnant women
- Toxicity risks are considerably lower in ART-experienced women who switch to NVP

- Several recent studies also combined toxicity data of NVP & nelfinavir as a single analysis
- Nelfinavir rarely associated with hepatotoxicity

WHO meta-analysis

- WHO 2009 meta-analysis did not include evaluation of cutaneous reaction in pregnancy
- The authors analysed NVP hepatotoxicity for all grades of severity (836 pregnant women)
- *All grades*: CD4 <250 (6%) v CD4 ≥250 (9%) $p = 0.55$
- *Severe hepatotoxicity*: CD4 <250 (0%) v ≥ 250 (6%) $p = 0.02$

Study Limitations

- Limited data on concurrent use of INH, rifampicin, CTX
- Variable reporting on Hepatitis B & C

- Scanty data on pre-eclampsia, HELLP, AFLP, obstetric cholestasis

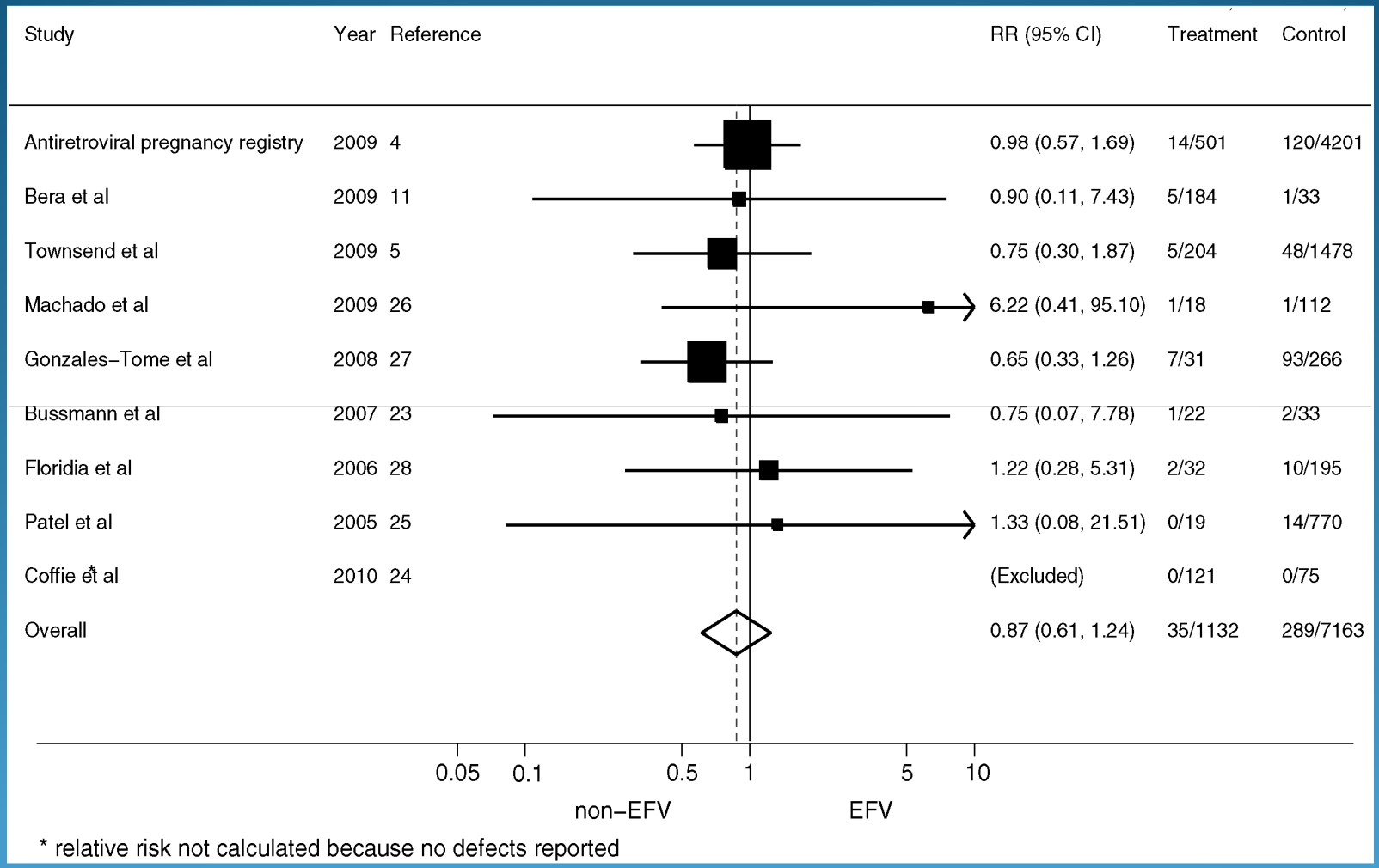
- Observational studies
- Only a single RCT, prematurely terminated

Conclusion

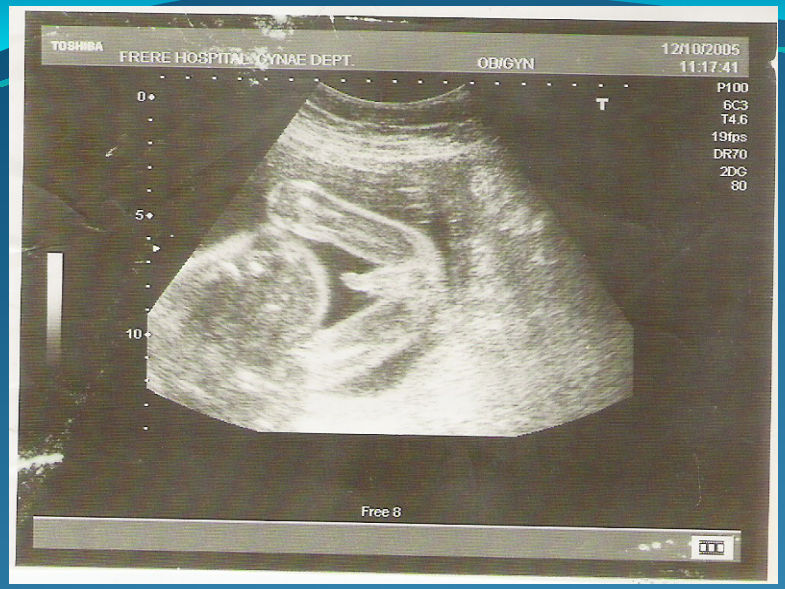
- Current guidelines supporting this use of NVP among ART-naïve pregnant women with CD4 ≥ 250 cells/uL require revision without delay

- Pharmacovigilance on ART use in pregnancy should be strengthened nationally

Why was EFV banned throughout Pregnancy?



N Ford, *AIDS 2010*; 24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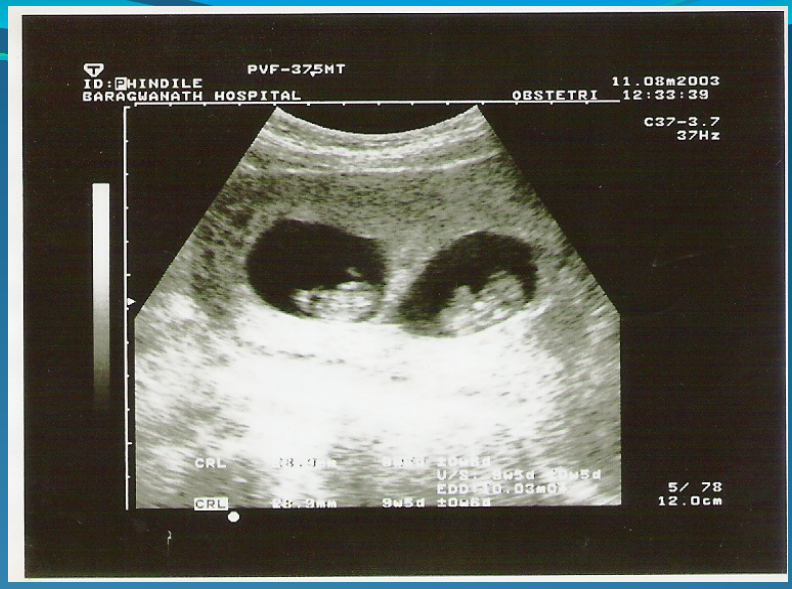
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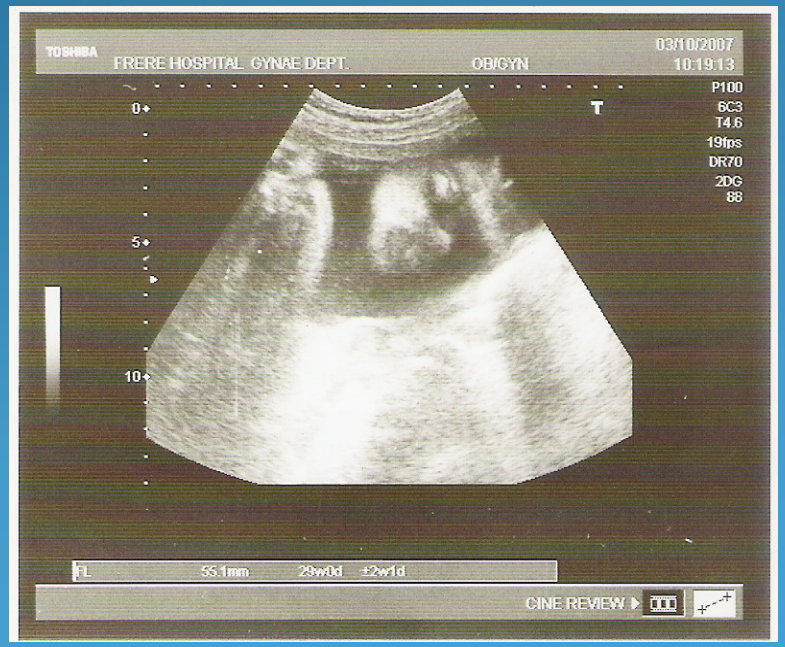
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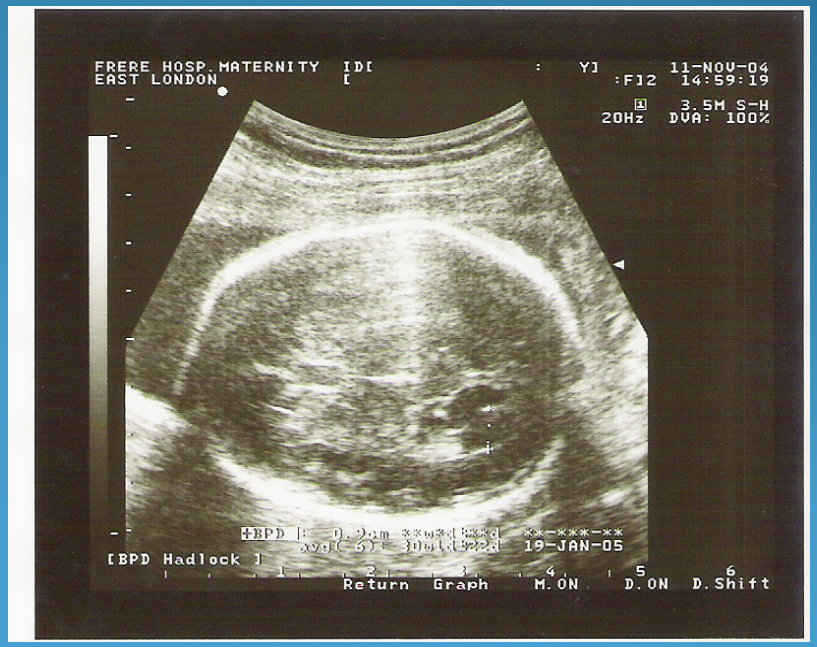
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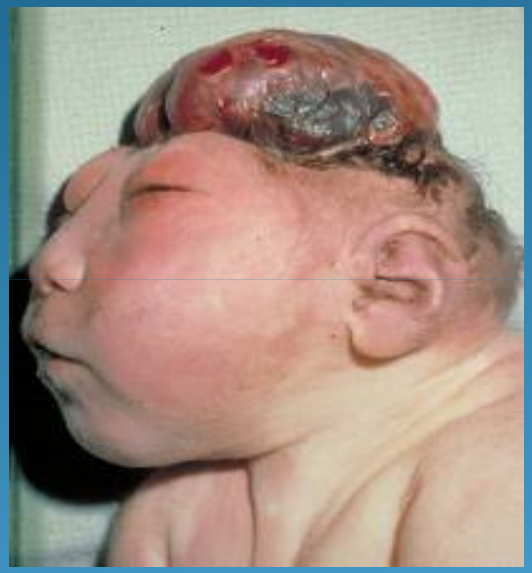

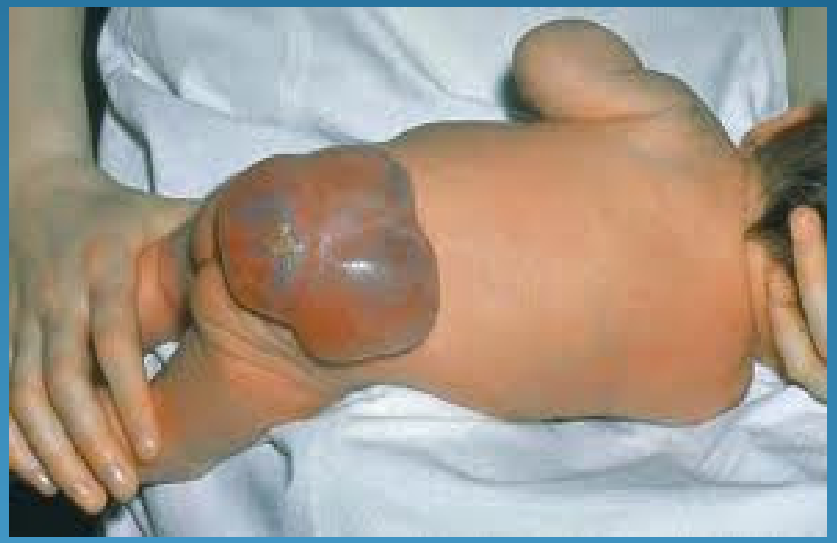

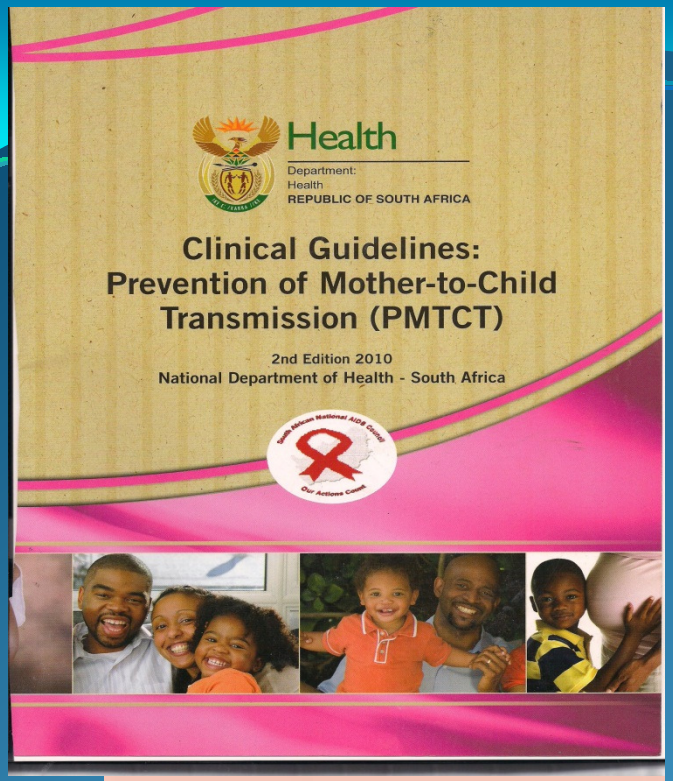
Health
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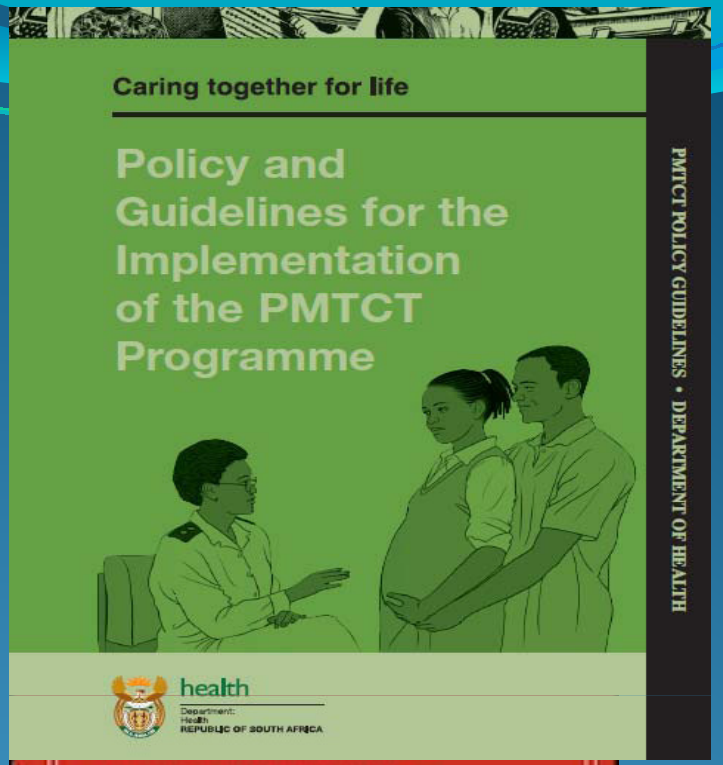
Health
REPUBLIC OF SOUTH AFRICA
Clinical Guidelines:
Prevention of Mother-to-Child
Transmission (PMTCT)
2nd Edition 2010
National Department of Health - South Africa


Caring together for life
Policy and
Guidelines for the
Implementation
of the PMTCT
Programme
PMTCT POLICY GUIDELINES • DEPARTMENT OF HEALTH
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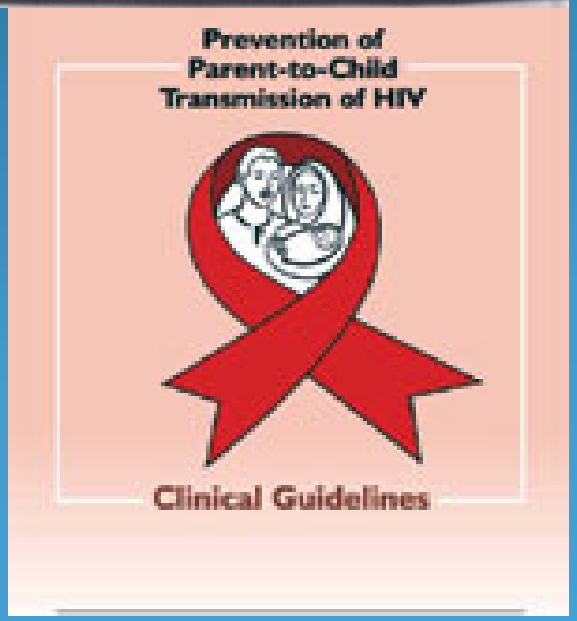
REPUBLIC OF SOUTH AFRICA


Prevention of
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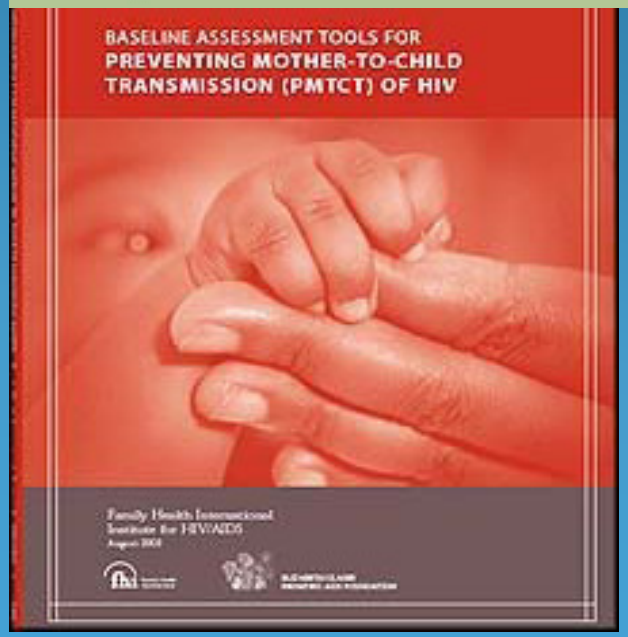
Clinical Guidelines


BASELINE ASSESSMENT TOOLS FOR
PREVENTING MOTHER-TO-CHILD
TRANSMISSION (PMTCT) OF HIV
Family Health International
Institute for HIV/AIDS

PARADIGM SHIFT

- PMTCT → → Rx for MATERNAL HEALTH
- REVIEW THE SCIENTIFIC EVIDENCE

- Replace unsafe ARV's in pregnancy with safer ones

  - Stavudine/didanosine → lactic acidosis
  - Nevirapine → hepatotoxicity, Stevens-Johnson Syndrome

Thank You

Conflict of Interest
None