Antiretrovirals in Pregnancy: "The Good, the Bad, and the Unknown"

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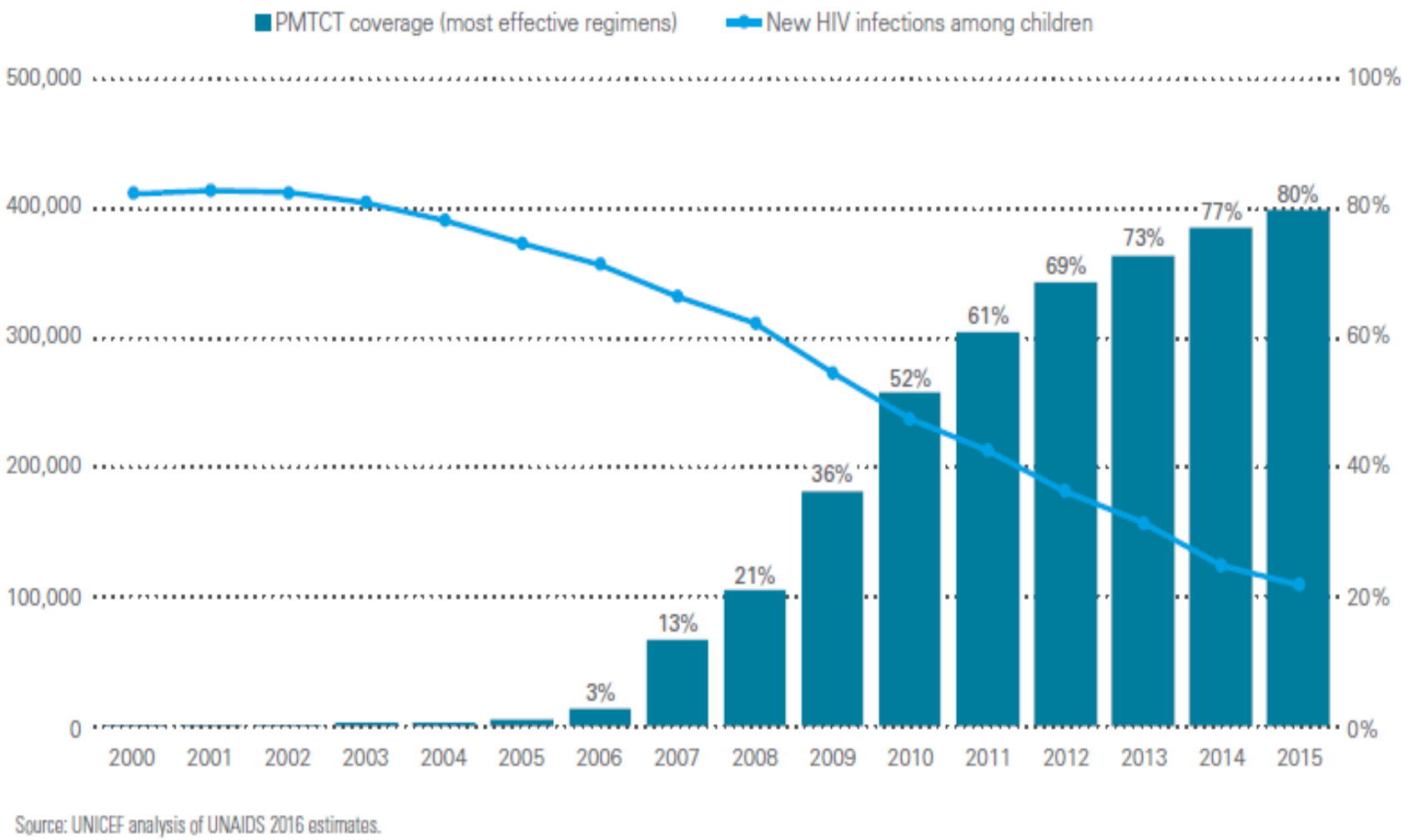
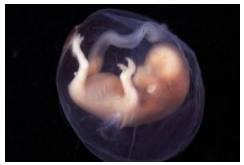
Mount Sinai

I receive financial support from the following company or companies related to the products listed below. These relationships may lead to bias in my presentation.

Entity	Type(s) of relationship(s)	Product name(s)	Relevant disease(s) or condition(s)
NONE			



UNAIDS 2016. For Every Child, End AIDS, 7th Stocktaking Report.



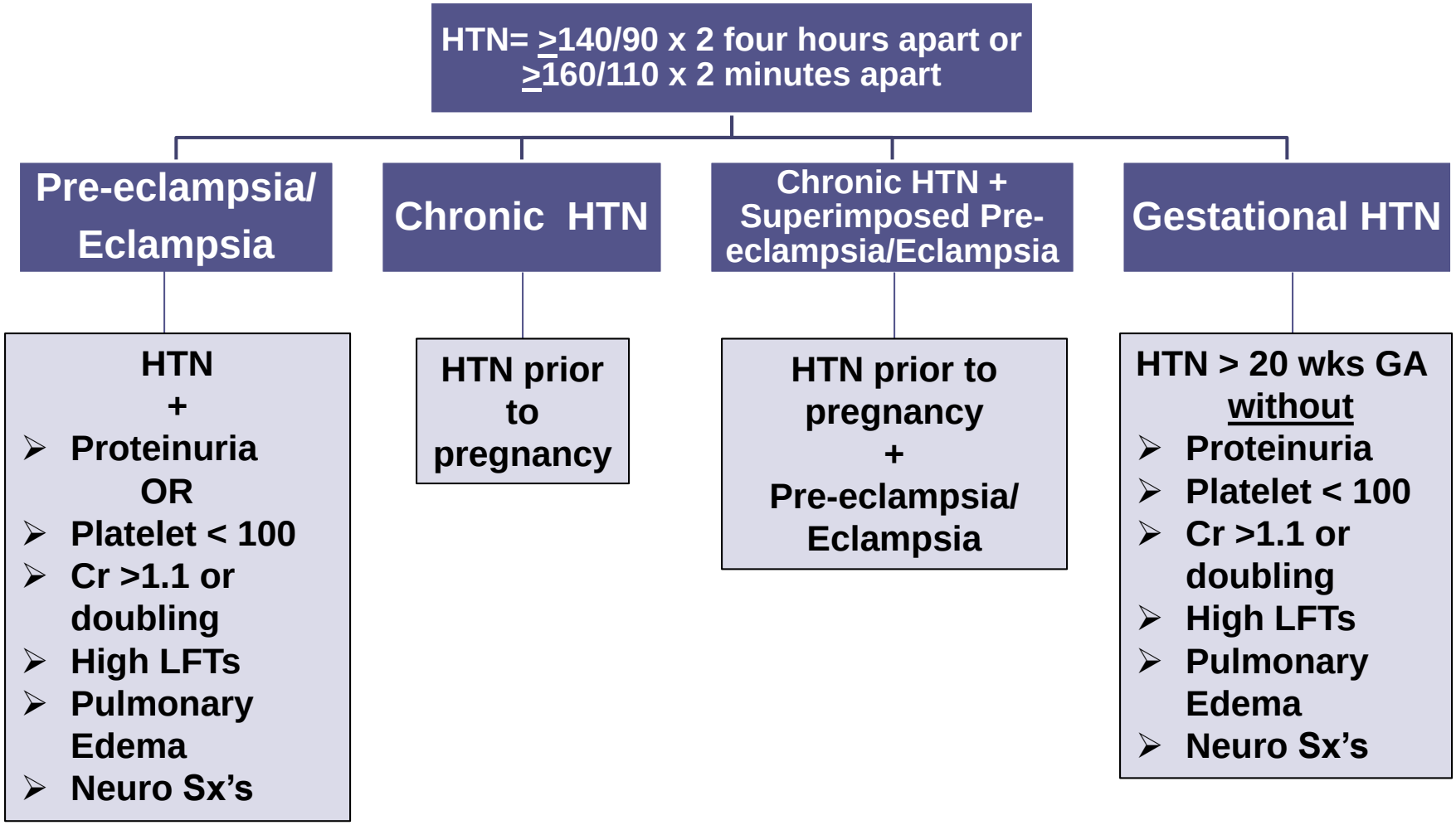
BIRTH

- Hypertensive disorders of pregnancy (Pre-eclampsia/eclampsia, PIH)
- Gestational DM

- Preterm birth
- Birth weight (LBW, SGA)

- Bone
- Mitochondrial Toxicity

Hypertensive Disorders of Pregnancy



ACOG. 2013. Obstetrics Gynecol. Hypertension in Pregnancy

Hypertensive Disorders in Pregnancy

- Overall prevalence of pre-eclampsia worldwide = 2-8% (1987-2005)

- WITS – 1989-1994
  - 9/634 (1.9%) PIH
  - 4/634 (0.7%) pre-eclampsia

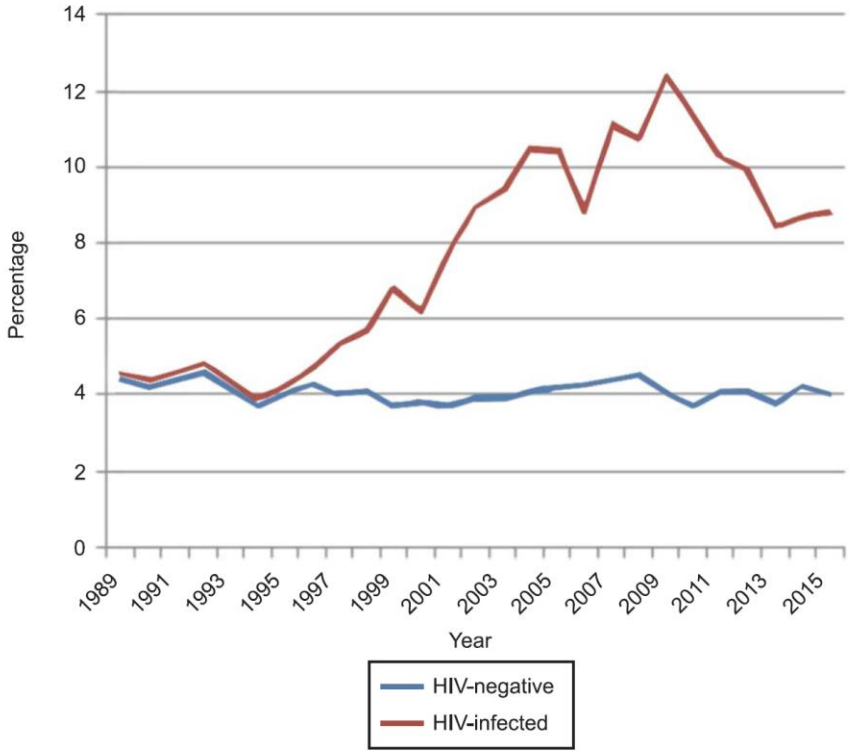


Fig. 3. Incidence of preeclampsia at University of Naples Federico II from 1989 to 2015. HIV, human immunodeficiency virus.

ACOG. Diagnosis Management Preeclampsia Eclampsia.2002
Wallis A et al. Am J Hyperten. 2008
Duley L et al. Semin Perinatol. 2009.
Dolea C et al. Global Burden of Disease. 2000.
Stratton P et al. JAIDS. 1999
Sansone M et al. Obstet Gynecol. 2016

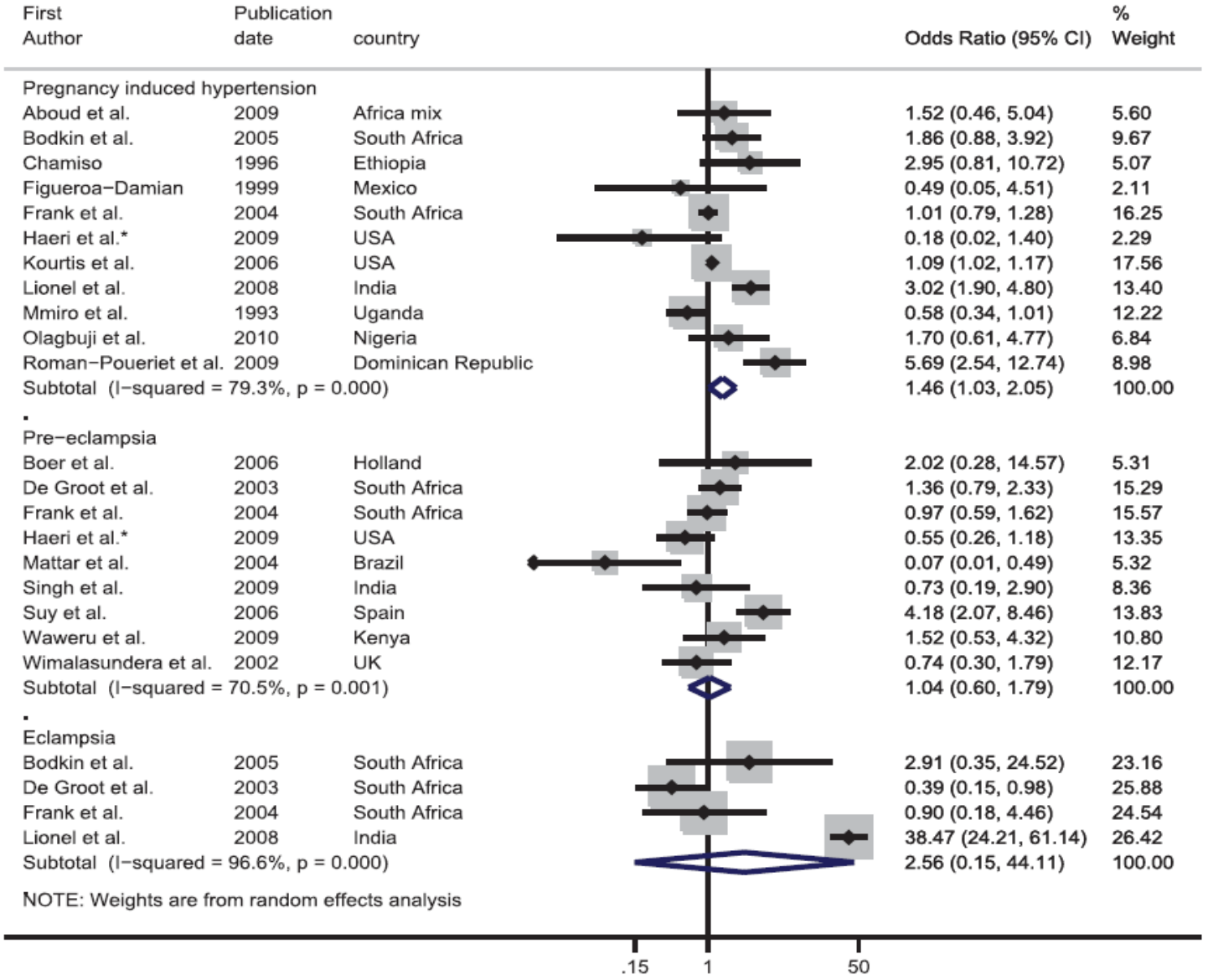
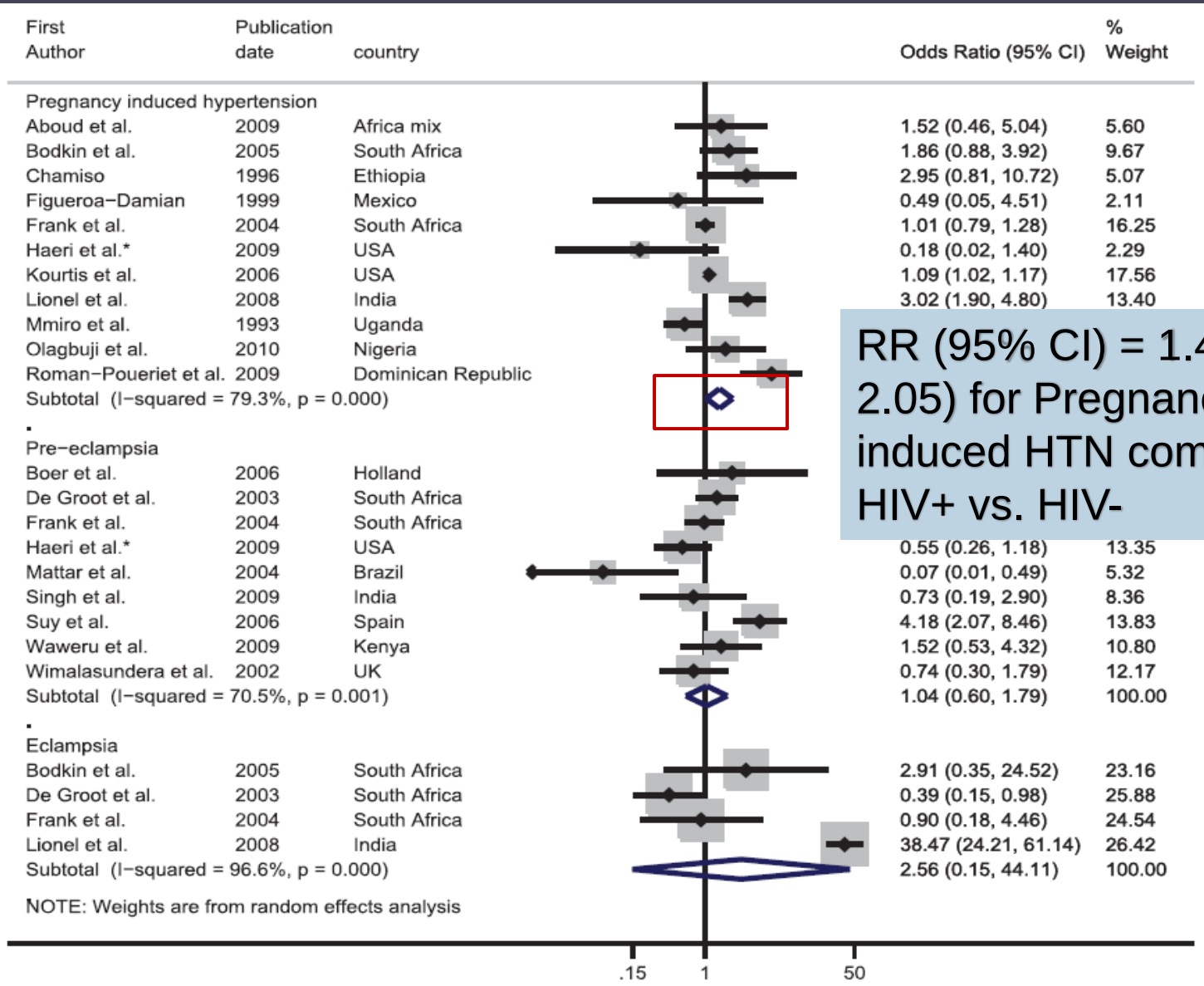


Figure 3. Forest plot showing the strength of association between HIV and hypertensive diseases of pregnancy. *Adjusted odds ratio.
doi:10.1371/journal.pone.0074848.g003

Calvert et al. PLOSOne. 2013



RR (95% CI) = 1.46 (1.03-2.05) for Pregnancy-induced HTN comparing HIV+ vs. HIV-

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doi:10.1371/journal.pone.0074848.g003

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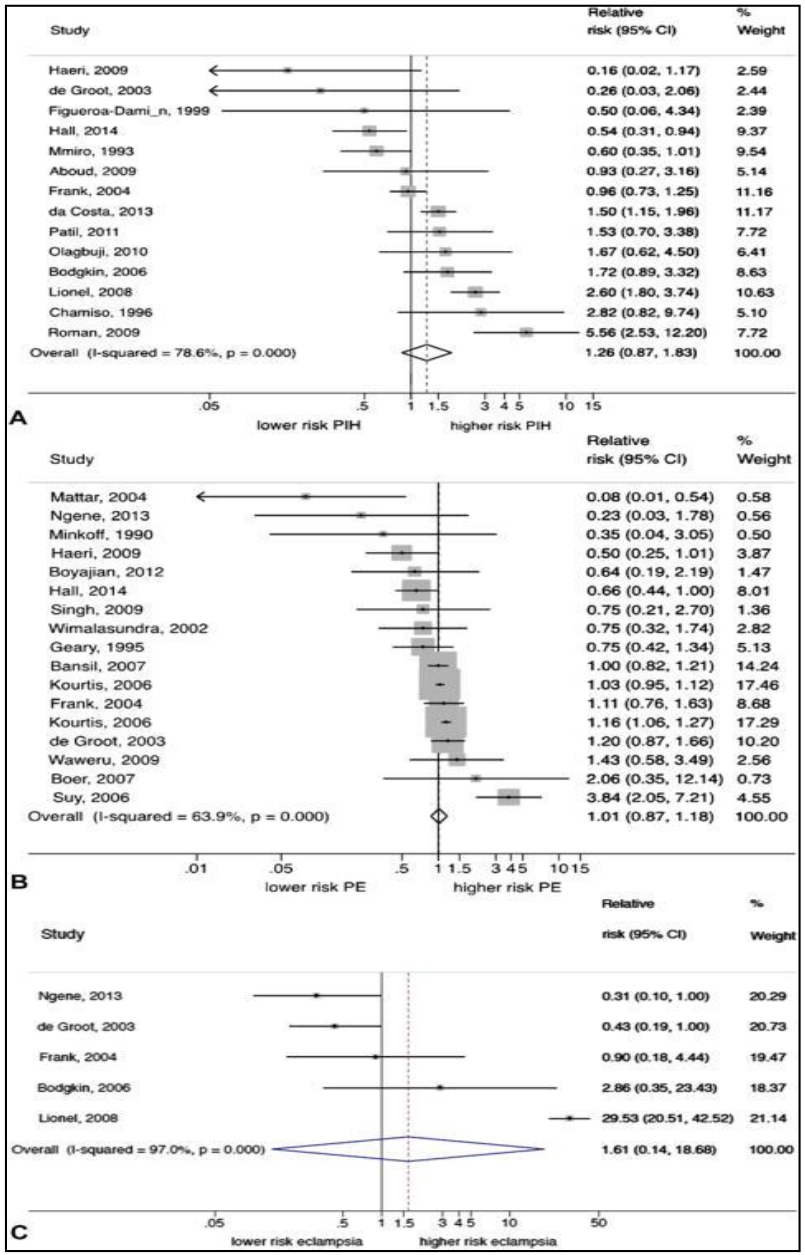
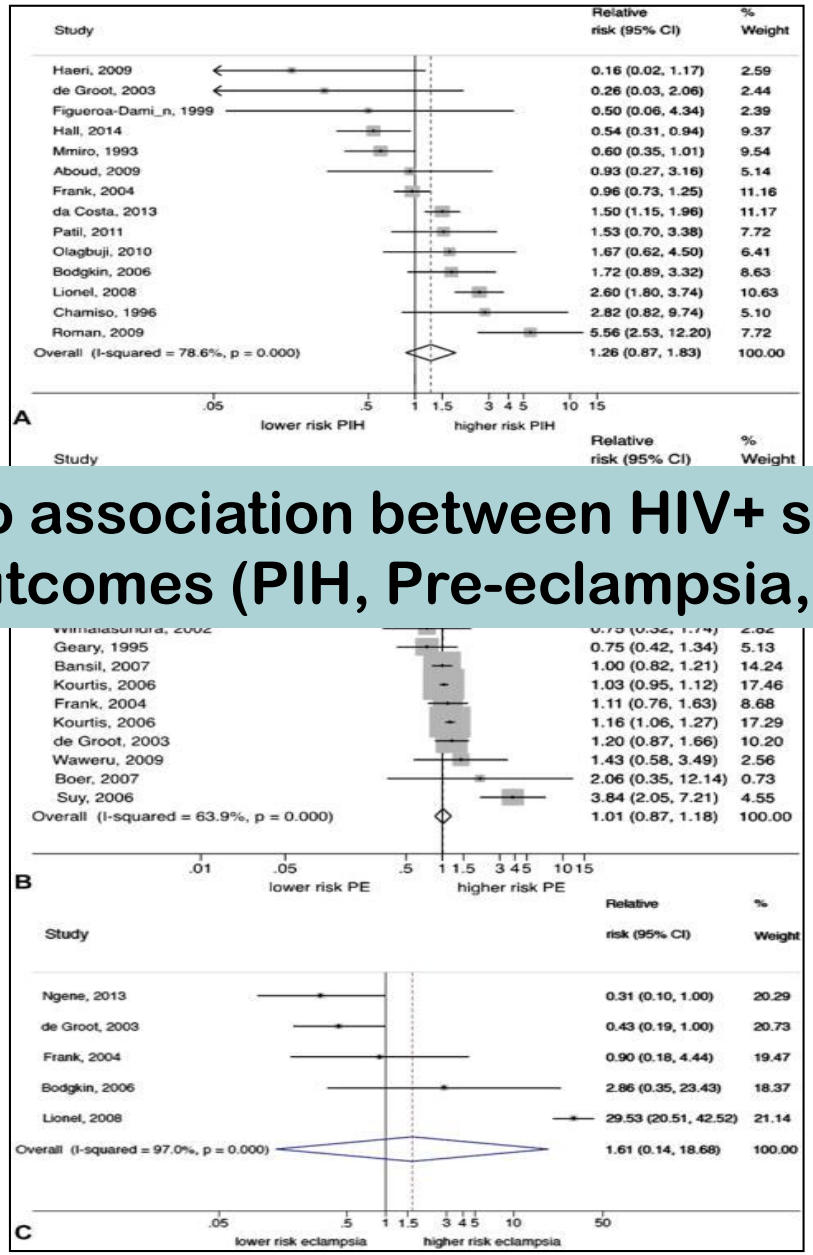


Pregnancy-induced HTN
RR (95% CI): 1.26 (0.87-1.83)

Pre-eclampsia:
RR (95% CI): 1.01 (0.87-1.18)

Eclampsia
RR (95% CI): 1.61 (0.14-18.68)

Browne et al. JAIDS 2015.



Pregnancy-induced HTN
RR (95% CI): 1.26 (0.87-1.83)

No association between HIV+ status and any of the outcomes (PIH, Pre-eclampsia, or Eclampsia

Eclampsia
RR (95% CI): 1.61 (0.14-18.68)

Browne et al. JAIDS 2015.

Original Research

Risk of Preeclampsia in Human Immunodeficiency Virus–Infected Pregnant Women

Matilde Sansone, MD, Laura Sarno, MD, Gabriele Saccone, MD, Vincenzo Berghella, MD, Giuseppe Maria Maruotti, MD, Annalisa Migliucci, MD, Angela Capone, MD, and Pasquale Martinelli, MD

Variables	HIV-Infected (n=453)	Comparison Group (n=84,272)	Crude OR (95% CI)	Adjusted OR (95% CI)
Preeclampsia	46 (10.2)	3,416 (4.1)	**3.01 (2.21–3.57)**	**2.68 (1.96–3.64)**
Preeclampsia with severe features	18 (4.0)	1,680 (2.0)	**2.57 (1.31–3.05)**	**2.03 (1.26–3.28)**
Early-onset preeclampsia	16 (3.5)	1,214 (1.4)	**2.87 (1.66–4.07)**	**2.50 (1.51–4.15)**
Late-onset preeclampsia	30 (6.6)	2.202 (2.6)	**2.77 (1.91–3.94)**	**2.64 (1.82–3.85)**
Preterm birth at less than 37 wk of gestation	50 (11.0)	3,982 (4.7)	**2.81 (1.94–3.44)**	**2.50 (1.86–3.37)**

Sansone et al. Obstet Gynecol. 2016

Original Research

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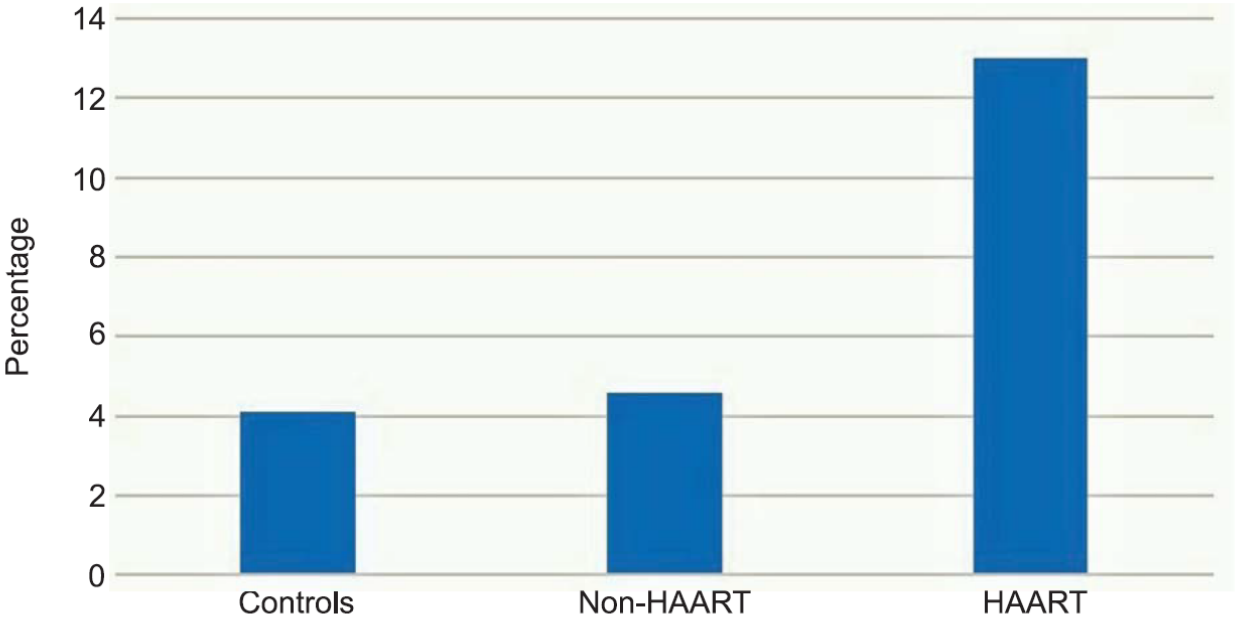

Fig. 2. Incidence of preeclampsia in HIV-negative pregnant women (4.1%; n=84,272) and in HIV-infected pregnant women stratified by therapy in the non-HAART (highly active antiretroviral therapy) group (4.6%; n=152) and in the HAART group (13.0%; n=301). HIV, human immunodeficiency virus.

Sansone et al. Obstet Gynecol. 2016

Hypertension, preeclampsia and eclampsia among HIV-infected pregnant women from Latin America and Caribbean countries☆

Elizabeth Stankiewicz Machado [a,*], Margot R. Krauss [b], Karen Megazzini [b], Conrado Milani Coutinho [c], Regis Kreitchmann [d], Victor Hugo Melo [e], José Henrique Pilotto [f], Mariana Ceriotto [g], Cristina B. Hofer [a], George K. Siberry [h], D. Heather Watts [h], for the NICHD International Site Development Initiative (NISDI) Pediatric Protocol

Hypertensive Disorder in Pregnancy = 4.8% (73/1513)
Pre-eclampsia/ Eclampsia = 2.3% (35/1513)

Table 3 Final logistic regression model.[a]

Covariates	Final model-HD OR (95%CI)	Final model-PE/E OR (95%CI)
gBMI: ≥25 kg/m^2 vs. <25 kg/m^2	3.1 (1.9–5.0)	3.0 (1.5–6.0)
Hg at L&D: ≥11 g/dL vs. <11 g/dL	2.1 (1.2–3.6)	2.8 (1.2–6.5)
Maternal age: ≥35 yr vs. <35 yr	1.8 (1.1–3.2)	NA
ARV type at conception: HAART vs. non-HAART	NA	2.3 (1.1–4.9)
Previous history of PE/E: Yes vs. No	NA	6.7 (1.8–25.5)

HD – hypertensive disorders; PE/E – preeclampsia/eclampsia; NA – not applicable.
[a] Forcing CD4 and viral load at enrollment or at L&D had no impact on the final models.

Machado E et al. J of Infection. 2014

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Hg at L&D: ≥11 g/dL vs. <11 g/dL	2.1 (1.2–3.6)	2.8 (1.2–6.5)
Maternal age: >35 yr vs. <35 yr	1.8 (1.1–3.2)	NA
ARV type at conception: HAART vs. non-HAART	NA	2.3 (1.1–4.9)
Previous history of PE/E: Yes vs. No	NA	6.7 (1.8–25.5)

HD – hypertensive disorders; PE/E – preeclampsia/eclampsia; NA – not applicable.
[a] Forcing CD4 and viral load at enrollment or at L&D had no impact on the final models.

Machado E et al. J of Infection. 2014

Increased risk of pre-eclampsia and fetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy

Anna Suy[a], Esteban Martínez[b], Oriol Coll[a], Montserrat Lonca[b], Montserrat Palacio[a], Elisa de Lazzari[b], María Larrousse[b], Ana Milinkovic[b], Sandra Hernández[a], José L. Blanco[b], Josep Mallolas[b], Agathe León[b], Juan A. Vanrell[a] and José M. Gatell[b,*]

Table. Multivariate Models Comparing HAART Use Prior to Pregnancy vs. No HAART Use Prior to Pregnancy Amongst HIV-infected Women Subgroup

Pre-eclampsia		Pre-eclampsia or Fetal Death	
aOR (95% CI)	***p* value**	**aOR (95% CI)**	***p* value**
8.9 (1.7-45.5)	0.009	5.6 (1.7-18.1)	0.004

** Adjusted for age, race, intravenous drug use, multiple gestation, multiparity, tobacco smoking*

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DOI: 10.1002/ijgo.12038

CLINICAL ARTICLE
Obstetrics

WILEY GYNECOLOGY OBSTETRICS

Associations between HIV, highly active anti-retroviral therapy, and hypertensive disorders of pregnancy among maternal deaths in South Africa 2011–2013

Hannah M. Sebitloane[1]* | Jagidesa Moodley[2] | Benn Sartorius[3]

- Secondary analysis of extrapolated report data from "Saving Mothers Report 2014" in South Africa
- Between 2011-2013:
  - n=4452 maternal deaths overall
  - n=640 maternal deaths due to hypertensive disorder of pregnancy (HDP)

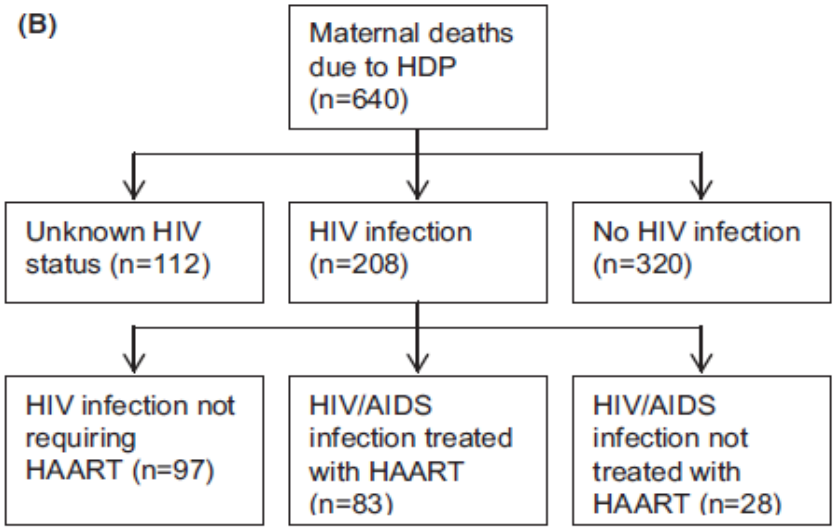


FIGURE 1 Flow of maternal death records for analysis. HIV status details among all maternal death records (A). HIV status details among maternal deaths due to hypertensive disorders of pregnancy (B). Abbreviations: HAART, highly active anti-retroviral therapy; HDP, hypertensive disorders of pregnancy.

TABLE 1 Comparison of relative risks of maternal death being due to HDP.

Comparison	No. of maternal deaths due to HDP[a]	RR (95% CI)
Effect of HIV infection on risk of death due to HDP		
All individuals with HIV infections (n=2516)	208 (8.3)	0.57 (0.51–0.64)
Individuals without HIV infections (n=1351)	320 (23.7)	Referent
Effect of HIV infection		
Individuals with HIV infections not requiring HAART (n=629)	97 (15.4)	0.68 (0.57–0.82)
Individuals without HIV infections (n=1351)	320 (23.7)	Referent
Effect of immuno-compromised conditions		
Individuals with AIDS not receiving HAART (n=647)	28 (4.3)	0.42 (0.30–0.58)
Individuals with HIV infections not requiring HAART (n=629)	97 (15.4)	Referent
Effect of immuno-compromised conditions		
Individuals with AIDS not receiving HAART (n=647)	28 (4.3)	0.21 (0.15–0.31)
Individuals without HIV infections (n=1351)	320 (23.7)	Referent
Effect of treatment with HAART		
Individuals with AIDS receiving HAART (n=1240)	83 (6.7)	0.39 (0.32–0.47)
Individuals without HIV infections (n=1351)	320 (23.7)	Referent
Effect of treatment with HAART		
Individuals with AIDS receiving HAART (n=1240)	83 (6.7)	0.67 (0.57–0.79)
Individuals with HIV infections not requiring HAART (n=629)	97 (15.4)	Referent
Effect of treatment with HAART		
Individuals with AIDS receiving HAART (n=1240)	83 (6.7)	1.15 (1.02–1.29)
Individuals with AIDS not receiving HAART (n=647)	28 (4.3)	Referent

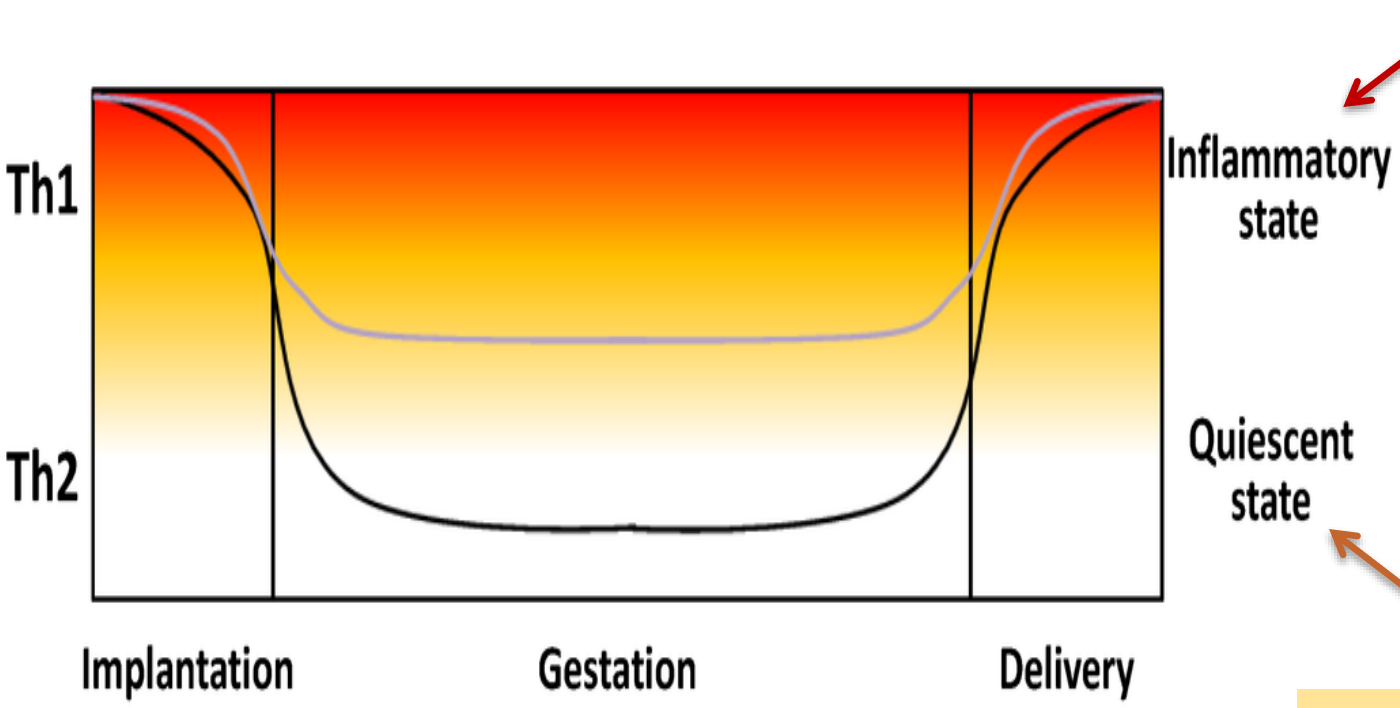
HIV+ (CD4>200) not requiring combination ART associated with LOWER risk than HIV-

Amongst those not receiving combination ART: AIDS/CD4<200 associated with LOWER risk than those with CD4>200

Amongst AIDS/CD4<200: Combination ART associated with HIGHER risk than those not receiving any ART

Sebitloane et al. Obstet Gynecol. 2016

Immune Reconstitution Via ART



AIDS Immune Suppression

Barrera et al. Nutrients. 2015.

Hypertensive Disorders of Pregnancy and HIV/ART

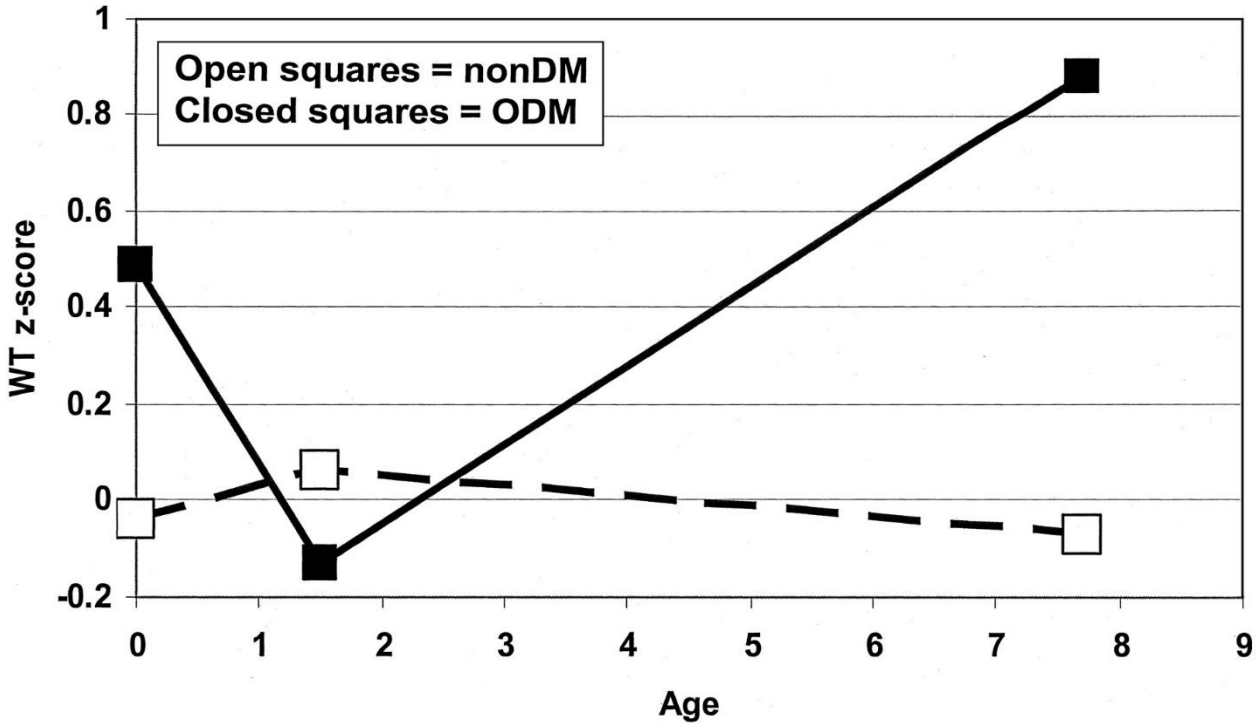
- **Difficulty in accurate assessments of incidence across time and geography due to heterogeneity diagnosis**
- **Conflicting epidemiological evidence**
- **Increased inflammation likely plays a role in pre-elampsia**
- **Immune reconstitution with combination ART era may have an effect on increasing rates of preeclampsia**

Gestational Diabetes

- **2-7% of all pregnancies**
- **GDM and poor maternal outcomes:**
  - Gestational hypertension
  - Pre-eclampsia/eclampsia
  - Increased UTI
  - Increased risk of thyroid disease
  - Increased risk of diabetes post-partum
- **GDM and fetal/infant outcomes:**
  - Congenital anomalies
  - Spontaneous abortion
  - Preterm birth
  - Macrosomia
  - IUGR/ SGA
  - Neonatal hypoglycemia

Gestational Diabetes

- GDM and long term infant outcomes:
  - Increased risk of developing obesity



Touger et al, Diabetes Care. 2005

Diagnostic thresholds for GDM Diagnosis

	75g OGTT			100g OGTT	
	WHO	ADA	IADPSG	Carpenter & Coustan	National Diabetes Data Group
Fasting (mg/dL)	126	92	92	95	105
1h	---	180	180	180	190
2h	140	153	153	155	165
3h	---			140	145
Criteria	≥ 1 abn	≥ 1 abn	≥ 1 abn	≥ 2 abn	≥ 2 abn

WHO. Definition, Diagnosis and Classification of DM and its Complications: Report of a WHO Consultation. Geneva. 1999.
ADA Position Statement. Diabetes Care. January 2011 and 2013.
IADPSG Consensus Panel Statement. Diabetes Care. March 2010.
Carpenter & Coustan. Am J Obstetrics & Gynecology. 1982.
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National Diabetes Data Group. Classification and diagnosis of DM and other categories of glucose intolerance. Diabetes. 1979.

The association between HIV, antiretroviral therapy, and gestational diabetes mellitus

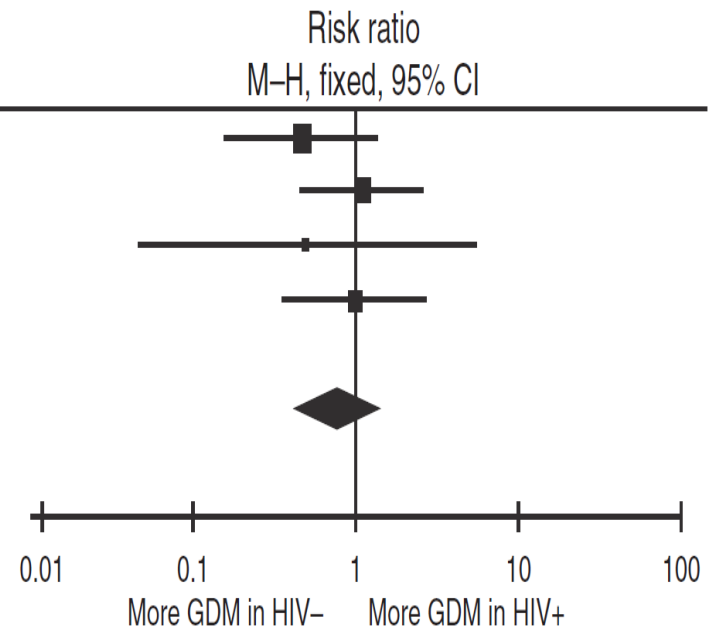
Larske M. Soepnel[a,b], Shane A. Norris[b], Verena J.M.M. Schrier[a], Joyce L. Browne[a], Marcus J. Rijken[a,c], Glenda Gray[d] and Kerstin Klipstein-Grobusch[a,e]

(a)

Study or subgroup	HIV+ Events	HIV+ Total	HIV− Events	HIV− Total	Weight	Risk ratio M–H, fixed, 95% CI
Haeri, 2009	4	151	17	302	37.4%	0.47 [0.16, 1.37]
Jao, 2013	11	166	9	150	31.2%	1.10 [0.47, 2.59]
Samuels, 2014	1	105	2	105	6.6%	0.50 [0.05, 5.43]
Tang, 2006	5	171	15	513	24.8%	1.00 [0.37, 2.71]
Total (95% CI)		593		1070	100.0%	0.80 [0.47, 1.37]
Total events	21		43			

Heterogeneity: $Chi^2 = 1.83$, df = 3 ($P = 0.61$); $I^2 = 0\%$

Test for overall effect: Z = 0.81 ($P = 0.42$)



No association between HIV infection and GDM

- **Cameroon Study of HIV+ and HIV- Pregnant Women**
- **n=316**
- **Rates GDM:**
  - **HIV+ 6.6%**
  - **HIV- 6.0%**

	HIV-infected women (n = 166)		
	GDM (n = 11)	Without GDM (n = 155)	P
Age (years)	30.5 (27.5–34.5)	28 (25–32)	0.04
Gestational age at OGTT (weeks)	29 (27–30)	27 (25–30)	NS
Gravidity	1 (1–3)	1 (0–2)	NS
Family history of DM	2 (18.2)	19 (12.3)	NS
Family history of hypertension	3 (27.3)	43 (27.7)	NS
Prepregnancy BMI (kg/m^2)	25.2 (24–29)	25.4 (23.5–28.2)	NS
Systolic BP at OGTT (mmHg)	118 (115–120)	105 (98–111)	0.02
Diastolic BP at OGTT (mmHg)	76 (72–80)	64 (63–69)	0.01
Preeclampsia during pregnancy	0 (0)	2 (1.3)	NS
CD4 cell count at OGTT (cells/mm^3)			NS
<50	0 (0)	13 (8.4)	
50–199	4 (36.4)	20 (12.9)	
200–350	2 (18.2)	42 (27.1)	
>350	5 (45.5)	80 (51.6)	
On cART at OGTT	10 (90.9)	84 (54.2)	0.02
C-section delivery	1 (9.1)	14 (9)	NS
Stillbirth/IUFD	0 (0)	3 (2.2)	NS
Birth weight (grams)	3,228 (3,000–3,500)	3,300 (3,000–3,500)	NS

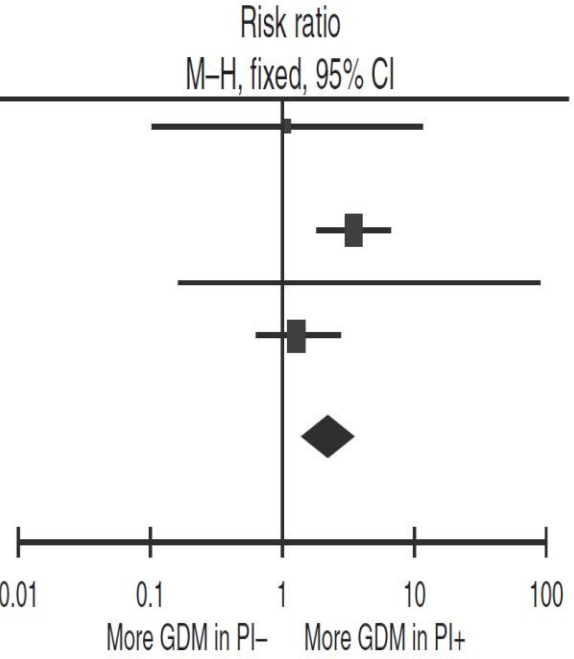
Jao et al. Diabetes Care. 2013.

(c)

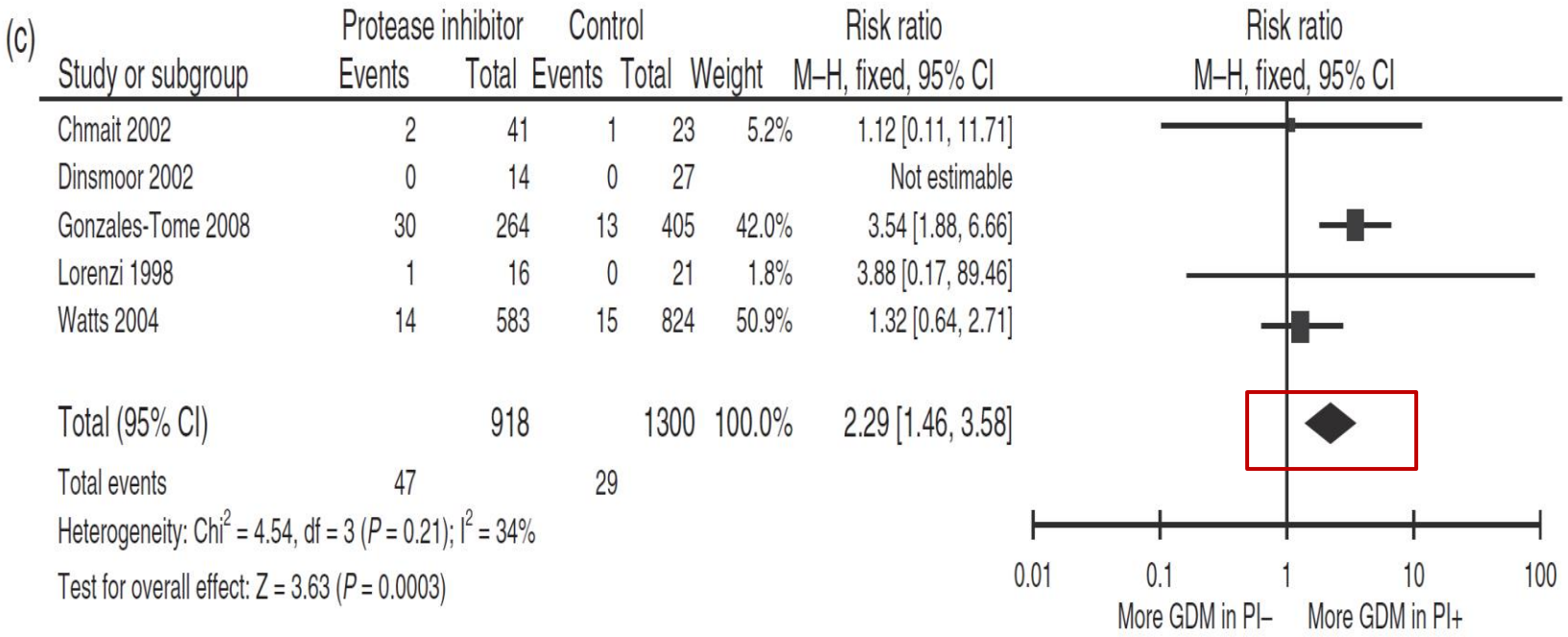
Study or subgroup	Protease inhibitor Events	Total	Control Events	Total	Weight	Risk ratio M–H, fixed, 95% CI
Chmait 2002	2	41	1	23	5.2%	1.12 [0.11, 11.71]
Dinsmoor 2002	0	14	0	27		Not estimable
Gonzales-Tome 2008	30	264	13	405	42.0%	3.54 [1.88, 6.66]
Lorenzi 1998	1	16	0	21	1.8%	3.88 [0.17, 89.46]
Watts 2004	14	583	15	824	50.9%	1.32 [0.64, 2.71]
Total (95% CI)		918		1300	100.0%	2.29 [1.46, 3.58]
Total events	47		29			

Heterogeneity: $Chi^2 = 4.54$, df = 3 ($P = 0.21$); $I^2 = 34\%$

Test for overall effect: Z = 3.63 ($P = 0.0003$)

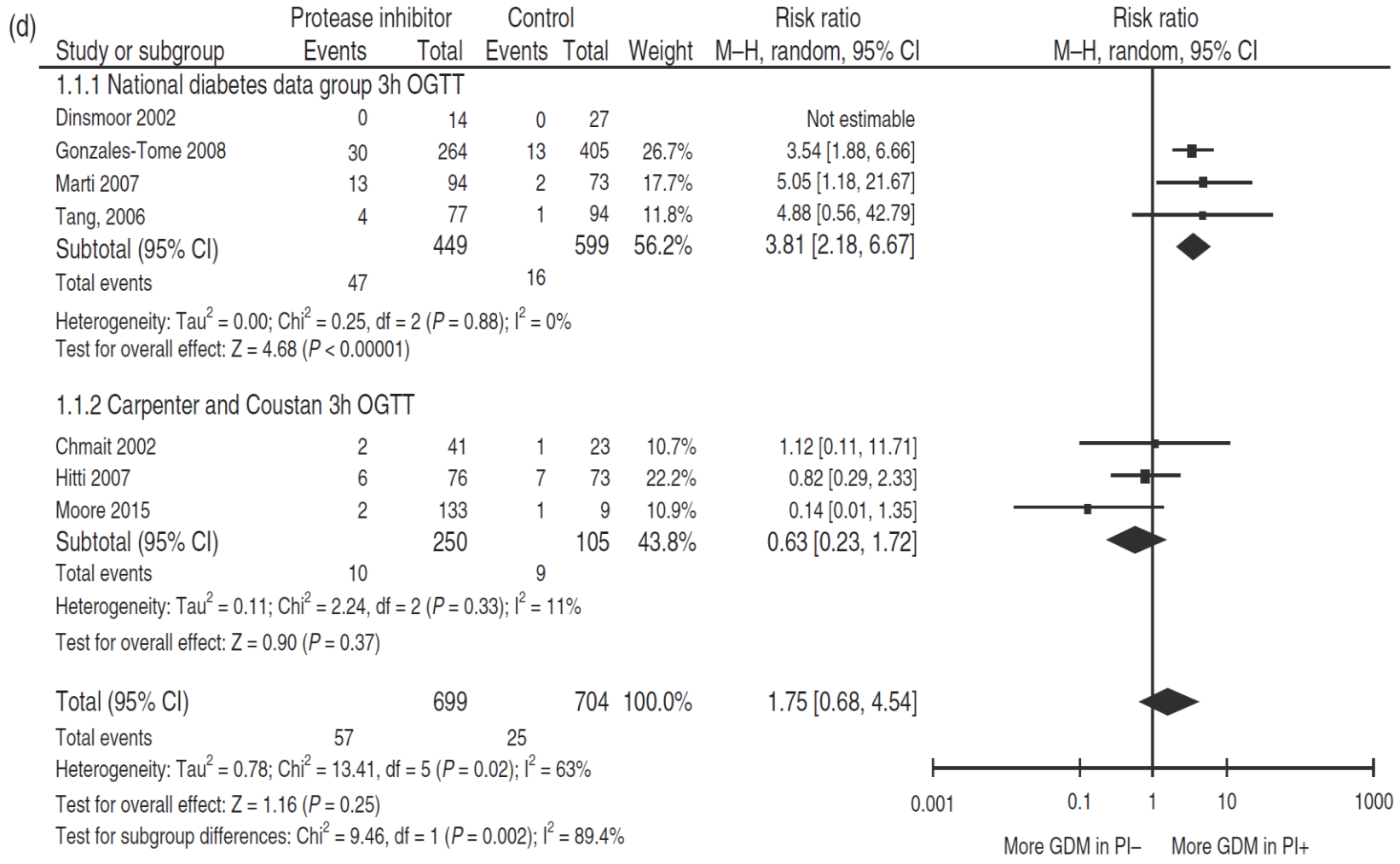


Soepnel et al. AIDS 2017.



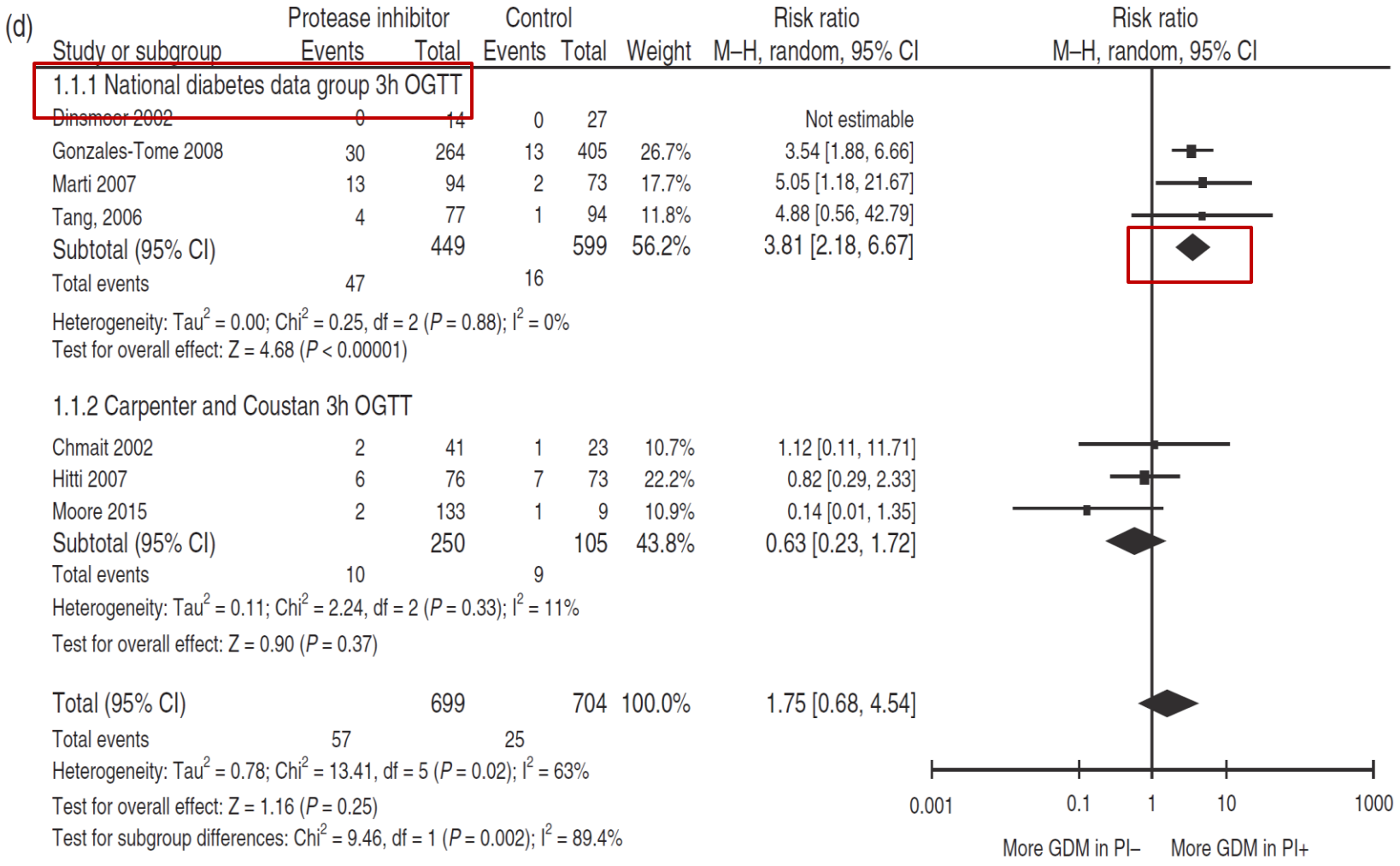
Increased risk of GDM with 1st generation PI use vs. no PI exposure

Soepnel et al. AIDS 2017.



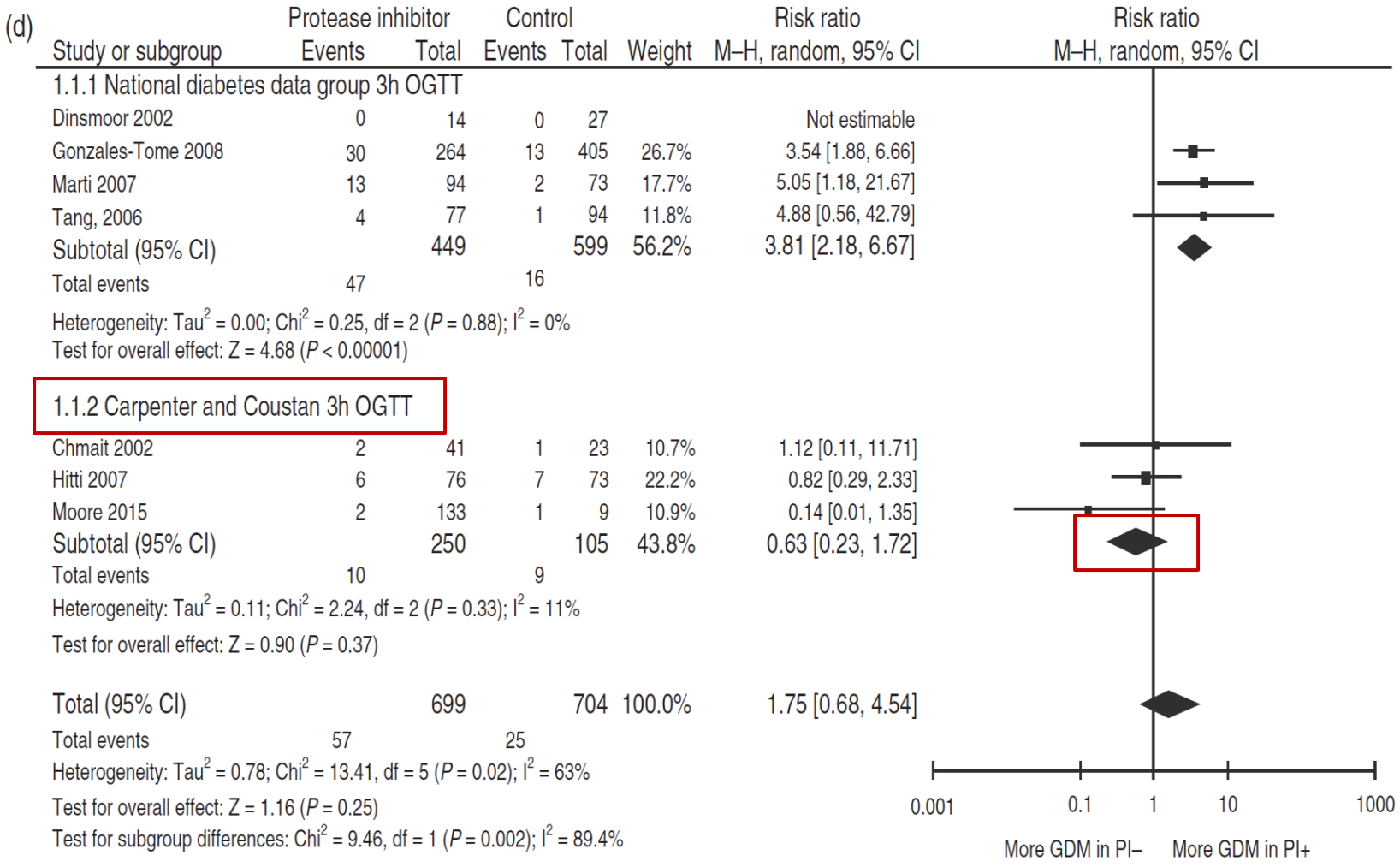
Soepnel et al. AIDS 2017.

(d)



Study or subgroup	Protease inhibitor Events	Total	Control Events	Total	Weight	Risk ratio M–H, random, 95% CI
1.1.1 National diabetes data group 3h OGTT						
~~Dinsmoor 2002~~	~~0~~	~~14~~	0	27		Not estimable
Gonzales-Tome 2008	30	264	13	405	26.7%	3.54 [1.88, 6.66]
Marti 2007	13	94	2	73	17.7%	5.05 [1.18, 21.67]
Tang, 2006	4	77	1	94	11.8%	4.88 [0.56, 42.79]
Subtotal (95% CI)		449		599	56.2%	3.81 [2.18, 6.67]
Total events	47		16			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.25$, df = 2 ($P = 0.88$); $I^2 = 0\%$						
Test for overall effect: Z = 4.68 ($P < 0.00001$)						
1.1.2 Carpenter and Coustan 3h OGTT						
Chmait 2002	2	41	1	23	10.7%	1.12 [0.11, 11.71]
Hitti 2007	6	76	7	73	22.2%	0.82 [0.29, 2.33]
Moore 2015	2	133	1	9	10.9%	0.14 [0.01, 1.35]
Subtotal (95% CI)		250		105	43.8%	0.63 [0.23, 1.72]
Total events	10		9			
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 2.24$, df = 2 ($P = 0.33$); $I^2 = 11\%$						
Test for overall effect: Z = 0.90 ($P = 0.37$)						
Total (95% CI)		699		704	100.0%	1.75 [0.68, 4.54]
Total events	57		25			
Heterogeneity: $Tau^2 = 0.78$; $Chi^2 = 13.41$, df = 5 ($P = 0.02$); $I^2 = 63\%$						
Test for overall effect: Z = 1.16 ($P = 0.25$)						
Test for subgroup differences: $Chi^2 = 9.46$, df = 1 ($P = 0.002$); $I^2 = 89.4\%$						

Soepnel et al. AIDS 2017.

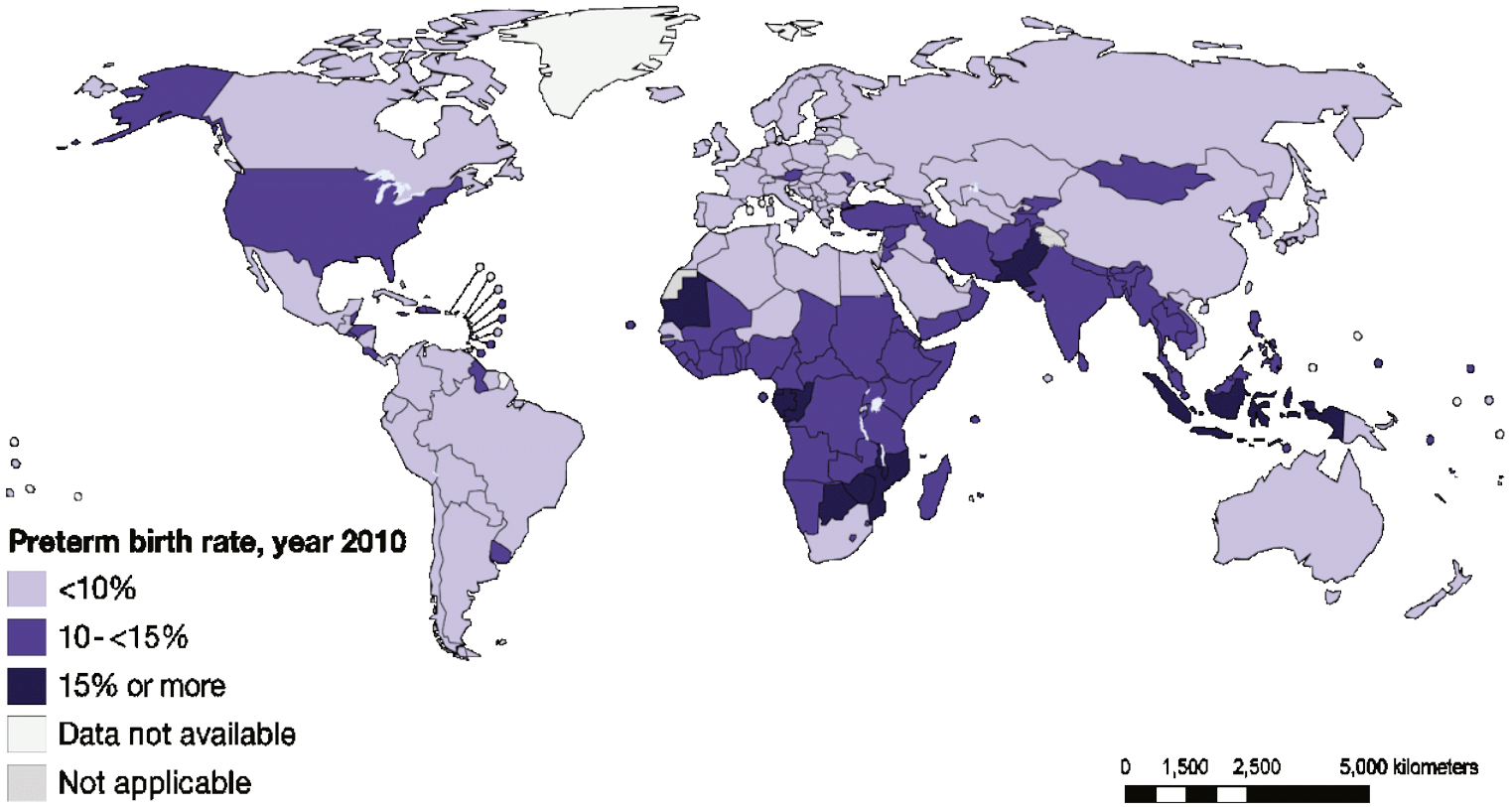


Soepnel et al. AIDS 2017.

Gestational Diabetes and HIV/ART

- **Overall rates of GDM in HIV+ and HIV- women appear to be similar**
- **However, large heterogeneity in ART used during pregnancy across studies**
- **1st generation PIs potentially associated with GDM, but relevancy is unclear given increasing use of other non-1st generation PI-based ART**

Figure 2: Global burden of preterm birth in 2010



11 countries with preterm birth rates over 15% by rank:

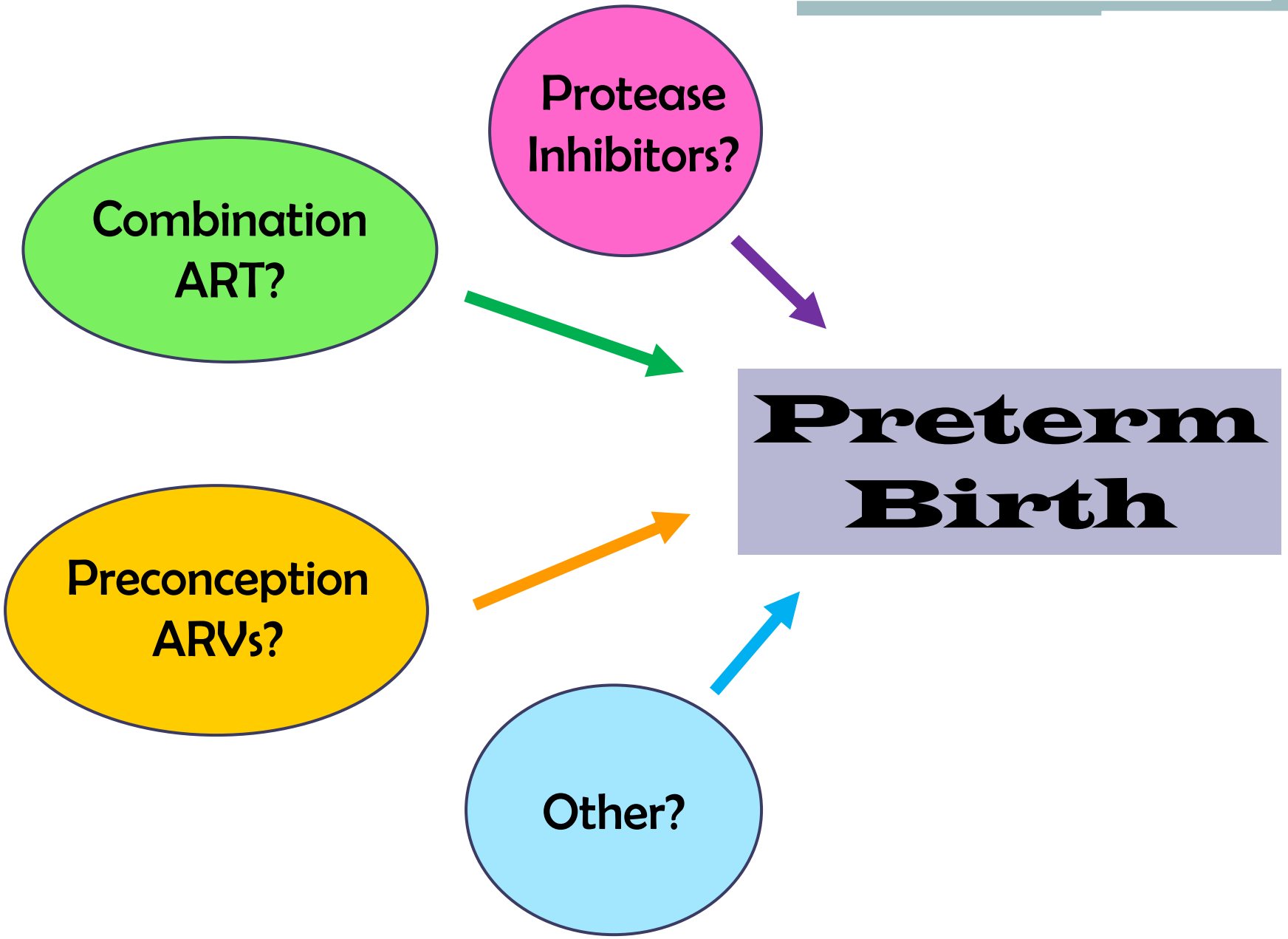
1. Malawi
2. Congo
3. Comoros
4. Zimbabwe
5. Equatorial Guinea
6. Mozambique
7. Gabon
8. Pakistan
9. Indonesia
10. Mauritania
11. Botswana

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Source: Blencowe et al National, regional and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications.
Note: rates by country are available on the accompanying wall chart.
Not applicable= non WHO Members State


Protease Inhibitors?
Combination ART?
Preterm Birth
Preconception ARVs?
Other?

n=19,585 (1990-2006)
Pediatric Spectrum of HIV Disease, European Collaborative Study, National Study of HIV in Pregnancy and Childhood

Table 4. Pooled analysis of the association between antiretroviral therapy and preterm delivery (<37 weeks of gestation) using data from the Pediatric Spectrum of HIV Disease project, the European Collaborative Study and the National Study of HIV in Pregnancy and Childhood

	Univariable (adjusting for study)*			Multivariable* (*n* = 10 110)		
	OR	95% CI	*P* value	AOR	95% CI	*P* value
Antiretroviral therapy						
Monotherapy	1.23	1.03–1.48	0.02	1.09	0.86–1.38	0.50
Dual therapy	1.00			1.00		
HAART	1.43	1.20–1.70	<0.001	1.49	1.19–1.87	0.001
Study						
PSD	1.00			1.00		
ECS	0.92	0.79–1.06	0.24	1.03	0.79–1.35	0.82
NSHPC	0.76	0.65–0.89	<0.001	0.92	0.69–1.22	0.55
Race/ethnicity						
White	1.00			1.00		
Black	0.95	0.85–1.08	0.45	1.41	1.14–1.75	0.002
Other/Hispanic	0.90	0.77–1.05	0.19	1.28	0.98–1.67	0.07
Region of birth						
Within study region	1.00			1.00		
Outside study region	0.77	0.69–0.86	<0.001	0.71	0.59–0.87	0.001
Injecting drug use						
Non-IDU	1.00			1.00		
IDU	1.76	1.57–1.98	<0.001	2.01	1.65–2.45	<0.001
Clinical status**						
Asymptomatic or CD4 ≥200 cells/μl	1.00			1.00		
Symptomatic or CD4 <200 cells/μl	1.62	1.41–1.87	<0.001	1.76	1.48–2.09	<0.001
Year of birth/delivery						
Per year	1.00	1.00–1.02	0.22	1.01	0.98–1.04	0.53

*Adjusted for study site using random effects.
**Refers to maternal HIV-related symptoms in pregnancy in the PSD and NSHPC, and to CD4 count <200 cells/μl in the ECS.

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n=19,585 (1990-2006)
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Study						
PSD	1.00			1.00		
ECS	0.92	0.79–1.06	0.24	1.03	0.79–1.35	0.82
NSHPC						0.55
Race/ethnici						
White						
Black						0.002
Other/Hispani						0.07
Region of birth						
Within study region	1.00			1.00		
Outside study region	0.77	0.69–0.86	<0.001	0.71	0.59–0.87	0.001
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**Refers to maternal HIV-related symptoms in pregnancy in the PSD and NSHPC, and to CD4 count <200 cells/μl in the ECS.

aOR=1.49, 95% CI: 1.19-1.87 for combination ART vs. monotherapy (AZT primarily)

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Table 3. Univariate and Multivariate Odds Ratios for Preterm Delivery Among HIV-Infected Women

Risk Factor	Number of PTD (%)	Unadjusted OR (95% CI)[a]	Continued HAART vs Others (N = 8725) Adjusted OR (95% CI)[b]	HAART Initiation vs ZDV Initiation (N = 4653) Adjusted OR (95% CI)[c]
Marital status				
Single/widowed/divorced	1861/7813 (23.8)	1.4 (1.2–1.6)	1.4 (1.2–1.7)	1.3 (.9–1.9)
Married	176/955 (18.4)			
Educational status[d]				
None or primary	412/1540 (26.8)	1.2 (1.1–1.4)	1.2 (1.0–1.3)	.8 (.7–1.1)
Secondary or tertiary	1583/6992 (22.6)			
History of past adverse outcome[e]				
Yes	359/1125 (31.9)	1.7 (1.5–2.0)	1.6 (1.4–1.9)	1.4 (1.1–1.8)
No	901/4167 (21.6)			
Smoking				
Yes	52/158 (32.9)	1.6 (1.1–2.2)	1.4 (1.0–2.1)	1.8 (1.0–3.0)
No or unknown	2092/8907 (23.5)			
Maternal hypertension in pregnancy[f]				
Yes	405/1516 (26.7)	1.3 (1.2–1.5)	1.4 (1.2–1.5)	1.2 (.9–1.4)
No	1512/7087 (21.3)			
Anemia in pregnancy[g]				
Yes	682/3004 (22.7)	5.8 (4.7–7.2)	…	4.1 (3.0–5.7)
No	102/2128 (4.8)			
$CD4^+$ cell count ≤200 μL				
Yes	110/549 (20.0)	1.1 (.9–1.3)	1.1 (.9–1.4)	1.0 (.7–1.3)
No	714/3768 (18.9)			
Unknown	1320/4748 (27.8)			
Continued HAART in pregnancy[b]				
Continued HAART	543/2050 (26.5)	1.2 (1.1–1.4)	1.2 (1.1–1.4)	…
All others	1515/6676 (22.7)			
Initiated HAART in pregnancy[c]				
Initiated HAART	177/892 (19.8)	1.5 (1.2–1.8)	…	1.4 (1.2–1.8)
Initiated ZDV	533/3762 (14.2)			

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History of past adverse outcome[e]				
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No	901/4167 (21.6)			
Smoking				
Yes	52/158 (32.9)	1.6 (1.1–2.2)	1.4 (1.0–2.1)	1.8 (1.0–3.0)
No or unknow				
Maternal hyperte				
Yes				9–1.4)
No				
Anemia in pregnancy[g]				
Yes	682/3004 (22.7)	5.8 (4.7–7.2)	…	4.1 (3.0–5.7)
No	102/2128 (4.8)			
CD4$^+$ cell count ≤200 μL				
Yes	110/549 (20.0)	1.1 (.9–1.3)	1.1 (.9–1.4)	1.0 (.7–1.3)
No	714/3768 (18.9)			
Unknown	1320/4748 (27.8)			
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Continued HAART	543/2050 (26.5)	1.2 (1.1–1.4)	1.2 (1.1–1.4)	…
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Initiated HAART in pregnancy[c]				
Initiated HAART	177/892 (19.8)	1.5 (1.2–1.8)	…	1.4 (1.2–1.8)
Initiated ZDV	533/3762 (14.2)			

aOR=1.4, 95% CI: 1.2-1.8 for combination ART vs. AZT monotherapy

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Table 2. Association Between Antiretroviral Therapy and Preterm Birth (Overall Study)

Therapy Type	Total No.	Premature Births, %	Bivariable Analysis (n = 11 377)			Multivariable Analysis (n = 10 402)		
			OR	95% CI	*P*	aOR	95% CI	*P*
ARV therapy					<.001			<.001
Monotherapy	2975	9.6	1			1		
Dual therapy	1664	11.3	1.27	(0.99–1.63)		1.24	(0.96–1.60)	
HAART	6738	14.7	1.92	(1.59–2.30)		1.69	(1.38–2.07)	
Initiation of ARV					<.001			.001
Before conception	3893	15.9	1.66	(1.43–1.93)		1.31	(1.11–1.55)	
During pregnancy	7413	11.2	1			1		
Missing	71	22.5						
Geographic origin					.03			.12
Mainland France	2599	12.9	1			1		
Sub-Saharan Africa	6661	12.3	0.92	(0.77–1.11)		1.00	(0.82–1.23)	
Other	1999	14.9	1.21	(0.96–1.52)		1.24	(0.97–1.58)	
Missing	118	13.6						
Maternal age, years					<.001			.05
<25	1398	11.4	1			1		
25–34	6842	11.9	1.12	(0.88–1.41)		0.91	(0.72–1.16)	
≥35	3116	15.5	1.67	(1.29–2.15)		1.12	(0.86–1.47)	
Missing	21	38.1						
Intravenous drug use (past or active)					.001			<.001
Yes	661	17.4	1.60	(1.20–2.13)		1.78	(1.30–2.45)	
No	10 568	12.6	1			1		
Missing	148	18.2						
CD4 cell count, cells/mL					<.001			.001
≥500	4483	11.5	1			1		
350–500	2787	12.2	1.12	(0.93–1.34)		1.05	(0.87–1.27)	
200–350	2313	13.5	1.26	(1.04–1.52)		1.17	(0.96–1.43)	
<200	1069	16.6	1.74	(1.26–2.22)		1.64	(1.28–2.11)	
Missing	725	17.1						

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Missing	71	22.5						
Geographic origin					.03			.12
Mainland France	2599	12.9	1			1		
Sub-Saharan Africa	6661	12.3	0.92	(0.77–1.11)		1.00	(0.82–1.23)	
Other	1999	14.9	1.21	(0.96–1.52)		1.24	(0.97–1.58)	
Missing								
Maternal age, years								.05
<25								
25–34								
≥35	3116	15.5	1.67	(1.29–2.15)		1.12	(0.86–1.47)	
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Missing	148	18.2						
CD4 cell count, cells/mL					<.001			.001
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<200	1069	16.6	1.74	(1.26–2.22)		1.64	(1.28–2.11)	
Missing	725	17.1						

aOR=1.69, 95% CI: 1.38-2.07 for combination ART vs. AZT monotherapy

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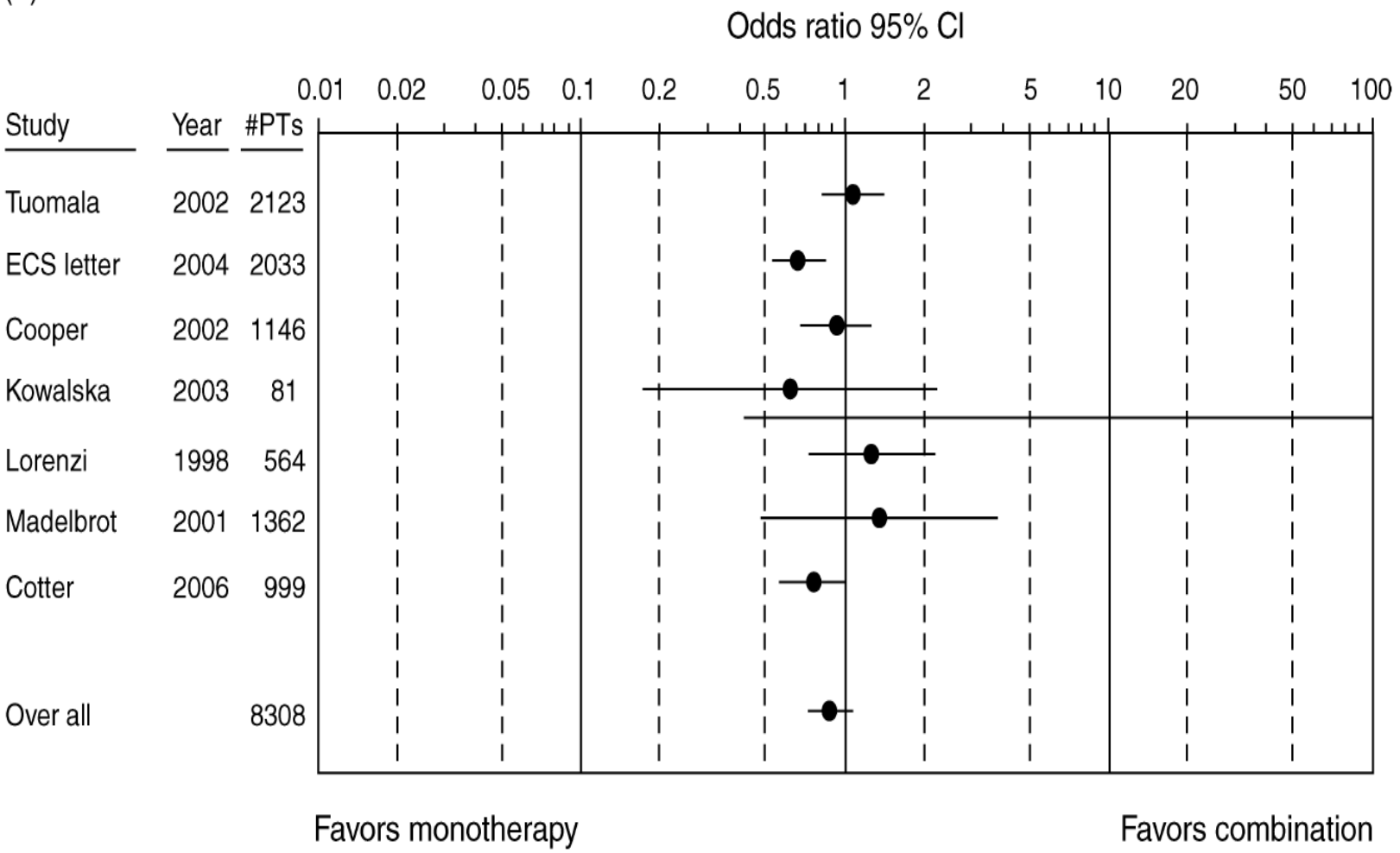
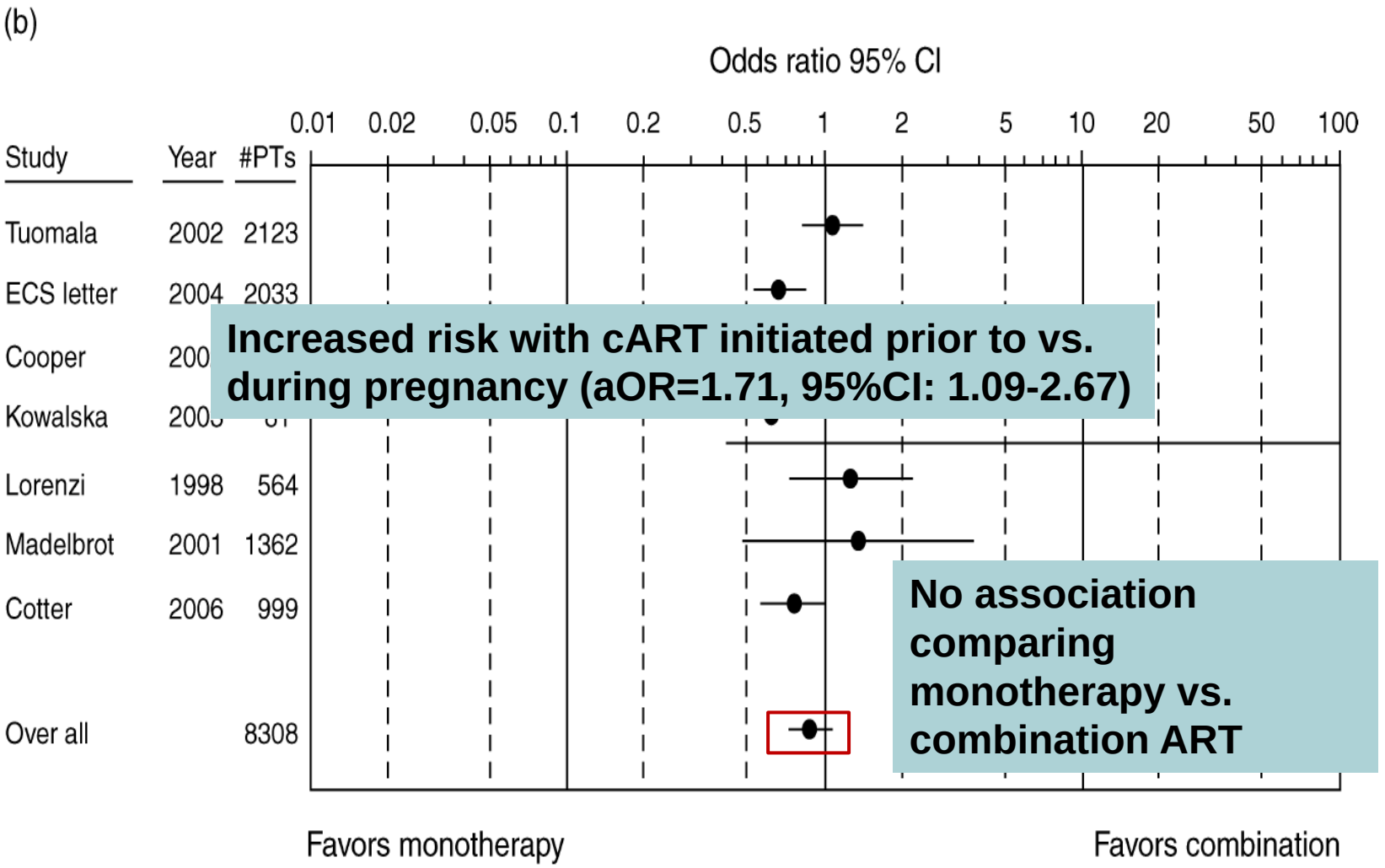
(b)



Kourtis et al. AIDS. 2007



Kourtis et al. AIDS. 2007

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Anemia in pregnancy[g]				
Yes	682/3004 (22.7)	5.8 (4.7–7.2)	…	4.1 (3.0–5.7)
No	102/2128 (4.8)			
$CD4^+$ cell count ≤200 μL				
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Initiated HAART	177/892 (19.8)	1.5 (1.2–1.8)	…	1.4 (1.2–1.8)
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Increased risk with cART initiated prior to vs. during pregnancy (aOR=1.2, 95%CI: 1.1-1.4)

Chen J et al . JID. 2012

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Other							-1.58)	
Missing								
Maternal age, ye								.05
<25								
25–34	6842	11.9	1.12	(0.88–1.41)		0.91	(0.72–1.16)	
≥35	3116	15.5	1.67	(1.29–2.15)		1.12	(0.86–1.47)	
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Missing	725	17.1						

Increased risk with cART initiated prior to vs. during pregnancy (aOR=1.31, 95%CI: 1.11-1.55)

Sibiude J et al. CID 2012

U.S. PHACS SMARTT Cohort (n=1869)

Table 3. Associations of First Trimester Exposures to Combination Antiretroviral (ARV) Regimens Including Protease Inhibitors (PIs), Nonnucleoside Reverse-Transcriptase Inhibitors (NNRTIs), and ≥3 Nucleoside Reverse-Transcriptase Inhibitors (NRTIs) With Preterm Birth and Small for Gestational Age (SGA)

Outcome, First-Trimester Combination ART Regimen	Unadjusted Models		Adjusted Models[a]	
	OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Preterm birth				
Contained PI	1.43 (1.11–1.85)	.006	1.55 (1.16–2.07)	.003
Contained NNRTI	1.26 (.77–2.06)	.37	1.34 (.78–2.30)	.28
Contained ≥3 NRTIs	0.75 (.35–1.60)	.45	0.84 (.37–1.91)	.68
None in first trimester	1.00 (reference)		1.00 (reference)	
Spontaneous preterm birth				
Contained PI	1.40 (1.00–1.95)	.048	1.59 (1.10–2.30)	.014
Contained NNRTI	1.25 (.66–2.36)	.50	1.42 (.72–2.81)	.31
Contained ≥3 NRTIs	0.68 (.24–1.92)	.47	0.66 (.20–2.18)	.49
None in first trimester	1.00 (reference)		1.00 (reference)	
SGA				
Co				
Contained NNRTI	1.19 (.60–2.37)	.62	1.17 (.54–2.54)	.70
Contained ≥3 NRTIs	1.05 (.41–2.69)	.92	0.99 (.34–2.86)	.99
None in first trimester	1.00 (reference)		1.00 (reference)	

For both overall preterm birth and spontaneous preterm birth, PI-based ART vs. no ARV in 1st trimester associated with preterm birth

Watts et al. JID. 2013

PI exposure					
Cotter et al (2006)	US	Registry	1337	PI-based cART vs. non PI-based cART	Increased risk preterm birth (OR=1.8, 95%CI: 1.1-3.0) for PI vs. non PI-based
Schulte et al (2007)	US (PSD)	Registry	8793	PI-based cART vs. dual therapy ART	Increased risk preterm birth (OR=1.21, 95%CI: 1.04-1.40)
Grosch-Woerner et al (2008)	Germany	Cohort	183	PI-based cART vs. AZT monotherapy	Increased risk preterm birth (OR=3.4, 95%CI: 1.1-10.2) with PI-based cART
Szyld et al (2006)	Latin America (NISDI)	Cohort	681	PI- vs. NNRTI- vs. 1-2 NRTI-based ART	No increased risk of preterm birth (OR=1.1, 95%CI: 0.5-2.8 for PI; OR=0.6, 95%CI: 0.2-1.7 for NNRTI)
Shapiro et al (2010)	Botswana	RCT	709	PI- vs. triple NRTI- vs NNRTI- based ART	Increased rate preterm birth in PI arm (23% vs. 15% vs. 10%)
Watts et al (2013)	US (PHACS)	Cohort	1869	1st trimester PI vs. NNRTI vs.≥3 NRTIs-based ART	Increased risk preterm birth with 1st trimester PI compared to no 1st trimester ARV use (OR=1.55, 95%CI: 1.16-2.07)
Kourtis et al (AIDS 2007)	Multiple	Meta analysis	11,224	PI-based vs. non-PI based	Increased risk with PI vs. non-PI based cART (aOR=1.35, 95%CI: 1.08-1.70)
Mesfin et al (Reproduc Health 2016)	Multiple	Meta analysis	23.490	PI-based vs. non PI-based	Increased risk with PI vs. non PI-based cART (aOR=1.32, 95%CI: 1.04-1.59)
Fowler et al (2016 NEJM)	Multiple PROMISE	RCT	3490	AZT-based ART (AZT/3TC/Lop/r) vs. AZT monotherapy	Increased risk AZT/3TC/Lop/r vs. AZT monotherapy (20.5% vs. 13.1%, p<0.001)
Koss et al (JAIDS 2014)	Uganda PROMOTE	RCT	356	Lop/r-based ART vs. EFV-based ART	No assoc with preterm birth when comparing Lop/r to EFV-based ART (OR=1.12, 95%CI: 0.63-2.00)
Zash et al (CROI 2017)	Botswana	Observational	5087	1st trimester TDF/FTC/Lop/r vs. TDF/FTC/EFV 1st trimester AZT/3TC/Lop/r vs. TDF/FTC/EFV	Increased risk for preterm and very preterm (<32 wks) for AZT/3TC/Lop/r vs. TDF/FTC/EFV; increased risk of preterm birth comparing TDF/FTC/Lop/r vs. TDF/FTC/EFV did not reach statistical significance but trended in same direction

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Shapiro et al (2010)	Botswana	RCT	709	PI- vs. triple NRTI- vs NNRTI- based ART	Increased rate preterm birth in PI arm (23% vs. 15% vs. 10%)
Watts et al (2013)	US (PHACS)	Cohort	1869	1st trimester PI vs. NNRTI vs.≥3 NRTIs-based ART	Increased risk preterm birth with 1st trimester PI compared to no 1st trimester ARV use (OR=1.55, 95%CI: 1.16-2.07)
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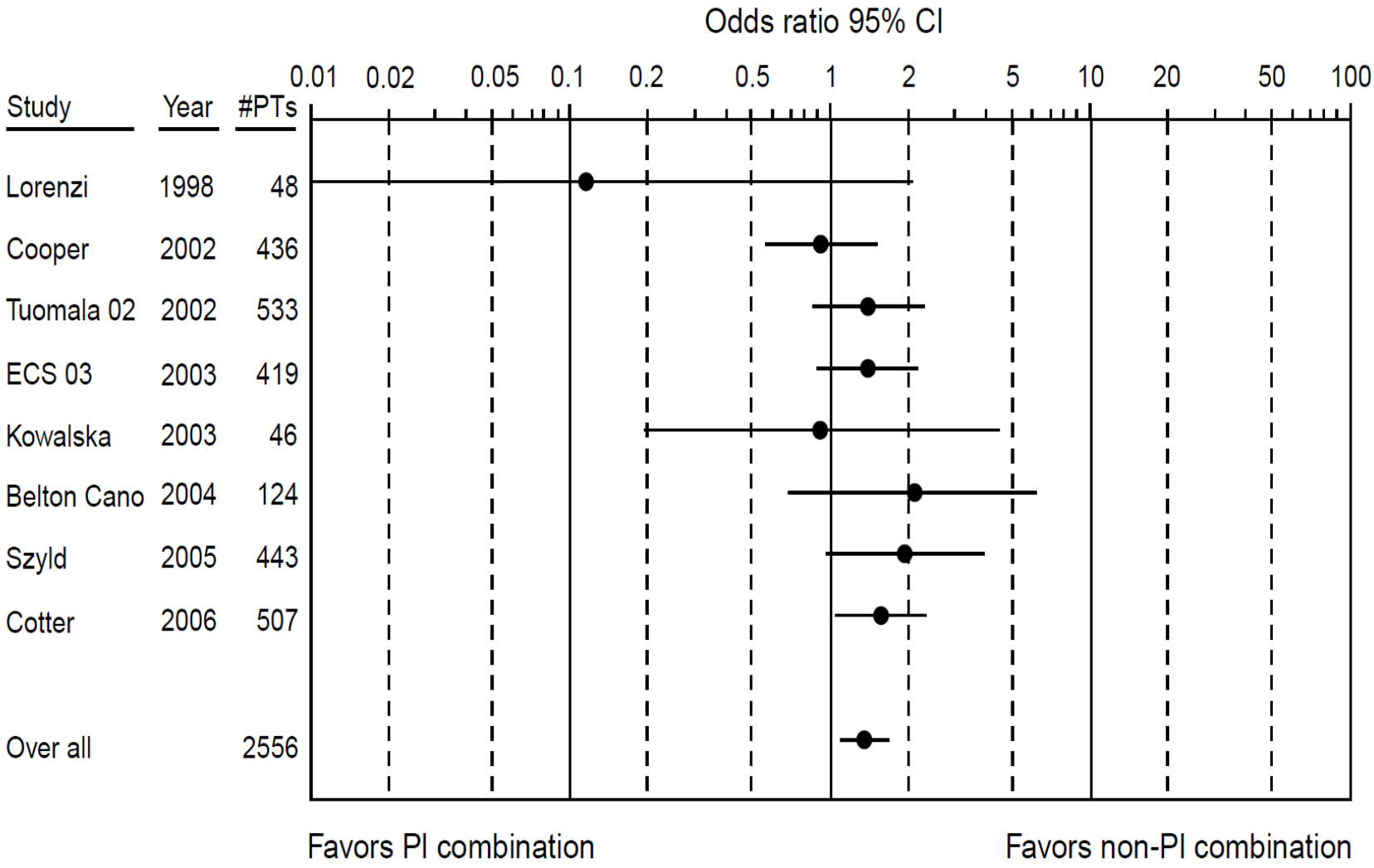
Zash et al (CROI 2017)	Botswana	Observational	5087	TDF/FTC/Lop/r vs. TDF/FTC/EFV AZT/3TC/Lop/r vs. TDF/FTC/EFV	Increased risk for preterm and very preterm (<32 wks) for AZT/3TC/Lop/r vs. TDF/FTC/EFV; increased risk of preterm birth comparing TDF/FTC/Lop/r vs. TDF/FTC/EFV did not reach statistical significance but trended in same direction

Meta-analysis (n=2556)



Kourtis et al. AIDS. 2007

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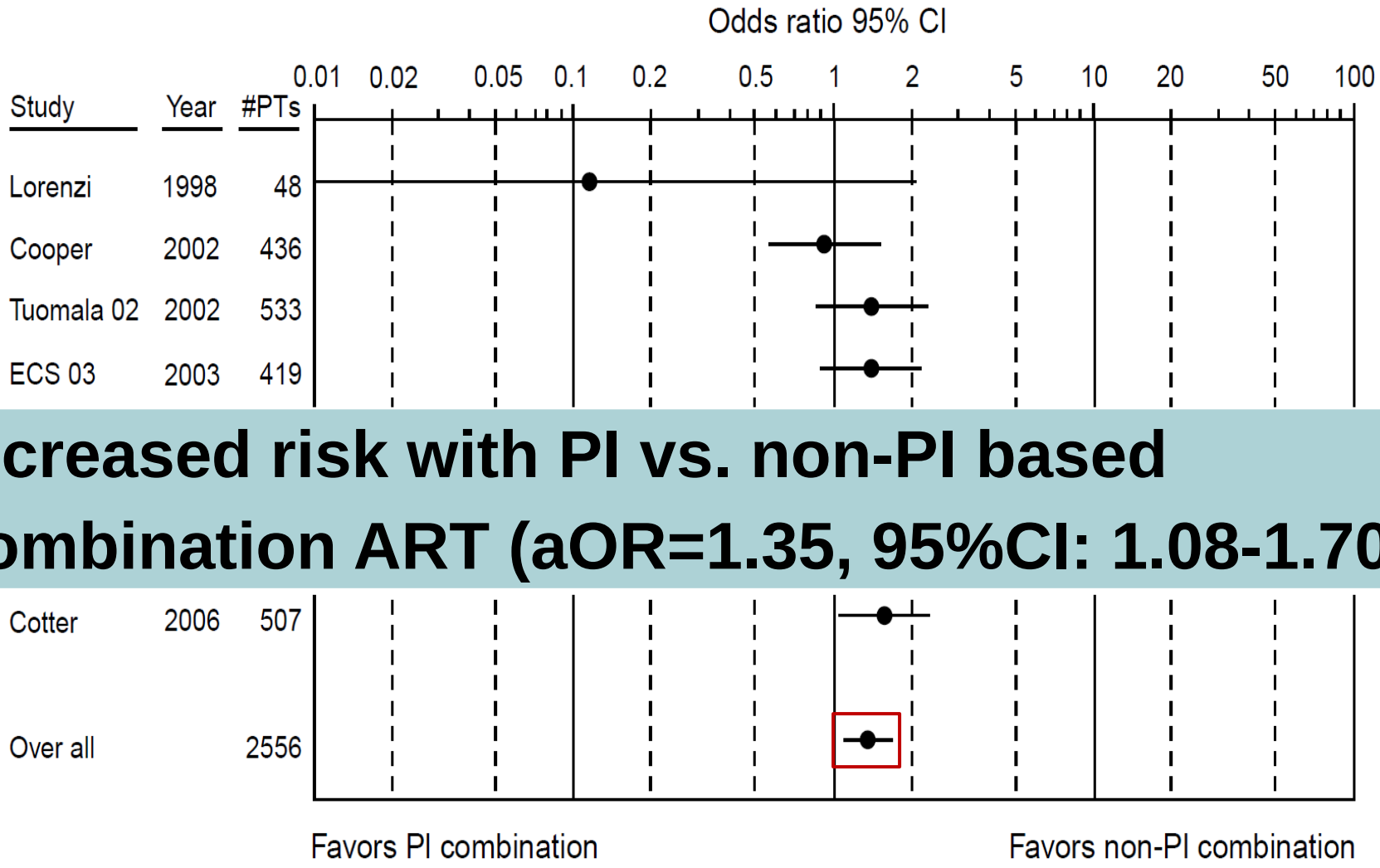
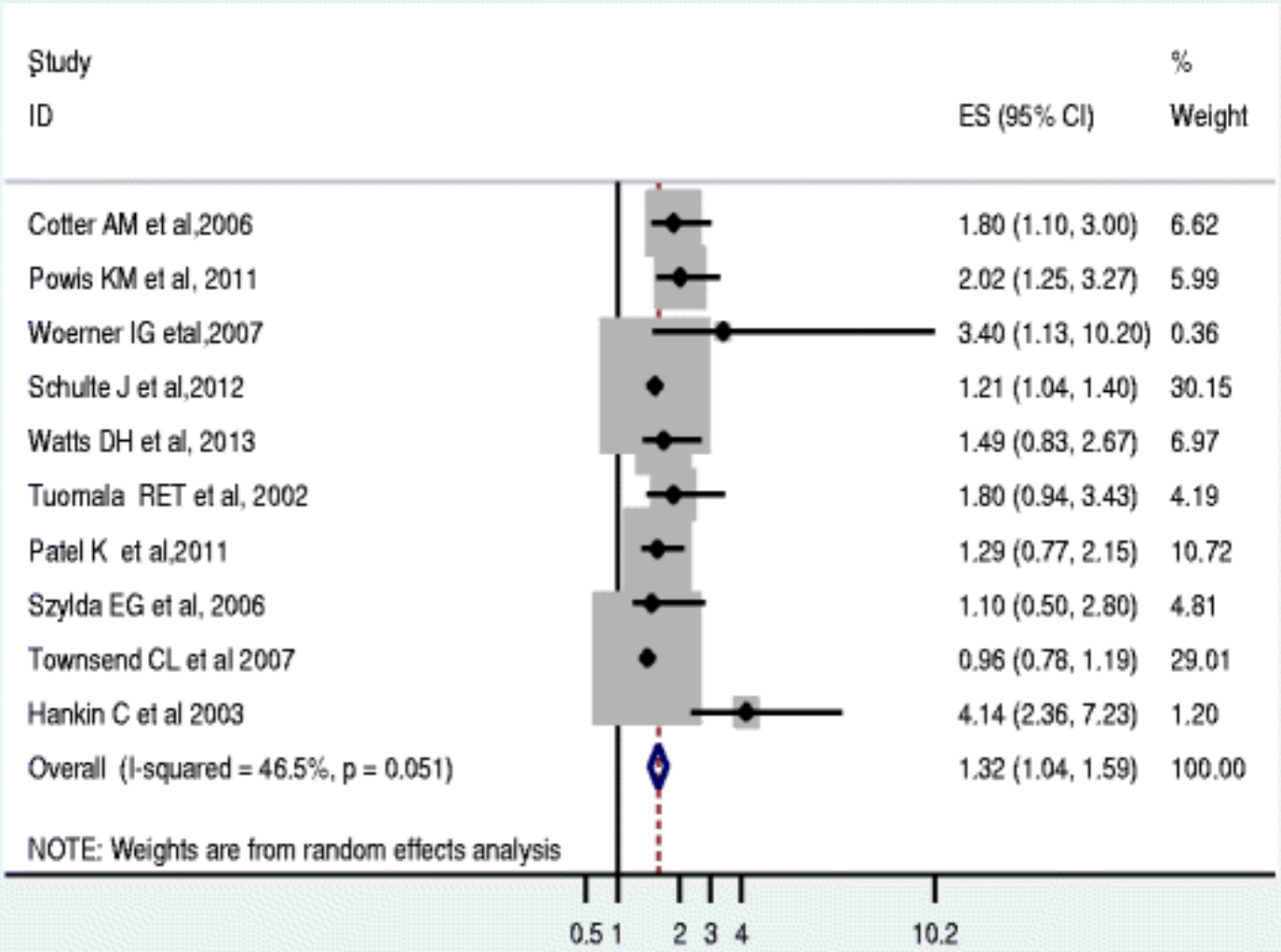


Increased risk with PI vs. non-PI based combination ART (aOR=1.35, 95%CI: 1.08-1.70)

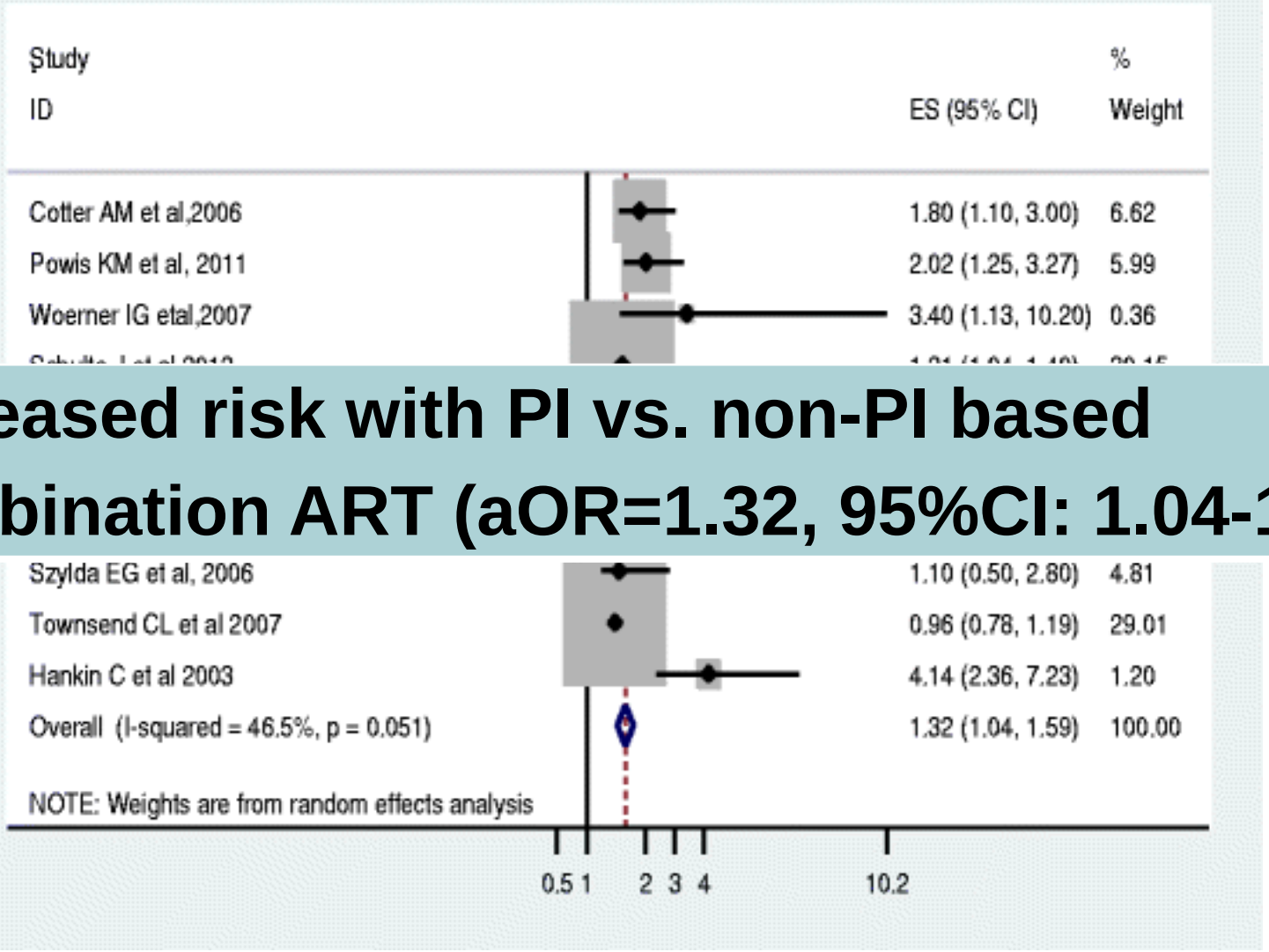
Kourtis et al. AIDS. 2007

Meta-analysis



Mesfin Y et al. Reprod Health. 2016

Meta-analysis



Increased risk with PI vs. non-PI based combination ART (aOR=1.32, 95%CI: 1.04-1.59)

Mesfin Y et al. Reprod Health. 2016

Table 3. Maternal Safety and Pregnancy Outcomes, including Infant Deaths, through Week 1 Post Partum.*

Outcome	Antepartum Randomization Group			P Value		
	ZDV Alone	ZDV-Based ART	TDF-Based ART	ZDV Alone vs. ZDV-Based ART	ZDV Alone vs. TDF-Based ART	ZDV-Based ART vs. TDF-Based ART
	number/total number (percent)					
Maternal adverse events						
Periods 1 and 2: ZDV alone vs. ZDV-based ART						
Any grade ≥2 adverse event†	261/1510 (17.3)	318/1505 (21.1)	—	0.008		
Grade ≥2 abnormal blood chemical value	19/1510 (1.3)	88/1505 (5.8)	—	<0.001		
Period 2 only: all three groups						
Any grade ≥2 adverse event†	59/393 (15.0)	61/385 (15.8)	60/380 (15.8)		0.77	>0.99
Grade ≥2 abnormal blood chemical value	3/392 (0.8)	18/385 (4.7)	11/380 (2.9)		0.03	0.26
Adverse pregnancy outcomes						
Periods 1 and 2: ZDV alone vs. ZDV-based ART						
Any adverse outcome‡	389/1414 (27.5)	563/1407 (40.0)	—	<0.001		
Low birth weight: <2500 g	161/1347 (12.0)	306/1332 (23.0)	—	<0.001		
Preterm delivery: <37 wk	185/1411 (13.1)	288/1406 (20.5)	—	<0.001		
Period 2: all three groups						
Any adverse outcome‡	91/334 (27.2)	123/328 (37.5)	111/320 (34.7)		0.04	0.46
Low birth weight: <2500 g	28/315 (8.9)	65/319 (20.4)	51/301 (16.9)		0.004	0.30
Preterm delivery: <37 wk	46/341 (13.5)	68/346 (19.7)	62/335 (18.5)		0.09	0.77

Fowler et al. NEJM. 2016.

Table 3. Maternal Safety and Pregnancy Outcomes, including Infant Deaths, through Week 1 Post Partum.*

Outcome	Antepartum Randomization Group			P Value		
	ZDV Alone	ZDV-Based ART	TDF-Based ART	ZDV Alone vs. ZDV-Based ART	ZDV Alone vs. TDF-Based ART	ZDV-Based ART vs. TDF-Based ART
	number/total number (percent)					
Maternal adverse events						
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Low birth weight: <2500 g	28/315 (8.9)	65/319 (20.4)	51/301 (16.9)		0.004	0.30
Preterm delivery: <37 wk	46/341 (13.5)	68/346 (19.7)	62/335 (18.5)		0.09	0.77

Fowler et al. NEJM. 2016.

Severe adverse pregnancy outcomes						
Periods 1 and 2: ZDV alone vs. ZDV-based ART						
Any severe adverse outcome§	83/1399 (5.9)	99/1385 (7.1)	—	0.22		
Very preterm delivery: <34 wk	37/1411 (2.6)	44/1406 (3.1)	—	0.43		
Infant deaths through wk 1	28/1432 (2.0)	17/1419 (1.2)	—	0.13		
Period 2 only: all three groups						
Any severe adverse outcome§	22/329 (6.7)	14/322 (4.3)	29/314 (9.2)		0.25	0.02
Very preterm delivery: <34 wk	11/341 (3.2)	9/346 (2.6)	20/335 (6.0)		0.10	0.04
Infant deaths through wk 1	11/349 (3.2)	2/346 (0.6)	15/341 (4.4)		0.43	0.001

Fowler et al. NEJM. 2016.

Adjusted Relative Risk of Preterm Delivery in Women on combination ART prior to conception in Botswana

	TDF FTC EFV (n=2503)	TDF FTC NVP (n=775)	AZT 3TC NVP (n=1403)	TDF FTC Lop/r (n=237)	AZT 3TC Lop/r (n=169)
Preterm (<37 wks)	REF	0.9 (0.8-1.1)	1.2 (1.0 – 1.3)	1.1 (0.9-1.4)	1.4 (1.1-1.8)
Very Preterm (<32 wks)	REF	1.2 (0.8-1.8)	1.4 (1.1-2.0)	1.4 (0.8-2.5)	2.2 (1.3-3.8)

Adjusted for maternal age, education, gravida

Zash R et al. CROI 2017 Seattle. Abstract #25.

Adjusted Relative Risk of Preterm Delivery in Women on combination ART prior to conception in Botswana

	TDF FTC EFV (n=2503)	TDF FTC NVP (n=775)	AZT 3TC NVP (n=1403)	TDF FTC Lop/r (n=237)	AZT 3TC Lop/r (n=169)
Preterm (<37 wks)	REF (22%)	0.9 (0.8-1.1) (19%)	1.2 (1.0 – 1.3) (25%)	1.1 (0.9-1.4) (24%)	1.4 (1.1-1.8) (30%)
Very Preterm (<32 wks)	REF (4.1%)	1.2 (0.8-1.8) (5.2%)	1.4 (1.1-2.0) (5.9%)	1.4 (0.8-2.5) (5.2%)	2.2 (1.3-3.8) (9.0%)

Adjusted for maternal age, education, gravida

5.2% VPTD 9.0% VPTD

PROMISE 6.0% VPTD 2.6% VPTD

Zash R et al. CROI 2017 Seattle. Abstract #25.

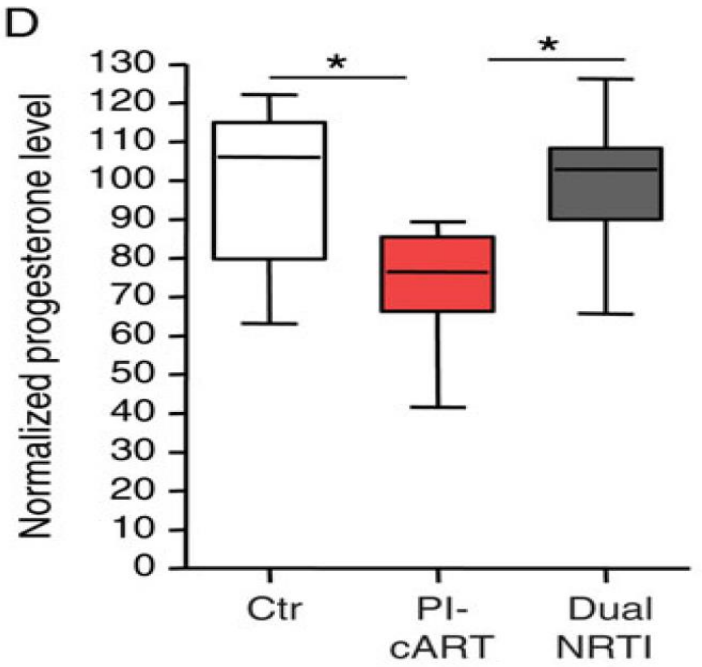
MAJOR ARTICLE

HIV Protease Inhibitor Use During Pregnancy Is Associated With Decreased Progesterone Levels, Suggesting a Potential Mechanism Contributing to Fetal Growth Restriction

Eszter Papp,[1] Hakimeh Mohammadi,[1] Mona R. Loutfy,[2,3] Mark H. Yudin,[3,4] Kellie E. Murphy,[3,5] Sharon L. Walmsley,[1,3] Rajiv Shah,[4] Jay MacGillivray,[4] Michael Silverman,[3,6] and Lena Serghides[1,2]

[1]Toronto General Research Institute, University Health Network, [2]Women's College Research Institute, Women's College Hospital, [3]University of Toronto, [4]St. Michael's Hospital, and [5]Mount Sinai Hospital, Toronto; and [6]Lakeridge Health, Rouge Valley Hospital, Ajax, Canada

In pregnant mice, PI-based ART resulted in significantly lower progesterone levels



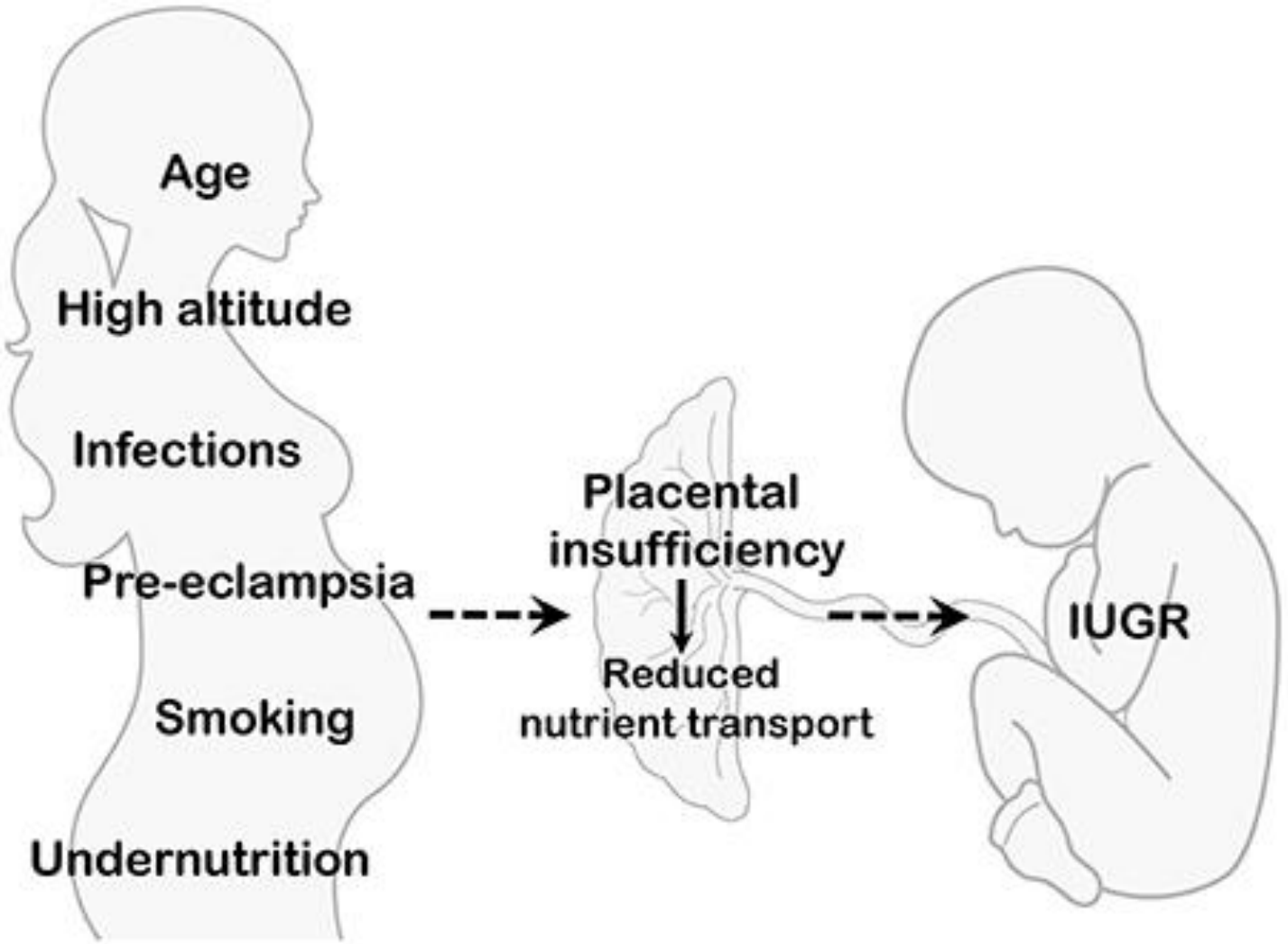
Progesterone's Role in Preterm Birth

- Implantation and placental formation early in pregnancy
- Maintains uterine quiescence later in pregnancy
- Anti-inflammatory effects which may improve tolerance of fetus allograft
- Supplementation in general population may reduce risk of preterm delivery in those with prior preterm delivery

Mendelson CR et al. Mol Endocrinol. 2009
Lachelin GCL et al. BJOG. 2009.
Johnson JW et al. NEJM. 1975.
Hassan SS et al. Ultrasound Obstet Gynecol. 2011

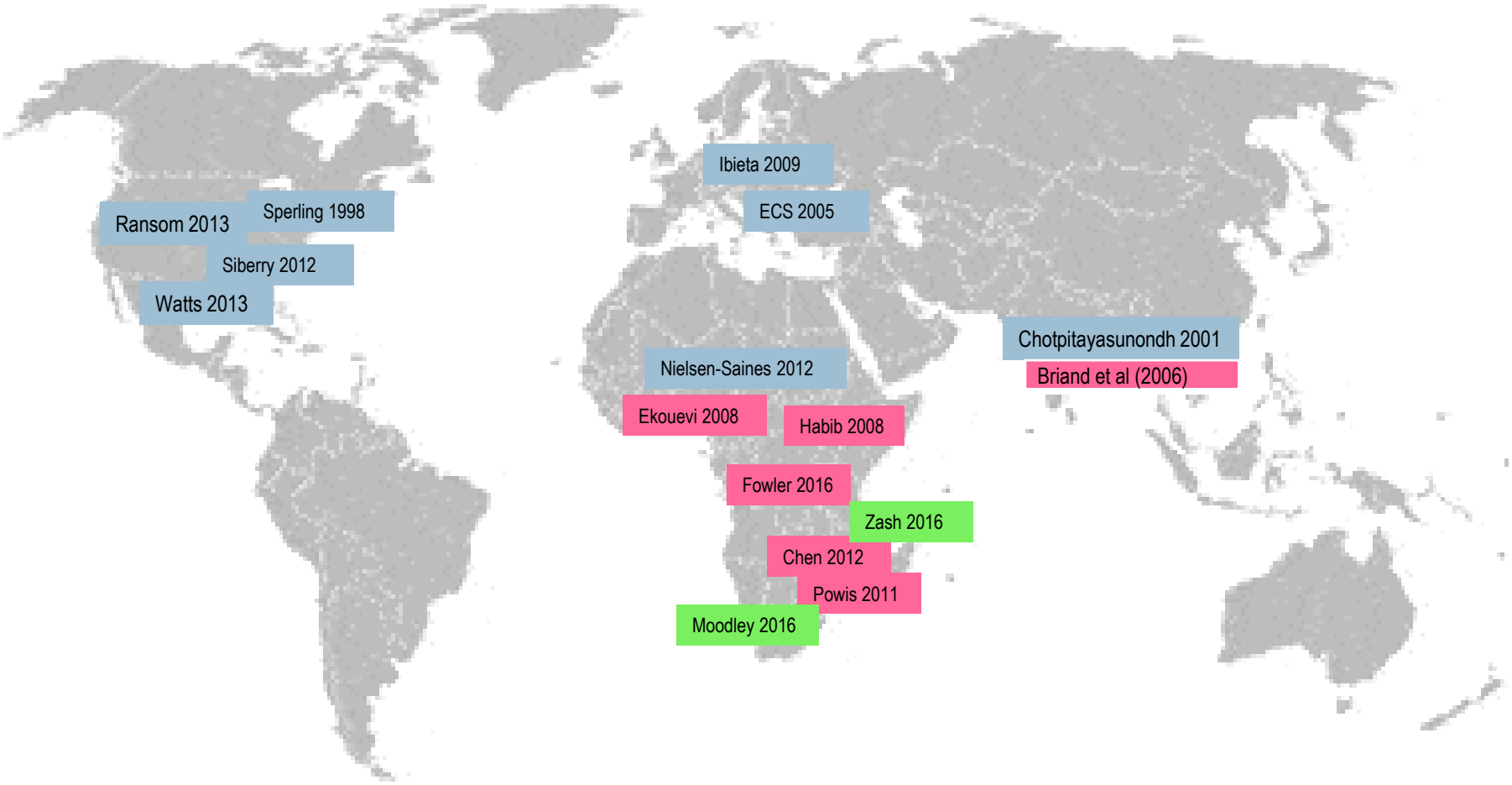
Preterm Birth and HIV/ART

- **Early studies observed signals for increased preterm birth with use of combination ART, but large heterogeneity in ART regimens**
- **PIs appear to be associated with preterm birth when compared to non-PI ART which mostly include NNRTI-based or NRTI-based.**
- **Few studies evaluating newer PIs or INSTIs**
- **Mechanisms by which PIs may affect preterm birth potentially include hormonal pathways via progesterone**



Gaccioli F et al. Frontiers in Physiology. 2016

Major Studies Evaluating Birth Weight Outcomes by Geography and Results



Decreased risk for poor Birth Weight Outcomes (SGA, LBW, Birth Weight Z)

Increased risk for poor Birth Weight Outcomes (SGA, LBW, Birth Weight Z)

No association with Birth Weight Outcomes

RESEARCH ARTICLE Open Access

Improved pregnancy outcomes with increasing antiretroviral coverage in South Africa

Theron Moodley[1], Dhayendre Moodley[2*], Motshedisi Sebitloane[1], Niren Maharaj[1] and Benn Sartorius[3]

Table 4 Small for gestational age overall and for HIV + ve only

All women

Variable	Normal for GA [i]: n (% [ii])	Small for GA [iii]: n (%)	*p*-value [iv]	Bivariate OR [v] (95 % CI)	Multivariable vi OR (95 % CI)	Adj. *p*-value
ART regimen						
Nil ARVs	133 (89.86)	15 (10.14)	0.464	1 (ref)	1 (ref)	
AZT/NVP i, ii	901 (92.51)	73 (7.49)		0.72 (0.40–1.29)	0.37 (0.10–1.45)	0.153
D4T/3TC/NVP iii	824 (90.85)	83 (9.15)		0.89 (0.50–1.59)	0.29 (0.08–1.07)	0.063
EFV/TDF/FTC	1533 (92.02)	133 (7.98)		0.77 (0.44–1.35)	0.25 (0.07–0.87)	0.030

i Gestational Age (GA), *ii* row percentage, *iii* below 10th percentile, *iv* Chi-square, *v* Odds Ratio, *vi* following variables were adjusted for in the multivariable adjusted model, *year* age group, mode of delivery, HIV status

i AZT/NVP vs D4T/3TC/NVP p-value = 0.410, *ii* AZT/NVP vs FTC p-value = 0.521, *iii* D4T/3TC/NVP vs FTC p-value = 0.800, *iv* following variables were adjusted for in the multivariable adjusted model, *year* age group, mode of delivery, HIV status, CD4 (HIV positive mothers only), ART regimen (HIV positive mothers only)

RESEARCH ARTICLE Open Access

Improved pregnancy outcomes with increasing antiretroviral coverage in South Africa

Theron Moodley[1], Dhayendre Moodley[2*], Motshedisi Sebitloane[1], Niren Maharaj[1] and Benn Sartorius[3]

TDF/FTC/EFV vs. no ARVs decreased the risk of SGA (aOR=0.25; 95% CI: 0.07-0.87; *p*=0.03)

d4T/3TC/NVP vs. no ARVs – similar trends (*p*=0.06)

Variable	Normal for GA[i]: n (%)[ii]	Small for GA[iii]: n (%)	*p*-value[iv]	OR[v] (95 % CI)	OR (95 % CI)	Adj. *p*-value[vi]
ART regimen						
Nil ARVs	133 (89.86)	15 (10.14)	0.464	1 (ref)	1 (ref)	
AZT/NVP i, ii	901 (92.51)	73 (7.49)		0.72 (0.40–1.29)	0.37 (0.10–1.45)	0.153
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TABLE 3. Adverse Birth Outcomes Among Women Who Initiated TDF/FTC/EFV Compared With Other ARV Regimens in Pregnancy

	CD4 <350*			CD4 >350*			All CD4 Strata†		
	Initiated Atripla in Pregnancy (N = 231)	Initiated Other 3-Drug ART in Pregnancy‡ (N = 243)	aOR (95% CI)	Initiated Atripla in Pregnancy (N = 335)	Initiated ZDV in Pregnancy (N = 752)	aOR (95% CI)	Initiated Atripla in Pregnancy (N = 1054)	Initiated Any other ARV in Pregnancy (N = 2172)	aOR (95% CI)
SB,§ n (%)	4 (1.7)	12 (4.9)	0.1 (0.01 to 1.0)	9 (2.7)	21 (2.8)	0.9 (0.4 to 2.1)	18 (1.7)	70 (3.2)	0.6 (0.3 to 1.3)
Preterm‖ <37 wks, n (%)	45 (19.5)	48 (19.8)	0.5 (0.2 to 1.2)	60 (17.9)	123 (16.4)	1.1 (0.6 to 2.1)	192 (18.2)	450 (20.7)	0.7 (0.5 to 1.1)
SGA,¶ n (%)									
Botswana norms	24 (10.4)	50 (20.6)	0.5 (0.3 to 1.1)	53 (15.8)	157 (20.9)	0.6 (0.4 to 1.0)	125 (11.9)	459 (21.1)	0.4 (0.3 to 0.6)
WHO norms	35 (15.2)	62 (25.5)	0.5 (0.3 to 0.8)	83 (24.8)	216 (28.7)	0.7 (0.5 to 1.0)	202 (19.2)	602 (27.7)	0.5 (0.4 to 0.7)
Any adverse outcome,# n (%)	61 (26)	97 (40)	0.4 (0.2 to 0.7)	104 (31)	272 (36)	0.4 (0.3 to 0.6)	287 (27)	880 (41)	0.4 (0.3 to 0.6)

Zash et al. JAIDS. 2016

TABLE 3. Adverse Birth Outcomes Among Women Who Initiated TDF/FTC/EFV Compared With Other ARV Regimens in Pregnancy

Risk reduction in SGA comparing TDF/FTC/EFV vs. all other 3-drug ART (aOR=0.5; 95% CI: 0.4-0.7)

Risk reduction in any adverse outcome comparing TDF/FTC/EFV vs. all other 3-drug ART (aOR=0.4; 95% CI: 0.3-0.6)

	CD4 <350*			CD4 >350*			All CD4 Strata†		
SB									.3)
Pre…¶ <37 wks, n (%)									1.1)
SGA,¶ n (%)									
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Any adverse outcome,# n (%)	61 (26)	97 (40)	0.4 (0.2 to 0.7)	104 (31)	272 (36)	0.4 (0.3 to 0.6)	287 (27)	880 (41)	0.4 (0.3 to 0.6)

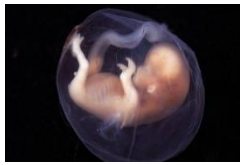
Zash et al. JAIDS. 2016

Adjusted Relative Risk of SGA Infant Outcomes in Women on combination ART prior to conception in Botswana

	TDF FTC EFV (n=2503)	TDF FTC NVP (n=775)	AZT 3TC NVP (n=1403)	TDF FTC Lop/r (n=237)	AZT 3TC Lop/r (n=169)
SGA (<10th percentile)	REF (17%)	1.4 (1.2-1.7) (25%)	1.7 (1.5 – 1.9) (29%)	1.6 (1.3-2.0) (28%)	1.1 (0.8-1.6) (21%)
Very SGA (<3rd percentile)	REF (7.3%)	1.5 (1.2-1.9) (11%)	1.8 (1.4-2.2) (13%)	1.8 (1.3-2.6) (14%)	1.7 (1.1-2.6) (13%)

Adjusted for maternal age, education, gravida

Zash R et al. CROI 2017 Seattle. Abstract #25.



BIRTH

- Hypertensive disorders of pregnancy (Pre-eclampsia/eclampsia, PIH)
- Gestational DM

- Preterm birth
- Birth weight (LBW, SGA)

- Bone
- Mitochondrial Toxicity

TDF/TAF??

Tenofovir and Effects on Bone

- Effects on bone health
- Concern for decreased bone mineral content
- Compromised intrauterine growth and slightly decreased fetal bone porosity in infants born to high dose (30 mg/kg) TDF-treated SIV-infected and –uninfected monkeys

Tarantal et al. JAIDS. 2002.
Siberry et al. CID. 2015

South Africa MCH-ART Study (n=646)

Table 2. Linear Regression Models for Change in Femur Length z Score and Humerus Length z Score[a]

	Change in FLZ		Change in HLZ	
Effect	Coefficient (95% CI)	*P* Value	Coefficient (95% CI)	*P* Value
Model Assessing TDF Exposure as Continuous Variable				
TDF exposure in pregnancy, per 1-wk increment before last US scan	0.00 (−.01 to .01)	.51	0.00 (−.01 to .01)	.40
Model Assessing TDF Exposure as Categorical Variable				
TDF exposure in pregnancy, wk before last US scan				
≥25	0.05 (−.13 to .23)	.56	−0.21 (−.43 to .03)	.07
10–24	0.08 (−.05 to .21)	.23	−0.11 (−.27 to .06	.21
<10	Reference	. . .	Reference	. . .

Jao et al. CID. 2016

South Africa MCH-ART Study (n=646)

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10–24	0.08 (−.05 to .21)	.23	−0.11 (−.27 to .06	.21
<10	Reference	. . .	Reference	. . .

No association between duration of *in utero* TDF exposure and fetal long bone growth

Jao et al. CID. 2016

J Antimicrob Chemother 2016; **71**: 3206–3211
doi:10.1093/jac/dkw268 Advance Access publication 11 July 2016

Journal of Antimicrobial Chemotherapy

Levels of bone markers in a population of infants exposed *in utero* and during breastfeeding to tenofovir within an Option B+ programme in Malawi

Marco Floridia[1]*, Giuseppe Liotta[2], Mauro Andreotti[1], Clementina M. Galluzzo[1], Roberta Amici[1], Haswell Jere[3], Jean-Baptiste Sagno[3], Maria C. Marazzi[4], Ersilia Buonomo[2], Paola Scarcella[2], Sandro Mancinelli[2], Stefano Vella[1], Marina Giuliano[1] and Leonardo Palombi[2]

- **n=136 Infants**
- **Comparison: TDF/3TC/EFV (OPTION B+) vs. d4T or AZT/3TC/NVP**
- **Bone markers:**
- **BAP and C-telopeptide of Type I Collagen at 6 mo, 12 mo**

No differences in bone markers between TDF vs. non-TDF exposed infants

Lower Newborn Bone Mineral Content Associated With Maternal Use of Tenofovir Disoproxil Fumarate During Pregnancy

George K. Siberry,[1] Denise L. Jacobson,[2] Heidi J. Kalkwarf,[3] Julia W. Wu,[4] Linda A. DiMeglio,[5] Ram Yogev,[6] Katherine M. Knapp,[7] Justin J. Wheeler,[8] Laurie Butler,[9] Rohan Hazra,[1] Tracie L. Miller,[10] George R. Seage III,[4] Russell B. Van Dyke,[11] Emily Barr,[12] Mariam Davtyan,[13] Lynne M. Mofenson,[1] and Kenneth C. Rich[14]; for the Pediatric HIV/AIDS Cohort Study

Table 4. Adjusted Differences in Whole-Body Bone Mineral Content in Tenofovir-Exposed Compared With Tenofovir-Unexposed Infants

	Mean Difference (g) in Whole Body Bone Mineral Content (With Head)			
	Unadjusted		Adjusted[a]	
Characteristic	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI)	*P* Value
Primary exposure				
Tenofovir vs no tenofovir exposure	−7.8 (−12.6, −3.1)	.001	−5.3 (−9.5, −1.2)	.013
Maternal characteristics				
Age, per year	0.08 (−.3, .5)	.69	0.04 (−.24, .33)	.77
Did not smoke in pregnancy	2.5 (−3.8, 8.7)	.43	1.1 (−3.4, 5.7)	.62
CD4 count ≥500 cells/mm^3 in 3rd trimester	1.7 (−4.4, 7.8)	.58	. . .	
Viral loa				
Infant cha				
Female				.91
Gestati				.013
Age at dual-energy X-ray absorptiometry, days	0.5 (.2, .9)	.004	0.53 (.23, .82)	.0006
Non-black vs black, non Hispanic	8.7 (3.8, 13.6)	.0006	3.2 (−1.2, 7.6)	.16
Body length (cm)	3.0 (2.3, 3.8)	<.0001	2.4 (1.7, 3.2)	<.0001

Lower mean BMC in TDF vs. non-TDF exposed infants (mean difference= -5.3, *p*=0.013)

PROMISE 1084s substudy

	AZT mono	AZT/3TC/Lop/r	TDF/FTC/Lop/r
Mean LS-BMC	1.73 g	1.64 g	1.72 g
Mean WB-BMC	73.1 g	65.1 g	63.3 g

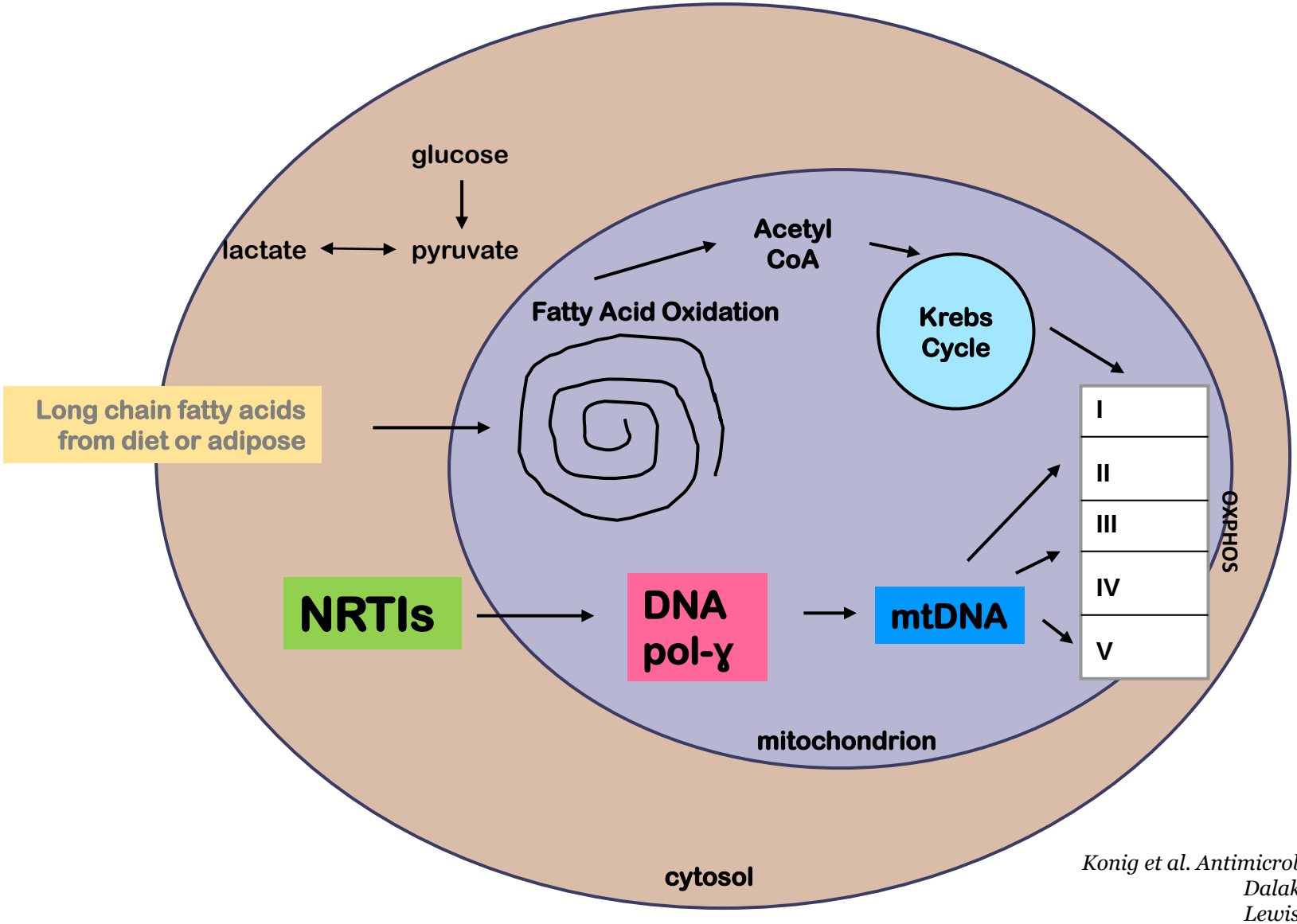
- No differences between AZT/3TC/Lop/r vs. TDF/FTC/Lop/r
- Significantly LOWER mean WB-BMC in

AZT/3TC/Lop/r vs. AZT mono

TDF/FTC/Lop/r vs. AZT mono

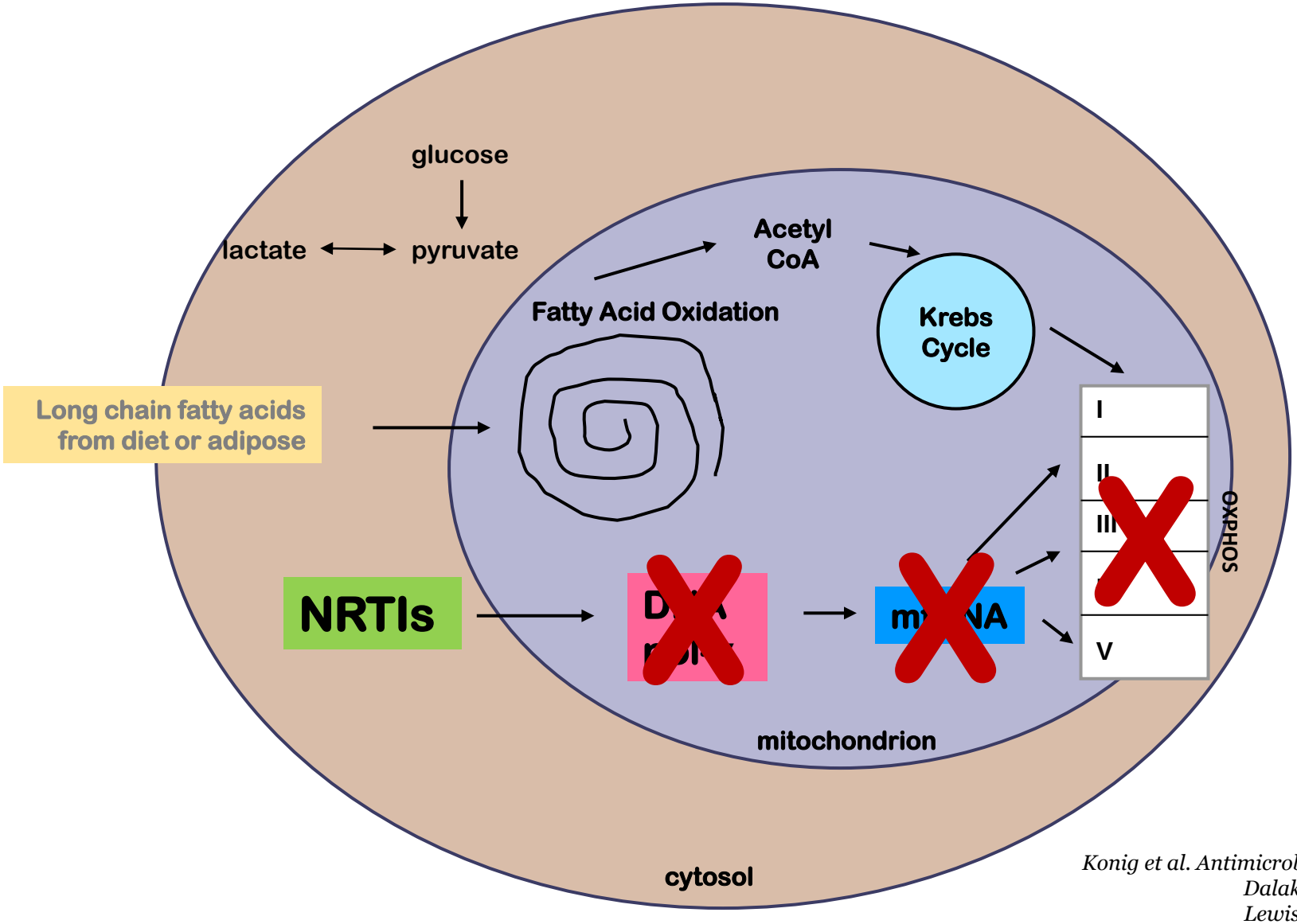
Siberry G et al. CROI 2016 Boston. Abstract #36.

Proposed Mechanism of NRTI Mitochondrial Toxicity



Konig et al. Antimicrob Agents Chem. 1989
Dalakas et al. NEJM 1990
Lewis et al. Circ Res. 1994
Kohler et al. Environ Mol Mutagen. 2007

Proposed Mechanism of NRTI Mitochondrial Toxicity



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In utero HIV/ARV is associated with mitochondrial toxicity

Authors	Study	Sample size	Findings
Poirier et al 2003	WITS	30	Decreased mtDNA
Ross et al 2011	U.S.	46	Abnormal mtDNA levels Decreased Complex II:IV
Gingelmaier et al 2009	Germany	77	Decreased mtDNA Decreased Complex II:IV
Aldrovandi et al 2010	WITS, PACTG 1009	624	Abnormal mtDNA levels
Côté et al 2008	Canada	154	Increased mtDNA levels Abnormal mitochondrial gene expression
McComsey et al 2008	ACTG 5084	136	Increased mtDNA levels
Torres et al 2009	U.S.	108	Increased mitochondrial mutations

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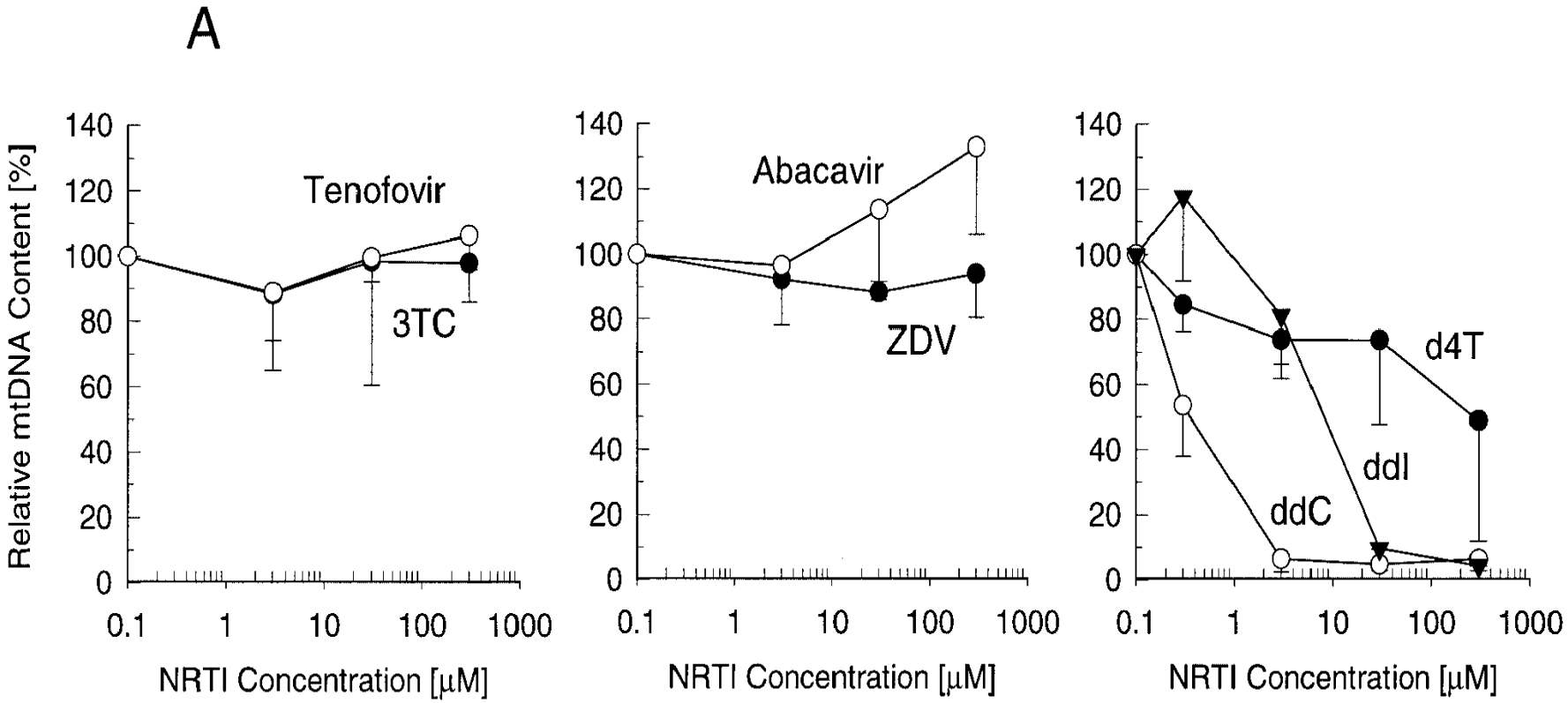
Most commonly recognized NRTI culprits:
d4T
ddI
AZT



Birkhus et al. Antimicrob Agents Chemo. 2002

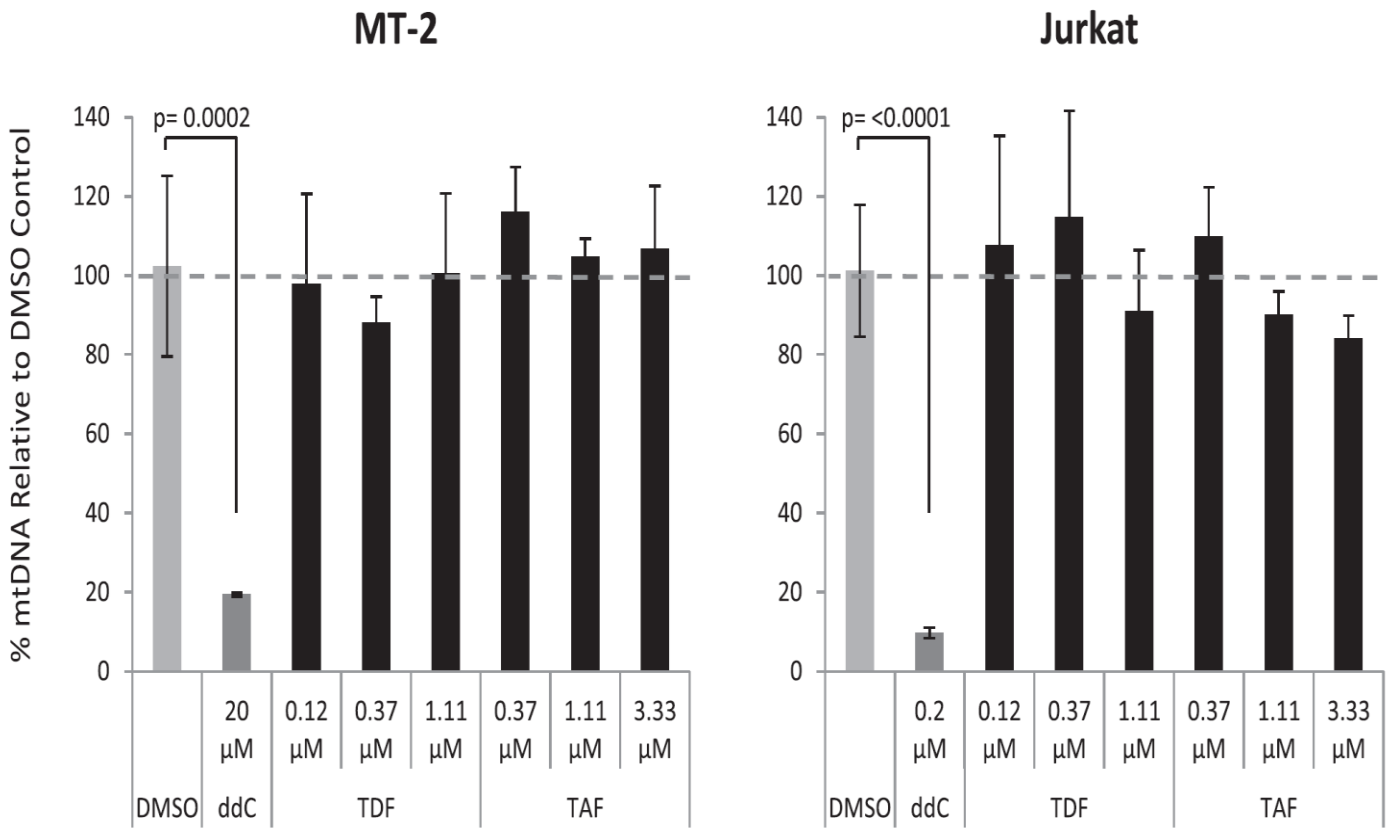


Fig. 3. Effect of ddC, TAF, and TDF on the levels of mtDNA in MT-2 and Jurkat T-cells. Data represent a mean ± SD of at least 3 independent experiments. Paired, two-tailed Student's t-test compared with DMSO control; statistically significant ($p < 0.05$) differences are shown.

TAF does not decrease mtDNA levels

Stray et al. Antimicrob Res. 2017

Some of the “Good” and the “Bad”

- **Combination ART in conjunction with immune reconstitution may play role in increasing rates of hypertensive disorders of pregnancy since 1990**
- **Older PIs may be associated with gestational DM**
- **PI use may be associated with preterm birth outcomes**
- **There is reassuring data on the safety of TDF and potentially TAF in pregnancy with regards to early bone and mitochondrial effects**

What's the Unknown?

- **SAFETY –**
  - ***Which ART regimens have the least adverse effects?***
- **TIMING OF ART IN PREGNANCY –**
  - ***What impact does this have on adverse outcomes?***
- **MONITORING OF HIV-INFECTED PREGNANT WOMEN & THEIR CHILDREN –**
  - ***How and who to target?***
- **MECHANISMS –**
  - ***How much are adverse effects attributable to actual pathophysiology resulting from HIV/ARV and how much can be mitigated by improved antenatal and postnatal care?***
- **NEW ARVs –**
  - ***What about newer drugs –Rilpivirine, Darunavir, Dolutegravir, Cabotegravir?***

pHACS
A Study of the National Institutes of Health

NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development

THANK YOU

CAMEROON BAPTIST CONVENTION HEALTH SERVICES 1975

Mount Sinai

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