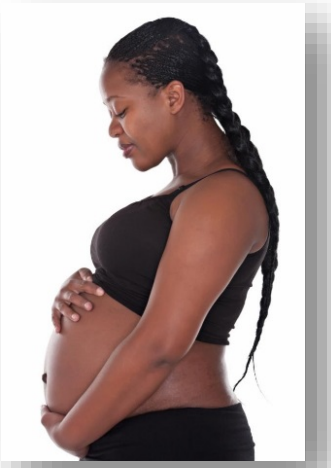
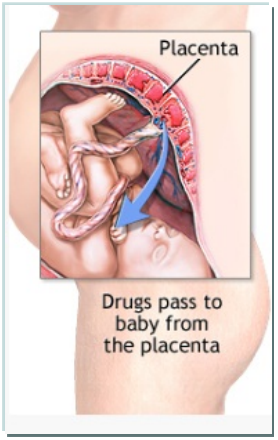




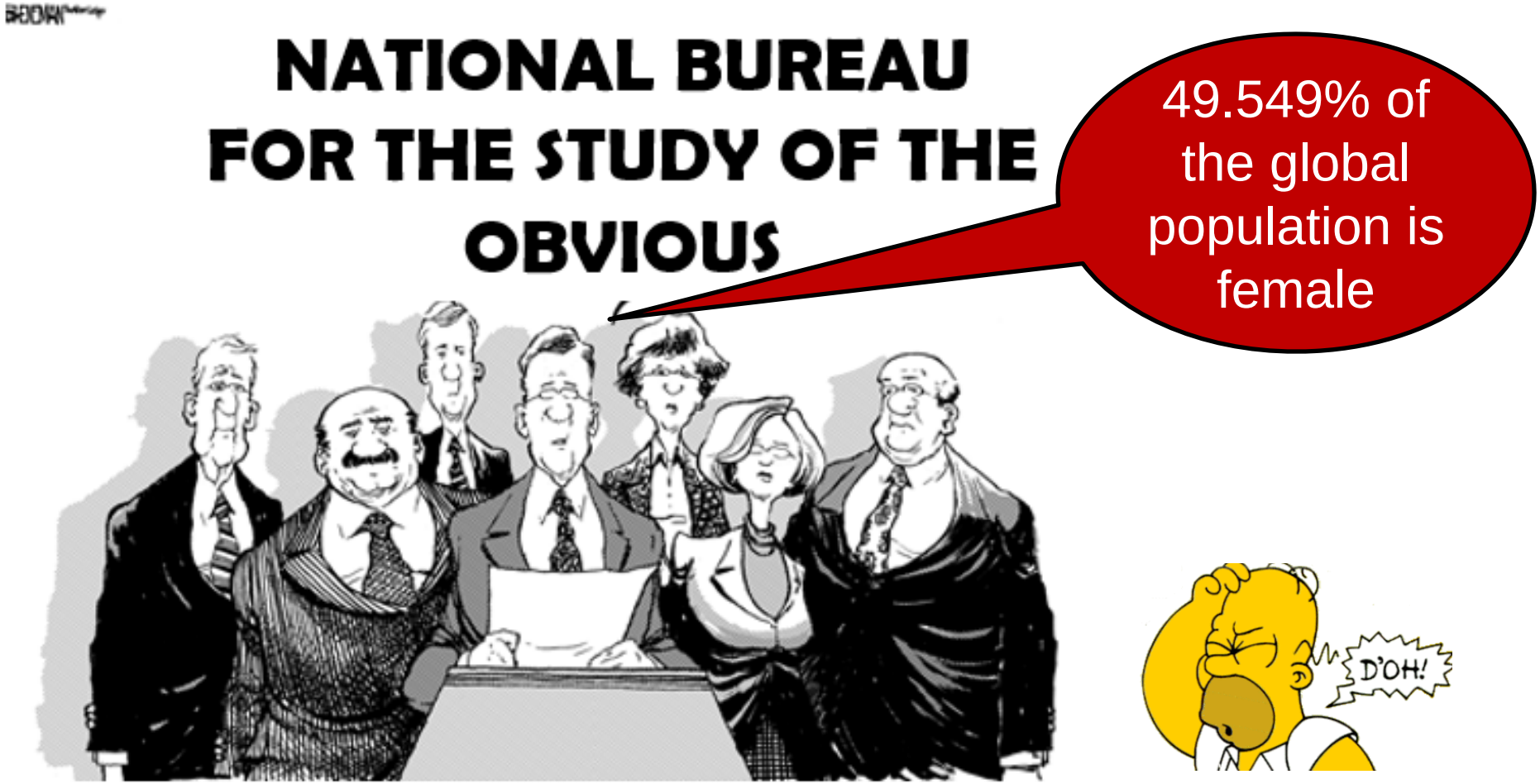
The Critical Need For Data on New Agents in Pregnant and Lactating Women

Lynne M. Mofenson, M.D.
Senior HIV Technical Advisor
Elizabeth Glaser Pediatric AIDS Foundation
March 21, 2017

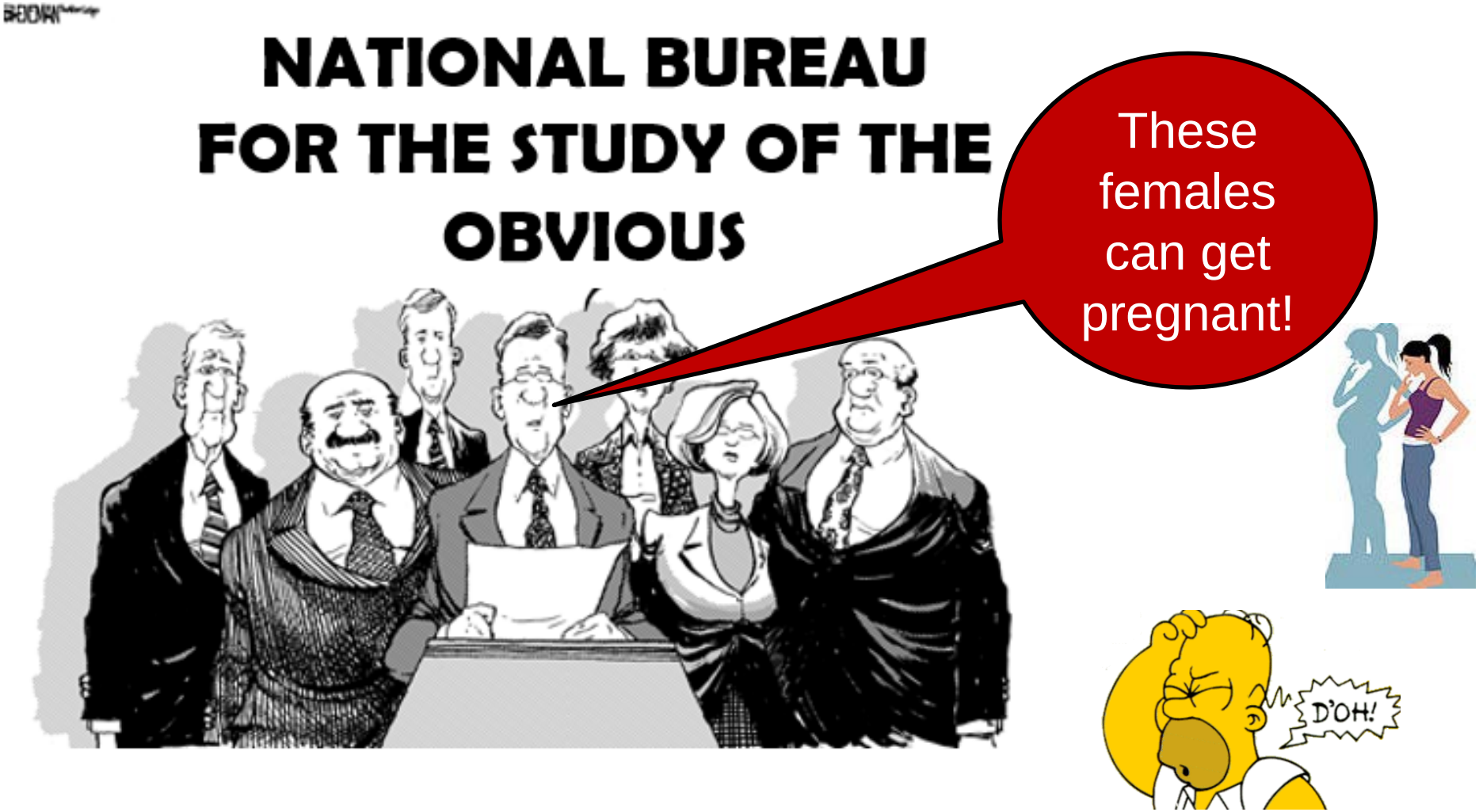
MTN
microbicide trials network

Elizabeth Glaser Pediatric AIDS Foundation
Until no child has AIDS.

Why Do We Need Data on Drugs in Pregnancy/Lactation?



Why Do We Need Data on Drugs in Pregnancy/Lactation?



Why Do We Need Data on Drugs in Pregnancy/Lactation?

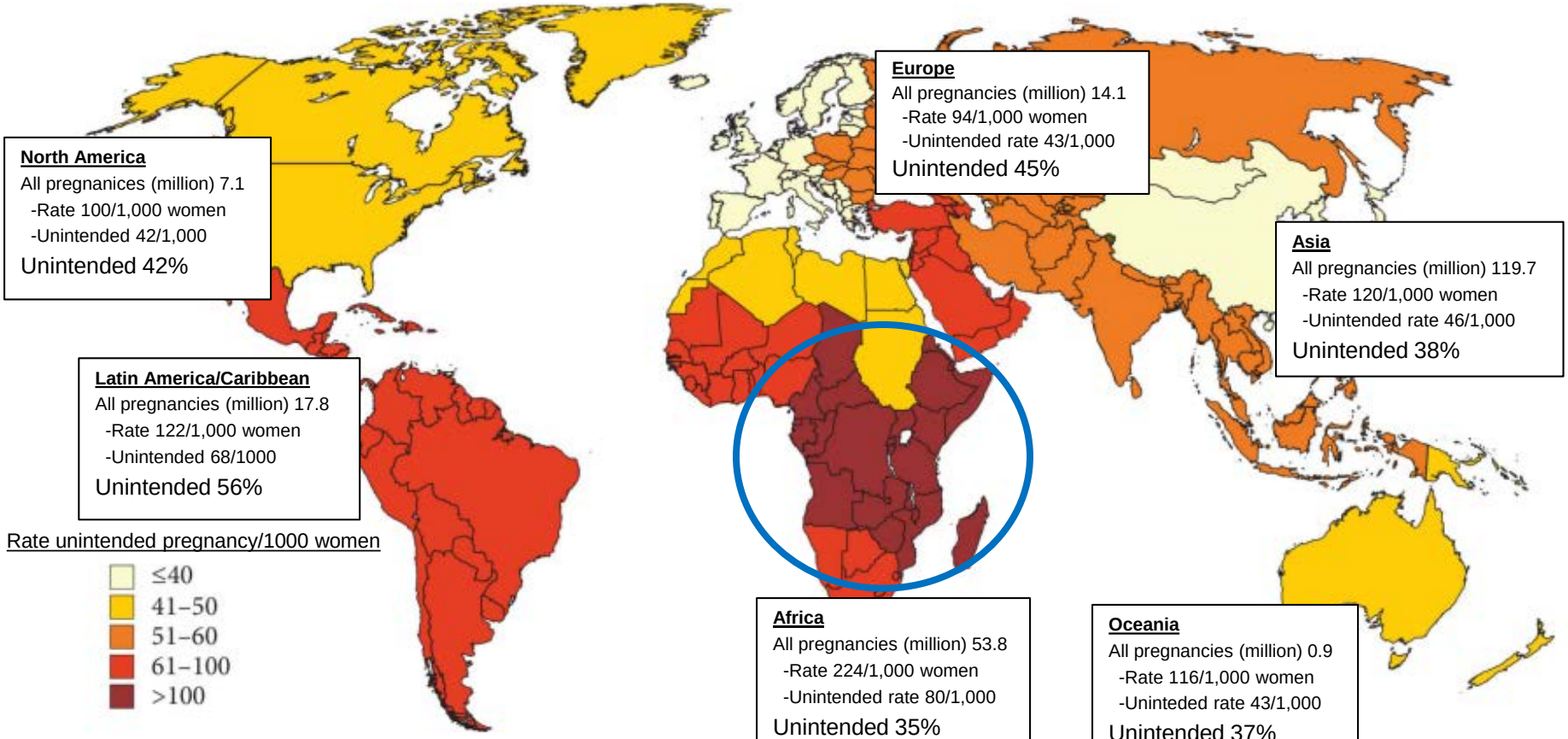
- ~40% of pregnancies globally are unplanned.
- Thus, inadvertent exposure to drugs before a woman even knows she is pregnant is common.
- Some drugs may interact with hormonal contraceptives to lower hormone levels, increasing risk of pregnancy and of drug exposure at conception.
- Therefore, essential to have data on safety in pregnancy because pregnancies will occur in real life.

Unintended Pregnancy Rate by Region, 2012

(nationally representative periodic surveys from 42 countries)

Sedgh G et al. Stud Fam Plann 2014;45:301-14

Unintended Pregnancies per 1,000 women age 15-44 yr, by sub-region 2012



North America
All pregnanices (million) 7.1
-Rate 100/1,000 women
-Unintended 42/1,000
Unintended 42%

Europe
All pregnancies (million) 14.1
-Rate 94/1,000 women
-Unintended rate 43/1,000
Unintended 45%

Asia
All pregnancies (million) 119.7
-Rate 120/1,000 women
-Unintended rate 46/1,000
Unintended 38%

Latin America/Caribbean
All pregnancies (million) 17.8
-Rate 122/1,000 women
-Unintended 68/1000
Unintended 56%

Africa
All pregnancies (million) 53.8
-Rate 224/1,000 women
-Unintended rate 80/1,000
Unintended 35%

Oceania
All pregnancies (million) 0.9
-Rate 116/1,000 women
-Uninteded rate 43/1,000
Unintended 37%

Worldwide

All pregnancies (millions): 213.4; unintended pregnancies (millions): 85
(Rates: All pregnancies: 133/1,000; unintended pregnancies 53/1,000)

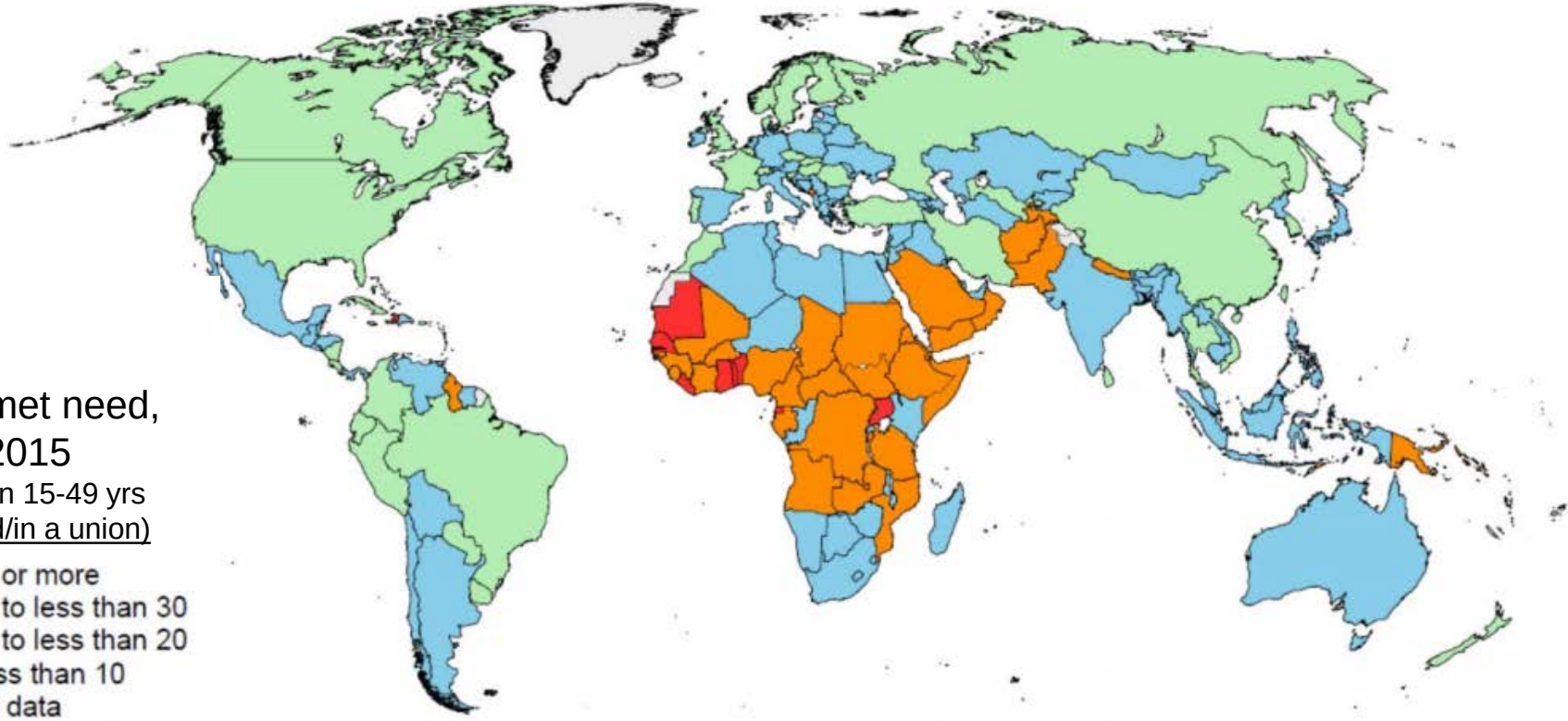
Unintended 40%

These Unintended Pregnancies Reflect Unmet Need for Family Planning

UN Data 2015

Globally in 2015, 12% women had unmet family planning need; 22% in the least developed countries.

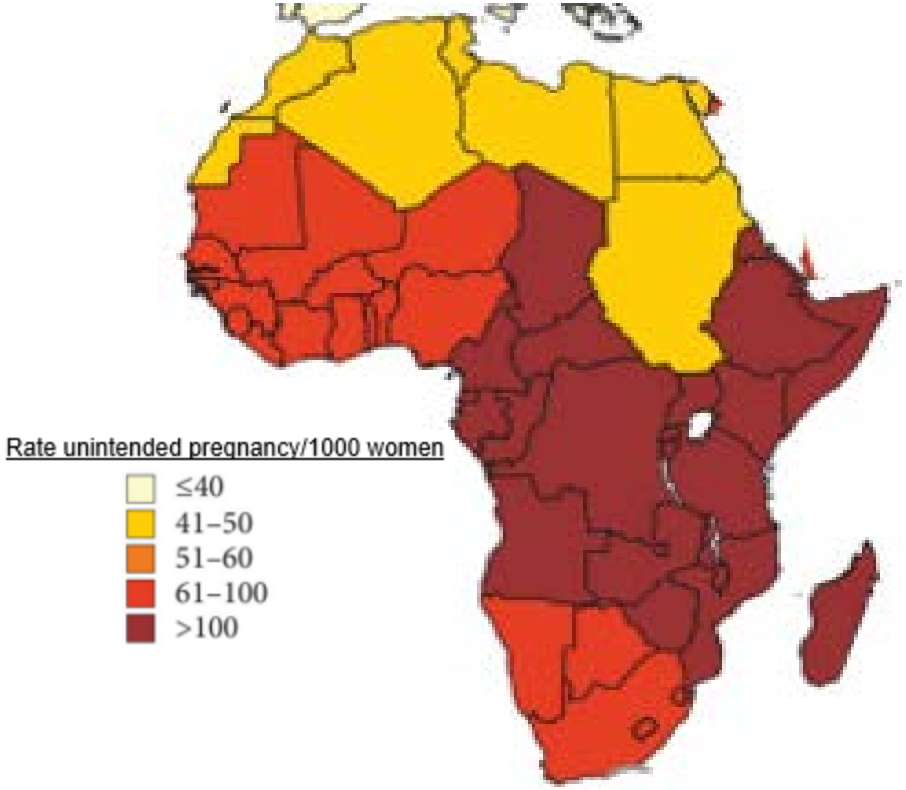
Sub-Saharan Africa need was 24%, double the world average in 2015.



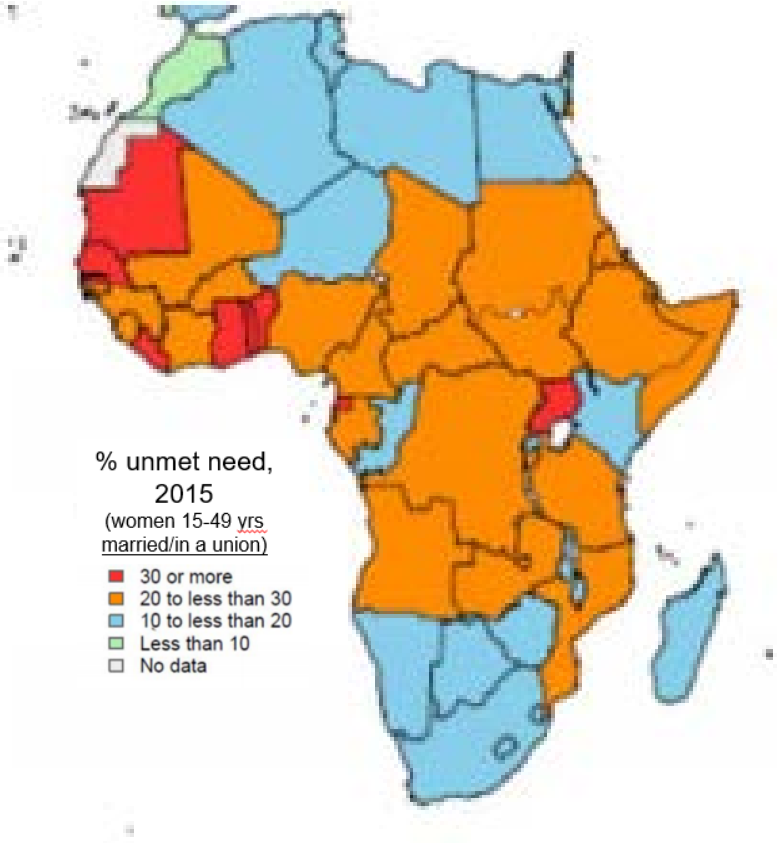
Source: United Nations, Department of Economic and Social Affairs, Population Division (2015a).

Africa – Almost Complete Overlap of Unplanned Pregnancy and Unmet Need Family Planning

Unplanned birth rate



Unmet need for family planning

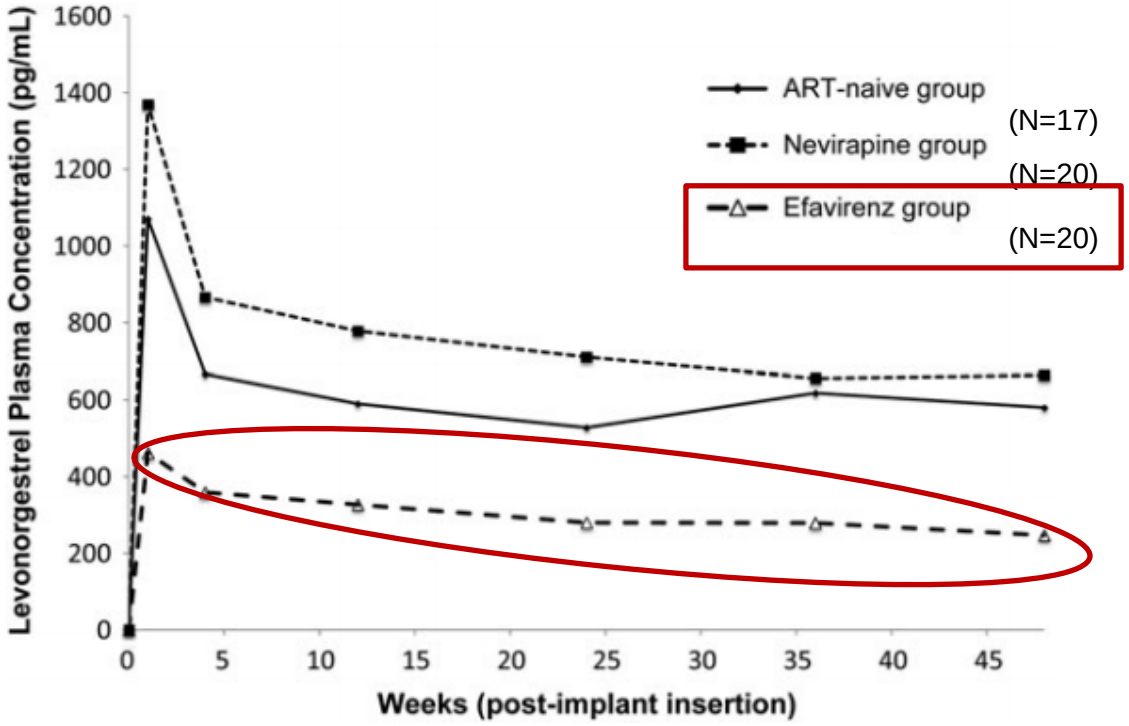


Even With Contraception, Unplanned Pregnancy Can Result from ↓ Contraceptive Efficacy Due to Drug-Drug Interactions

Scarsi KK, et al. Clin Infect Dis 2016;62:675-82

Levonorgestrel implant – LNG levels over 48 weeks post-implant by ART group

LNG Concentration-Time Profile by ART Group



- # pregnancies (contraceptive failure):
  - EFV: 3 (15%)
  - NVP: 0
  - ART-naïve: 0

EFV group had significantly lower LGN levels by week 1 post implant which persisted over time

Final Reason - Why Do We Need Data on Drugs in Pregnancy/Lactation?

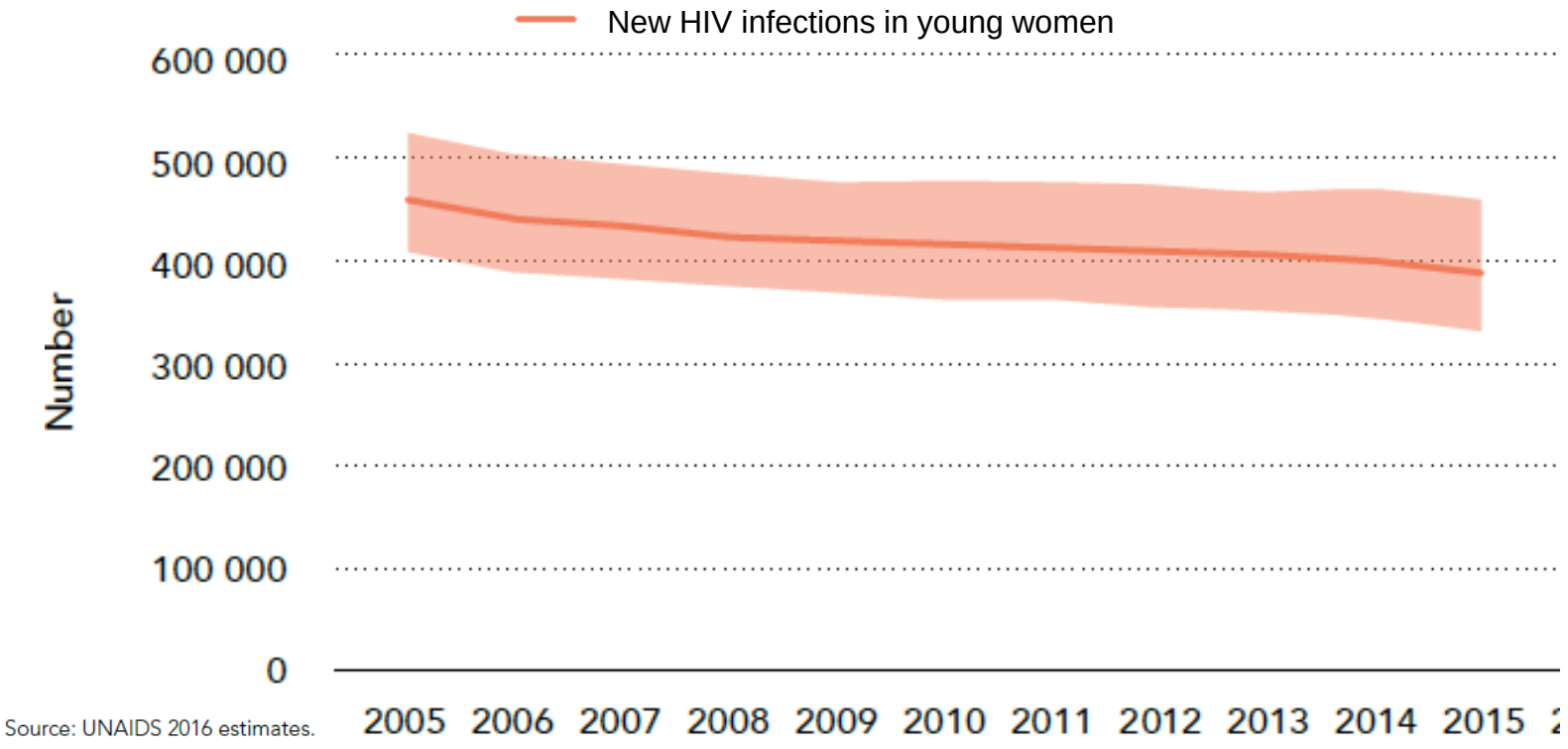
- Pregnant/lactating women can get sick.
- Treatment may be needed for:
  - Maternal conditions, such as asthma, hypertension, diabetes, seizures, HIV infection
  - Pregnancy-related conditions such as gestational diabetes, pre-eclampsia
  - Fetal conditions, such as preterm delivery

Prevalence - Number of people living with HIV in 2015

Total	36.7 million [34.0 million – 39.8 million]	
Adults	31.8 million [30.1 million – 33.7 million]	
Women	16.0 million [15.2 million – 16.9 million]	= **50.3% of adults**
Children <15 years	3.2 million [2.9 million – 3.5 million]	

Source: UNAIDS 2016 estimates.

Incidence - New HIV Infections Among Young Women Aged 15-24 Years Global 2005-2015



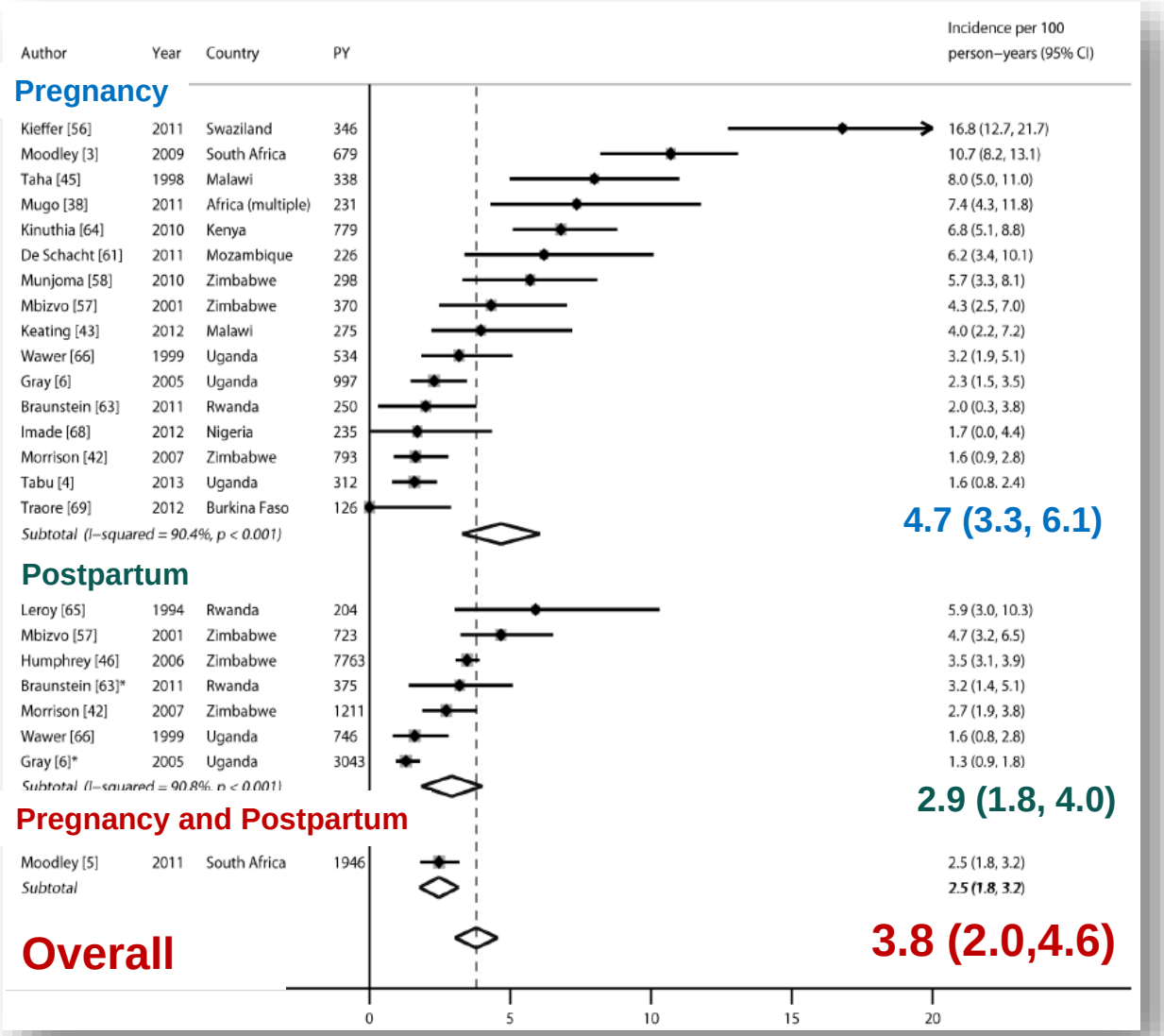
- Between 2010 and 2015, new infections in young women aged 15-24 years ↓ by only 6%, from 420,000 to 390,000.

OVER 1,000 NEW INFECTIONS EVERY DAY

High Rates of Incident HIV during Pregnancy/BF

Drake AL et al. PLosMed 2014;11:e1001608

- Meta-analysis of data from 19 studies (all Africa)

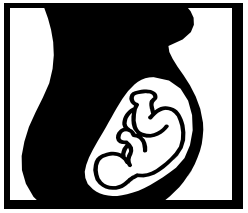


Biomedical HIV prevention interventions are critically needed during pregnancy and lactation.

But need dosing/safety data first!!

Despite These (Obvious) Reasons

Pregnant Women are “Therapeutic Orphans” as Most Current Therapeutics Have Never Been Studied in Pregnancy



BJCP British Journal of Clinical Pharmacology

Prescribing without evidence – pregnancy

Simon H. L. Thomas[1,2] & Laura M. Yates[1,3]

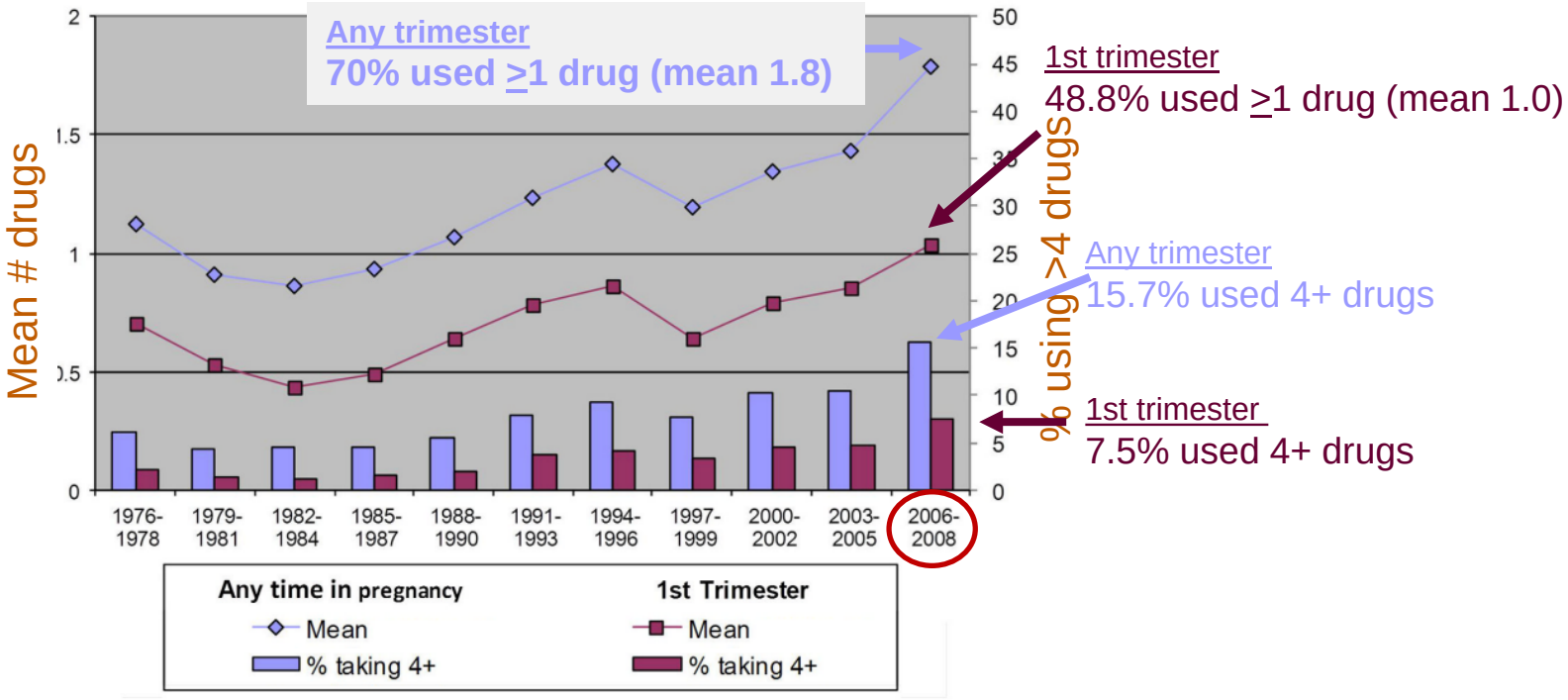
[1]UK Teratology Information Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK and [2]Institute of Cellular Medicine and [3]Institute of Genetic Medicine, Newcastle University, Newcastle, UK

Despite Lack of Data, There is Growing Use of Prescription Drugs During Pregnancy

Mitchell AA et al. Am J Obstet Gynecol. 2011;205:51.e1-51.e8

- 2 large studies in US (*Slone Epidemiology Center Birth Defects Study-BDS, 1976-2008; and National Birth Defects Prevention Study-NBDPS 1997-2003*) together interviewed >30,000 women about their antenatal medication use.

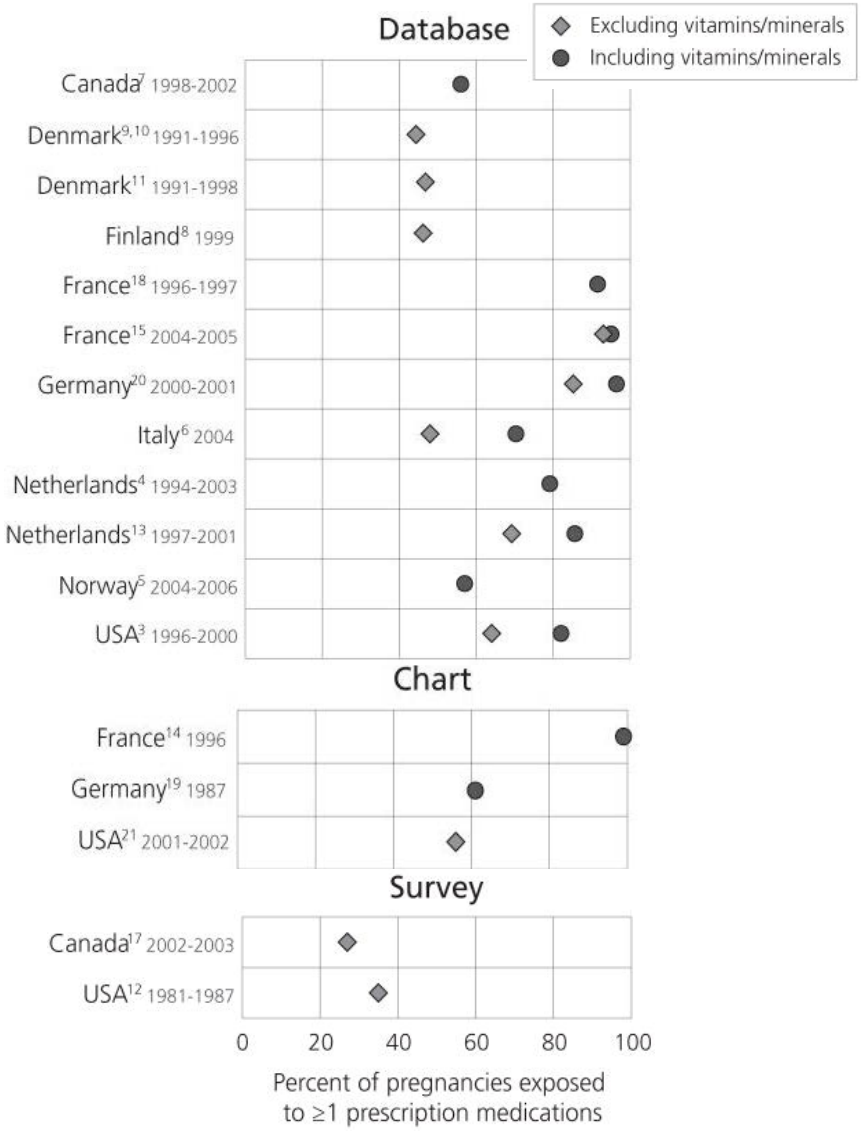
Use of Prescription Drugs During Pregnancy
Anv Time/1st Trimester 1976-2008 (BDS: N=25,313)



Prescription Drug Use During Pregnancy in North America and Europe – Systematic Review

Daw JR et al. Pharmacoepidemiol Drug Saf 2011;20:895-902

- Systematic review yielded 19 studies evaluating individual-level prescription drug exposures in a community setting anytime in pregnancy.
- Overall estimate prescription drug use excluding vitamin/ minerals ◇: 27-93%
- Mean number of different drugs reported used ranged from 1.7 to 13.6.



% of Pregnancies Exposed to Prescription Drugs with Potential for Fetal Harm (by Risk Classification System)

Daw JR et al. Pharmacoepidemiol Drug Saf 2011;20:895-902

USA (FDA)	**D** **Positive evidence of risk**	**X** **Contraindicated**
USA (1996–00)(3)	4.8	4.6
USA (2001–02) (21)	3.0	1.0
Italy (2004)(6)[a]	2.0	1.0
France (1996)(14)	59.3	1.6
Swedish (FASS)	**C** Positive evidence of risk	**D** Primary teratogenic effects
Denmark (1991–96)(9)	18.7	0.9
Australian (ADEC)	**B3/C/D/X** Positive evidence of risk/contraindicated	
Netherlands (1997–01)(13)	21	
Author Defined[b]	Potential for harm[c]	
Canada (1998–02)(7)	6.3	

- For drugs with positive evidence of risk: ranged from 2% to 19% (France was outlier, 59%).
- For drugs <u>contraindicated in pregnancy</u>: ranged from 1% to 5%.

[a] The ADEC system was used if a product label with a corresponding FDA risk classification could not be identified.

[b] Based on consultation of established sources, review articles, and an expert panel.

[c] Recognized embyrotoxic, fetotoxic, or teratogenic potential

Drug Therapy in Pregnancy

Balancing act

Benefit of Maternal Treatment

Risk of Adverse Fetal Effects

Unfortunately, Often Insufficient Scientific Data to Make Recommendations

Drug Therapy in Pregnancy

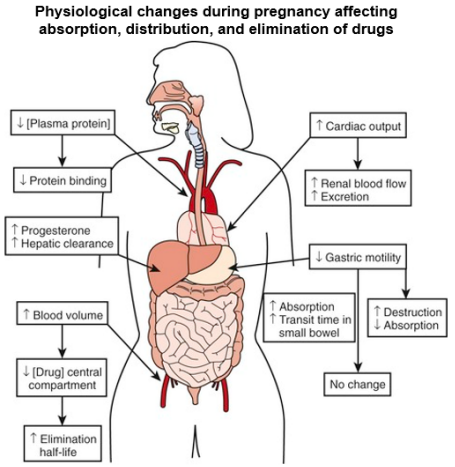
Unfortunately, Often Insufficient Scientific Data to Make Recommendations

What is Needed?

- Need pharmacokinetic/safety studies in pregnancy:
  - Drug dosing may need modification.
- Placental passage of drug:
  - Important for infant safety, teratogenicity, but also for prevention of transmission of viruses like HIV or HBV.
- Breast milk passage of drug:
  - Important for issues of infant safety but also for prevention of postnatal HIV (?other infections) and also issue of development/transmission of HIV drug resistance.

Drug Dosing in Pregnancy:

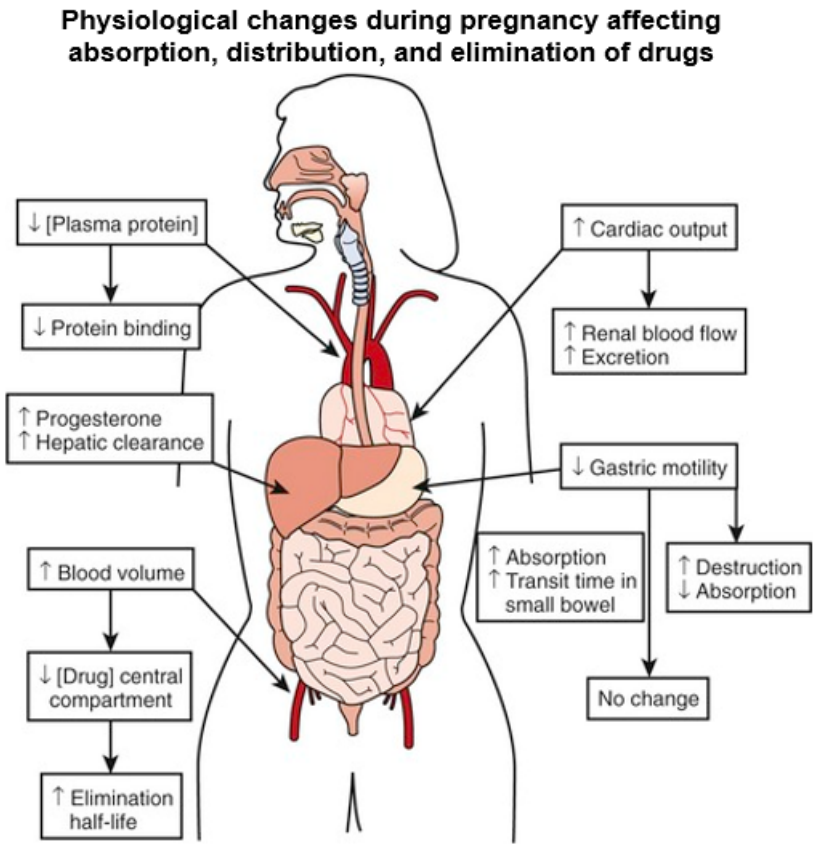
Modification of Drug Pharmacokinetics by Pregnancy



Burkart TA, Conti J. http://clinicalgate.com/arrhythmias-during-pregnancy

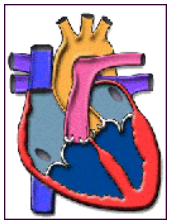
Physiologic Changes During Pregnancy Can Affect Therapeutic Drug Administration

- Cardiovascular changes
- Gastrointestinal changes
- Renal changes
- Hepatic enzyme activity changes



Burkart TA, Conti J. http://clinicalgate.com/arrhythmias-during-pregnancy

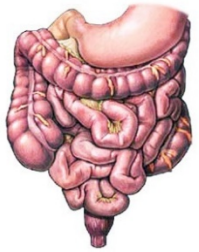
Cardiovascular Changes in Pregnancy



- Gestational age dependent
- Plasma volume expansion
  - Start 6-8 weeks, peaks at 32 weeks; additional 1.5 liters
  - Decrease in serum albumin concentration
- Increase in cardiac output
  - Increase 30-50% (stroke volume early, heart rate late)
- Alterations in regional blood flow
  - Increased flow uterus, kidney, breast, skin

Changes in Other Organ Systems in Pregnancy

Gastrointestinal Changes

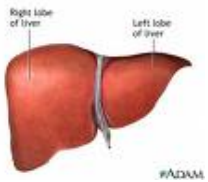


- Gastric emptying delayed
- Transit time increased (progesterone)
- Gastric acidity decreased

Renal Changes

- Increase in glomerular filtration rate 20-60% beginning 1st trimester

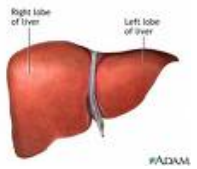
Hepatic Enzymatic Changes



- Related to pregnancy hormonal changes

Hepatic Enzyme Changes in Pregnancy

Thomas SHL, Yates LM. Brit J Clin Pharmacol. 2012;74:691-7



Enzyme	Pregnancy Effect	Trimesters	Therapeutic Drugs (examples)
CYP 1A2	Decreased	I - III	Caffeine Paracetamol Theophylline
CYP 2A6	Increased	III	Nicotine Sodium valproate
CYP 2C9	Increased	III	Angiotensin-converting enzyme inhibitors Nonsteroidal anti-inflammatory drugs Phenytoin Warfarin
CYP 2C19	Decreased	II – III	Citalopram Proguanil
CYP 2D6	Increased	I – III	Methadone Metoprolol Tricyclic antidepressants Selective serotonin reuptake inhibitors
CYP 3A4	Increased	I – III	Carbamazepine Nifedipine **Protease inhibitors** **Integrase strand transfer inhibitors**
Uridine 5'-diphospho-glucuronosyltransferases	Increased	I – III	Lamotrigine Morphine **Integrase strand transfer inhibitors**
N-Acetyltransferase 2	Decreased	I	Isoniazid Hydralazine

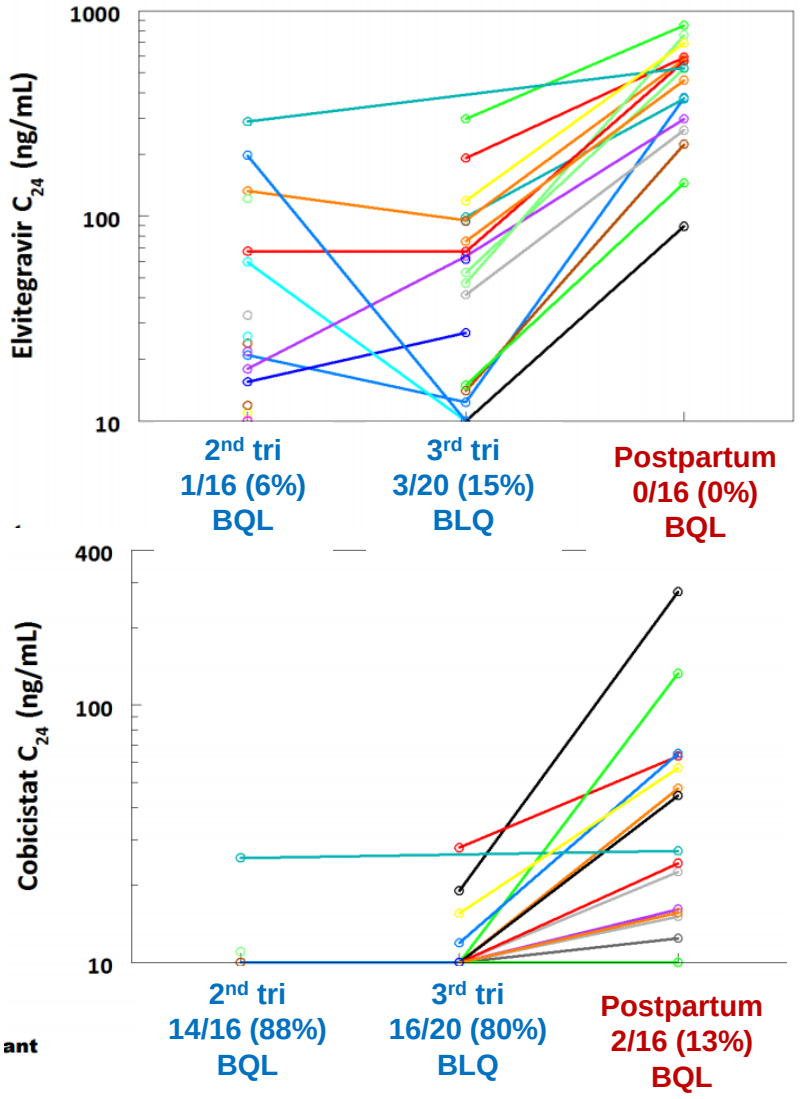
Consequences of Physiologic Changes During Pregnancy

- Volume expansion = dilution effect
- Increase in free fraction of protein-bound drug
  - Due to decreased albumin
- Clearance changes (increase or decrease)
  - Renal and enzymatic
- Gastrointestinal changes that can affect oral drug absorption

Result: Dosing changes may be needed

Elvitegravir/Cobicistat PK in 2nd/3rd Trimester Pregnancy Compared to Postpartum

Best B et al. CROI 2017, Seattle, WA. Poster 755

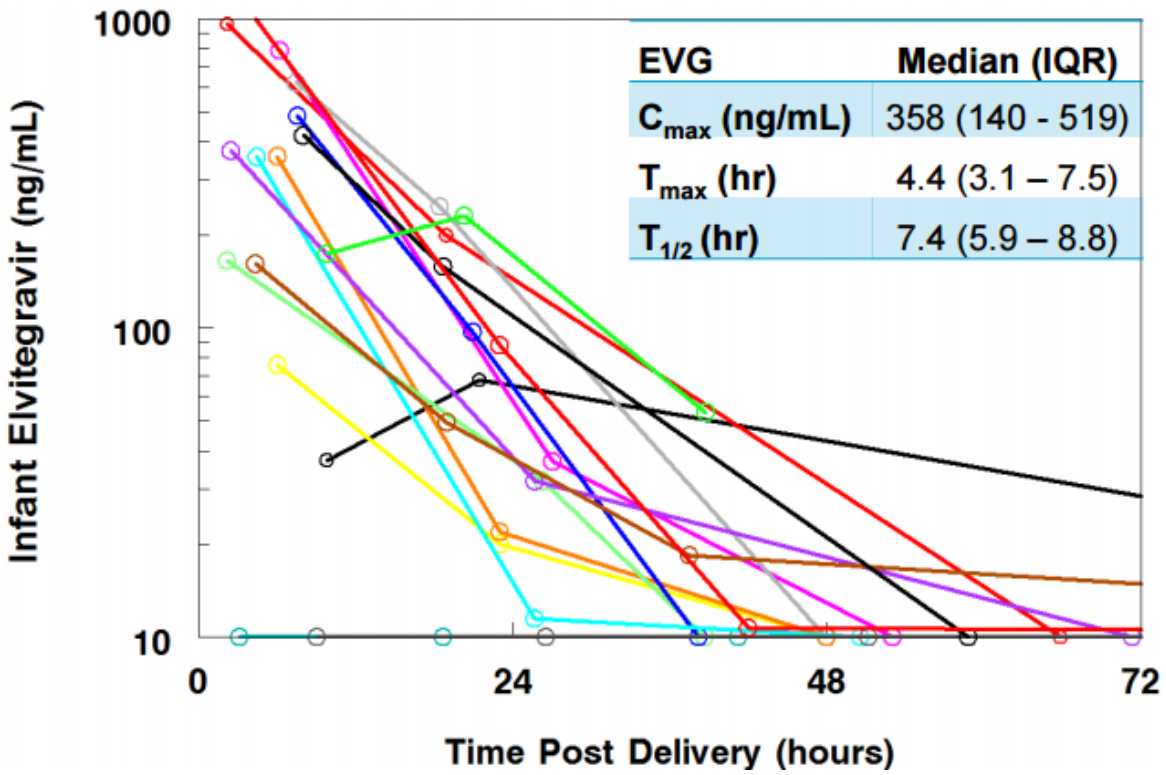


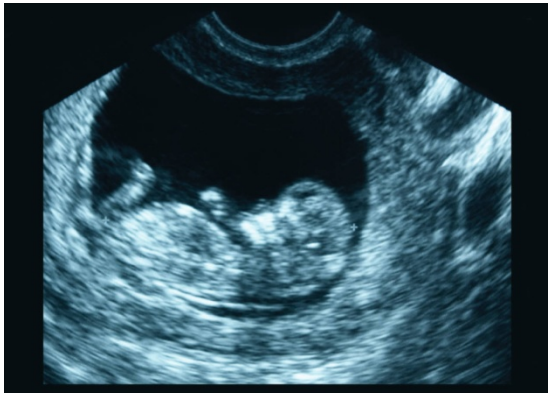
- EVG and COBI exposure are substantially lower during pregnancy compared to postpartum.
- Viral suppression to <50 c/mL was 74% (14/19) at delivery.
- Standard doses may not be adequate for sustained viral suppression.

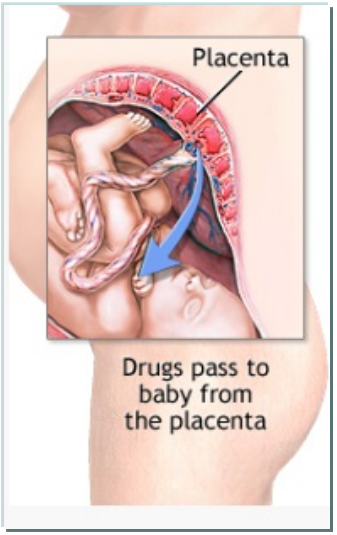
Elvitegravir/Cobicistat Infant Washout PK

Best B et al. CROI 2017, Seattle, WA. Poster 755

- EVG readily crosses the placenta and has a half-life in newborns similar to non-pregnant adults; COBI was not detectable in neonates.







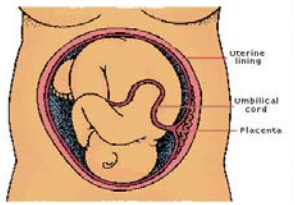
Maternal and Fetal Drug Safety and Pregnancy

What are Potential Risks of Drug Exposure for the Woman and her Infant?

- Short-term
  - Maternal - pregnancy-related changes in drug dose requirements(could lead to toxicity or resistance); immediate and postpartum toxicity
  - Fetus - pregnancy outcome, birth defects
  - Infant - neonatal and infant toxicity
- Long-term example of diethylstilbesterol (DES)

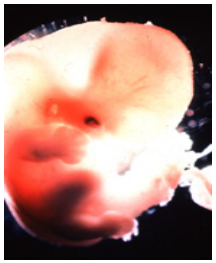
Advertisement for DES from a 1957 medical journal

  - Effects in female offspring not recognized for decades
  - 40-fold ↑ risk of rare cervical/ vaginal cancer in young women (30s-40s)
  - 25-33% with cervical malformations



Issues Related to Toxicity of Drugs in Pregnancy

- The extent of fetal risk may vary by:
  - Timing of exposure
  - Dose
  - Route of exposure
  - Duration of exposure



Gestational Age at Time of Drug Exposure Affects Fetal Risk

Embryogenesis

potential for
major organ defects
(eg, cardiac, CNS)

Ex: Neural tube closure by day 28 (neural tube defect risk)
Oral structures form by day 36 (cleft palate risk)

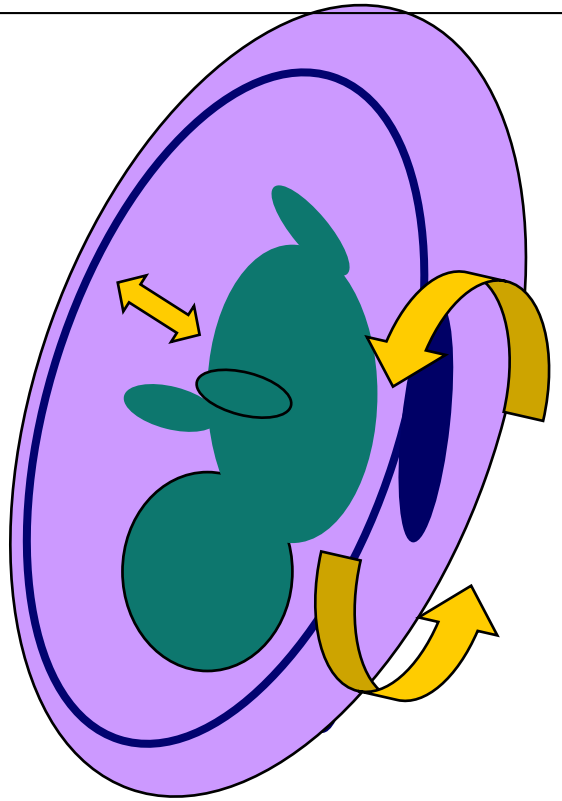
Fetal development

potential for
developmental defects
(eg, brain development,
fetal growth)

Ex: Alcohol after 24 wks (fetal alcohol syndrome)
Smoking after 20 wks (growth restriction)

Determinants of Fetal and Infant Drug Exposure and Risk

- Placental transfer:
  - Does drug cross placenta?
- Placental/fetal metabolism:
  - Potential toxic metabolites
- Fetal GI re-absorption:
  - Is drug concentrated in amniotic fluid?
- Drug transfer via breastmilk:
  - Is drug secreted into milk?



Antiretroviral Medications and Fetal Risk: Prior FDA Pregnancy Categories

A: No risk in adequate human studies

B: Animal studies do not demonstrate risk but no adequate human studies (or animal studies positive but human studies negative)

C: Animal studies positive for fetal risk or not done and safety in humans not determined

D: Positive evidence of human risk based on adverse event reporting, but potential benefits may outweigh risk

X: Positive evidence animal studies or human risk that indicate risk outweighs benefit

Current Antiretroviral Medications and Fetal Risk: FDA Pregnancy Categories

NRTIs

Abacavir	C
Didanosine	B
Emtricitabine	B
Lamivudine	C
Stavudine	C
Zidovudine	C

NNRTIs

Efavirenz	D
Etravirine	B
Nevirapine	B

PIs

Atazanavir	B
Darunavir	B
Fosamprenavir	C
Indinavir	C
Lopinavir/rit	C
Nelfinavir	B
Ritonavir	B
Saquinavir	B
Tipranavir	C

NUCLEOTIDES

TDF	B
TAF	B

FUSION INHIBITORS

Enfuvirtide	B

CCR5 CO-RECEPTOR ANTAGONISTS

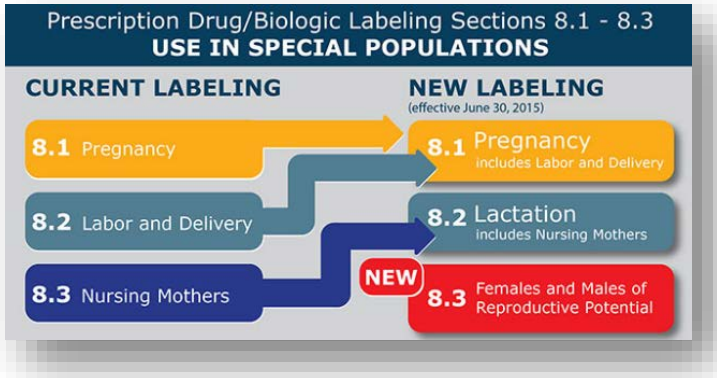
Maraviroc	B

INTEGRASE INHIBITORS

Raltegravir	C
Dolutegravir	B
Elvitegravir	B

PK ENHANCER

COBI	B



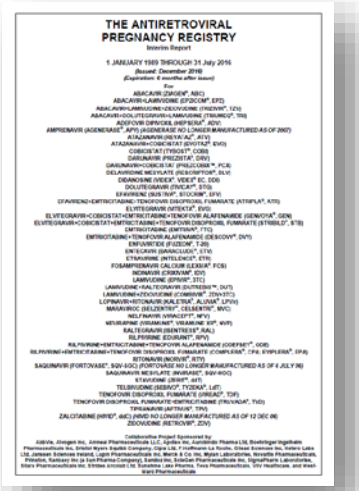
2015 FDA Drug Label Revision Eliminating A,B,C,D,X Pregnancy Categories

(for new drug labels; for already approved drugs made gradually as new drug labels are approved)

- Pregnancy:
  - Pregnancy registry information/contact if exists
  - Adverse pregnancy outcome & fetal risk (birth defect, miscarriage/ stillbirth, neonatal death, functional and growth abnormalities).
  - Standardized risk statement differentiating animal and human data
  - Clinical including gestational use, dosing in pregnancy
- Lactation:
  - Use of drug while breastfeeding, such as the amount of drug in breast milk and potential risk of effects on the breastfed child
- Females and Males of Reproductive Potential
  - Information about pregnancy testing, contraception and about infertility as it relates to the drug

Antiretroviral Pregnancy Registry

- International registry jointly sponsored by manufacturers of all ARV drugs.
- Voluntary registration of prenatal exposures by treating providers (international).
- Purpose: to estimate risk of major birth defects and compare to that of general population (CDC's MACDP population-based birth defects surveillance system and Texas Birth Defects Registry).
- Contact information:
  - Telephone: (800) 258-4263
  - Fax: (800) 800-1052
  - Available at http://www.apregistry.com


THE ANTIRETROVIRAL PREGNANCY REGISTRY

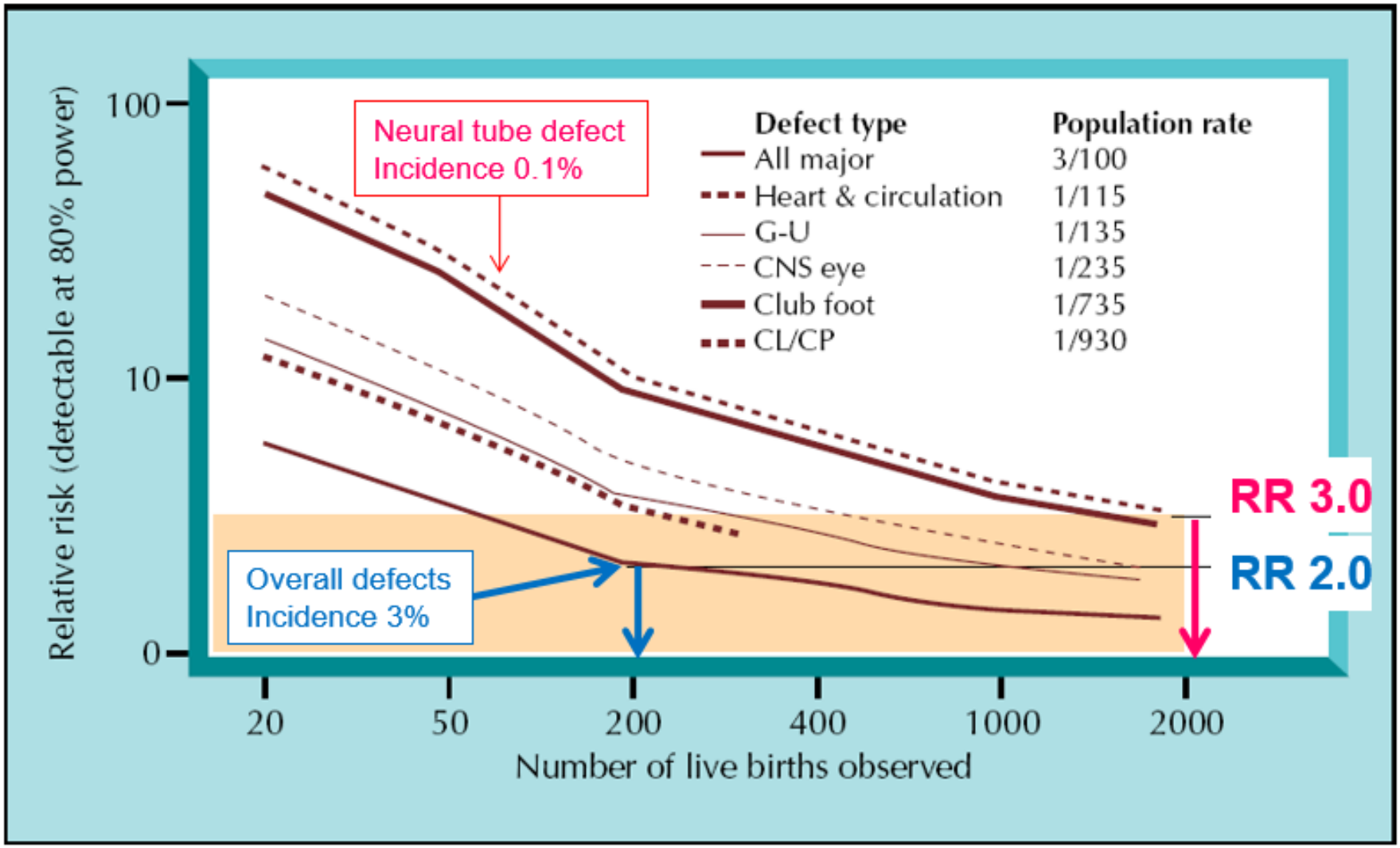
Interim Report

1 JANUARY 1989 THROUGH 31 July 2016

Issued: December 2016

(Expiration: 6 months after issue)

Ability to Detect an Increase Birth Defect Risk is Related to Incidence Defect & Number Observed 1st Trimester Exposures



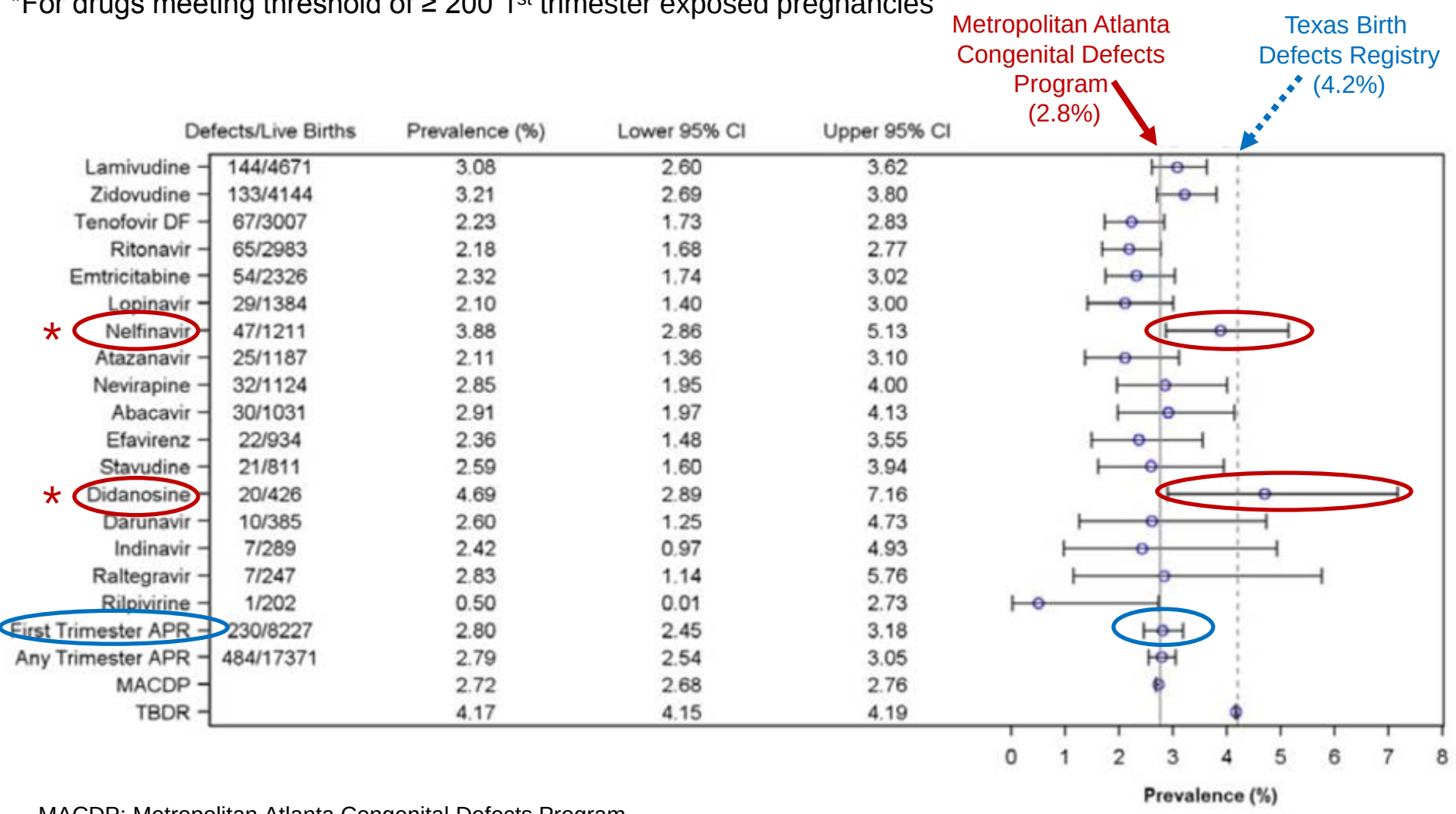
Watts DH. Curr HIV/AIDS Rep 2007;4:135-140

Drug-Specific Birth Defect Rates*

Prevalence of Birth Defects (95% CI): 1 January 1989 – 31 July 2016
First Trimester Exposure

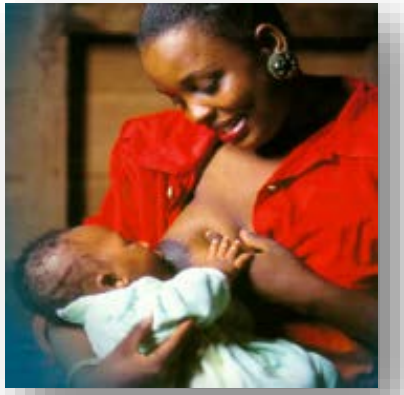
*For drugs meeting threshold of ≥ 200 1st trimester exposed pregnancies

	Defects/Live Births	Prevalence (%)	Lower 95% CI	Upper 95% CI
Lamivudine	144/4671	3.08	2.60	3.62
Zidovudine	133/4144	3.21	2.69	3.80
Tenofovir DF	67/3007	2.23	1.73	2.83
Ritonavir	65/2983	2.18	1.68	2.77
Emtricitabine	54/2326	2.32	1.74	3.02
Lopinavir	29/1384	2.10	1.40	3.00
* Nelfinavir	47/1211	3.88	2.86	5.13
Atazanavir	25/1187	2.11	1.36	3.10
Nevirapine	32/1124	2.85	1.95	4.00
Abacavir	30/1031	2.91	1.97	4.13
Efavirenz	22/934	2.36	1.48	3.55
Stavudine	21/811	2.59	1.60	3.94
* Didanosine	20/426	4.69	2.89	7.16
Darunavir	10/385	2.60	1.25	4.73
Indinavir	7/289	2.42	0.97	4.93
Raltegravir	7/247	2.83	1.14	5.76
Rilpivirine	1/202	0.50	0.01	2.73
First Trimester APR	230/8227	2.80	2.45	3.18
Any Trimester APR	484/17371	2.79	2.54	3.05
MACDP		2.72	2.68	2.76
TBDR		4.17	4.15	4.19



MACDP: Metropolitan Atlanta Congenital Defects Program
TBDR: Texas Birth Defects Registry

*No specific defect pattern or organ system



Antiretroviral Drugs and Breast Milk

Potential Toxicity but Also Potential Protection for HIV

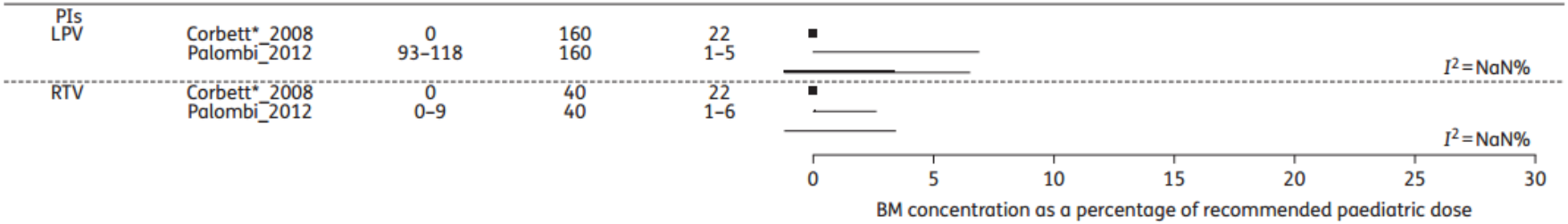
Particularly important in Africa and other LMIC where breastfeeding is critical for infant survival.

ARV Transfer from Breast Milk to Infant Appears Potentially Important for Some NRTIs/NNRTIs: Meta-analysis 24 PK Studies

Waitt CJ et al. J Antimicrob Chemother 2015;70:1928-41

Daily "Dose" Ingested by BF Infant as % Recommended Pediatric Dose

Drug	Study	Infant concentration (ng/mL)	Daily infant dose	Number of infants
NNRTIs				
EFV	Olagunju*_2014	178	100	51
	Schneider_2008	870	100	13
				I^2=0%
NVP	Mirochnick_2009	734	15	34
	Palombi_2012	795	15	9
				I^2=0%
NRTIs				
3TC	Corbett*_2008	2.8	12	23
	Mirochnick_2009	32	12	39
	Palombi_2012	12.5	12	9
	Shapiro_2005	28	12	20
				I^2=0%
d4T	Fogel_2012	0.05	6	52
	Palombi_2012	1.25	6	4
				I^2=0%
ZDV	Corbett*_2008	0	24	6
	Mirochnick_2009	0	24	24
	Palombi_2012	0	24	5
	Shapiro_2005	123	24	20
				I^2=NaN%
PIs				
LPV	Corbett*_2008	0	160	22
	Palombi_2012	93–118	160	1–5
				I^2=NaN%
RTV	Corbett*_2008	0	40	22
	Palombi_2012	0–9	40	1–6
				I^2=NaN%



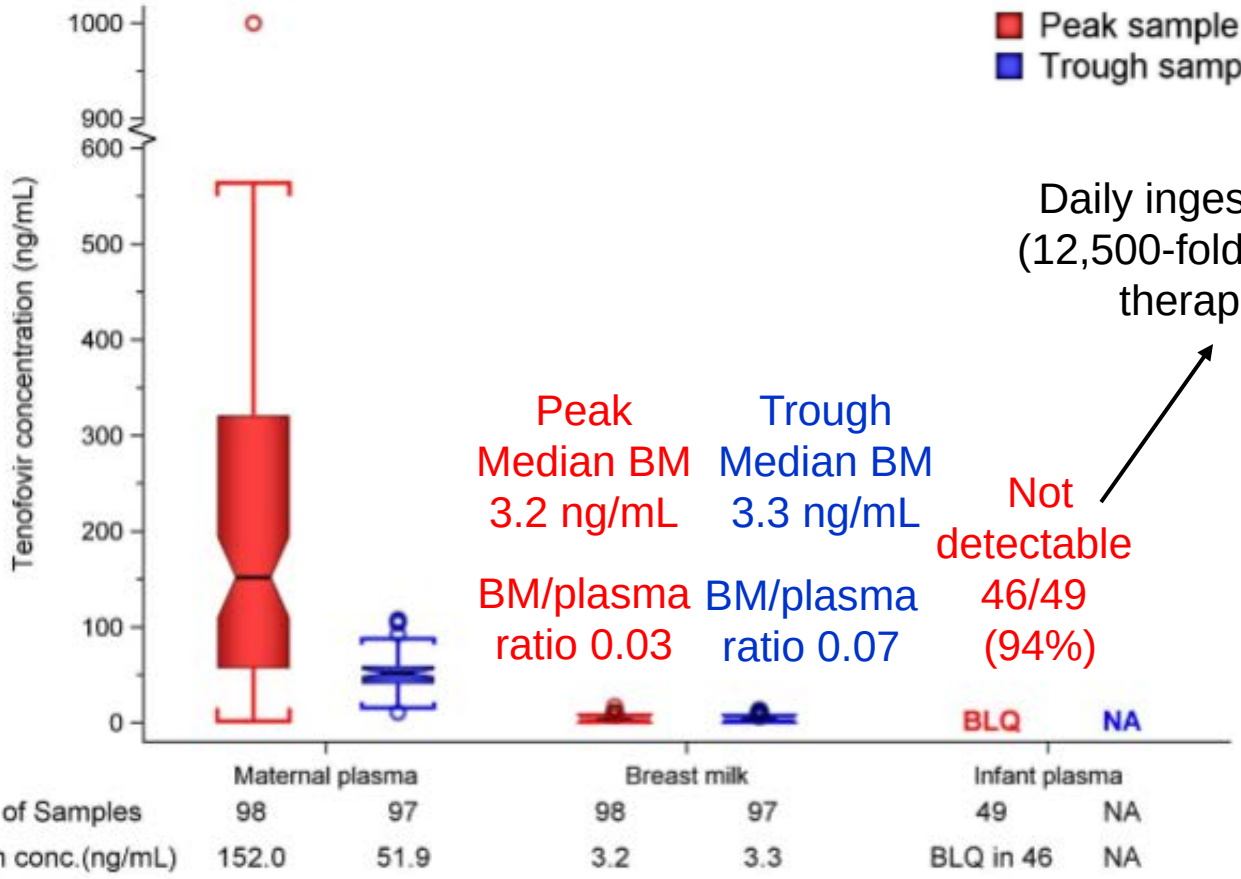
- Relative to recommended pediatric ARV dose, a breast-fed infant may ingest 1.1% (95% CI 0–3.6) of EFV, 12.5% (95% CI 2.6–22.3) of NVP, and 8.4% (95% CI 1.9–15.0) of 3TC via BM, but ~0% for PIs.

Tenofovir Levels in Breast Milk

Mugwanya KK et al. PLosMed 2016;13:e1002132

- Concern regarding potential for renal/bone toxicity to infant.
- Tenofovir low bioavailability; given as water soluble di-ester prodrug and rapidly converted TDF to tenofovir in blood; would expect minimal penetration of tenofovir from blood into BM.

50 HIV-women receiving daily TDF/FTC PrEP btn 1-24 wk PP



Peak Median BM 3.2 ng/mL

BM/plasma ratio 0.03

Trough Median BM 3.3 ng/mL

BM/plasma ratio 0.07

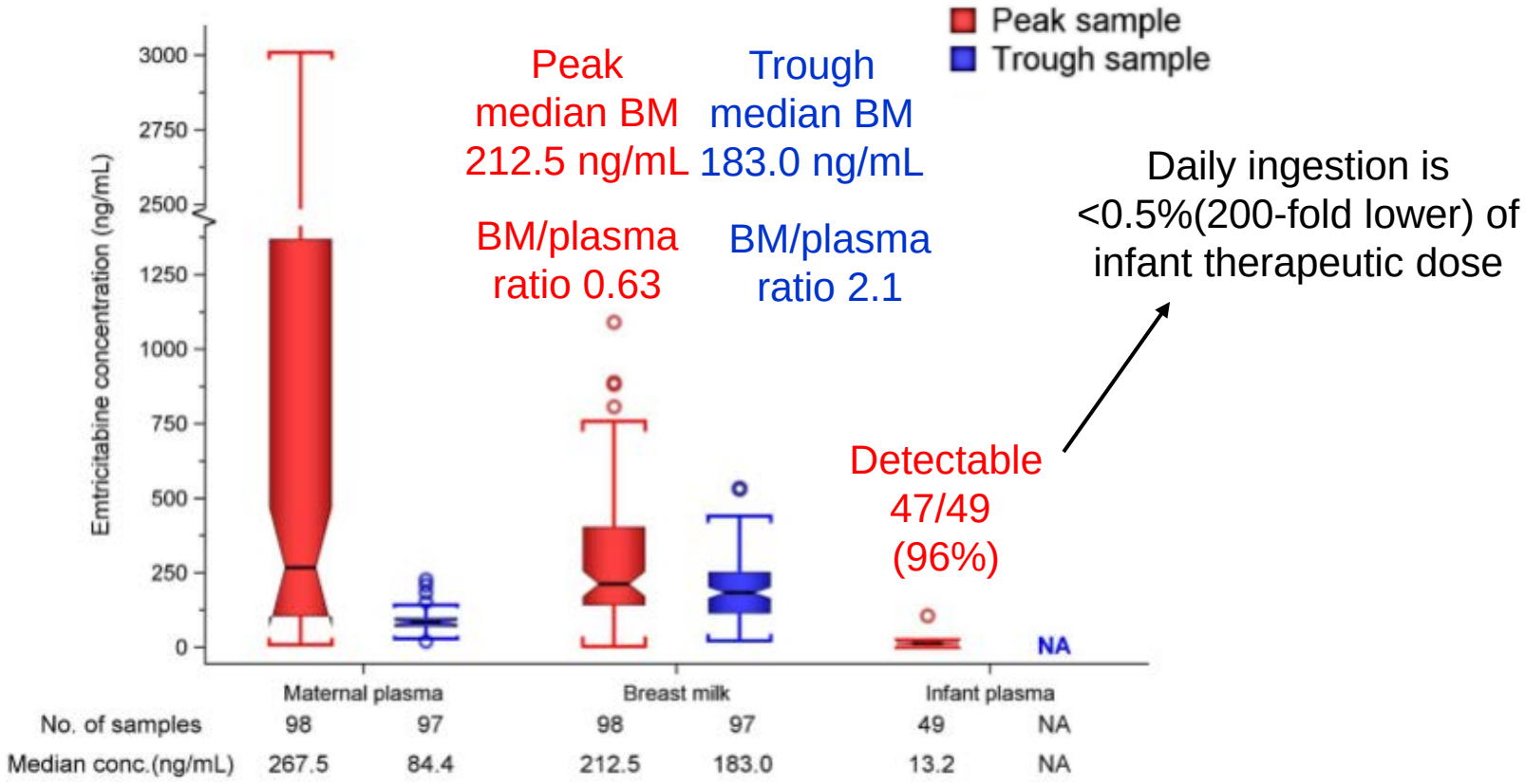
Not detectable 46/49 (94%)

Daily ingestion is <0.01% (12,500-fold lower) of infant therapeutic dose

Emtricitabine (FTC) Levels in Breast Milk

Mugwanya KK et al. PLosMed 2016;13:e1002132

- Other NRTI and NNRTI drugs have shown higher penetration in milk: BM/plasma ratio 0.44-3.21 for ZDV, 2.56-3.34 for 3TC, 0.67-0.75 NVP, 0.54 EFV *(Shapiro JID 2005; Schneider JAIDS 2008; Mirochnick AAC 2009)*.



Drug Resistance: Breast Milk as a Separate Compartment:

Low drug levels in BM can result in selection of resistance in BM not found in plasma

Lee EJ et al. J Infect Dis 2005;192:1260-4

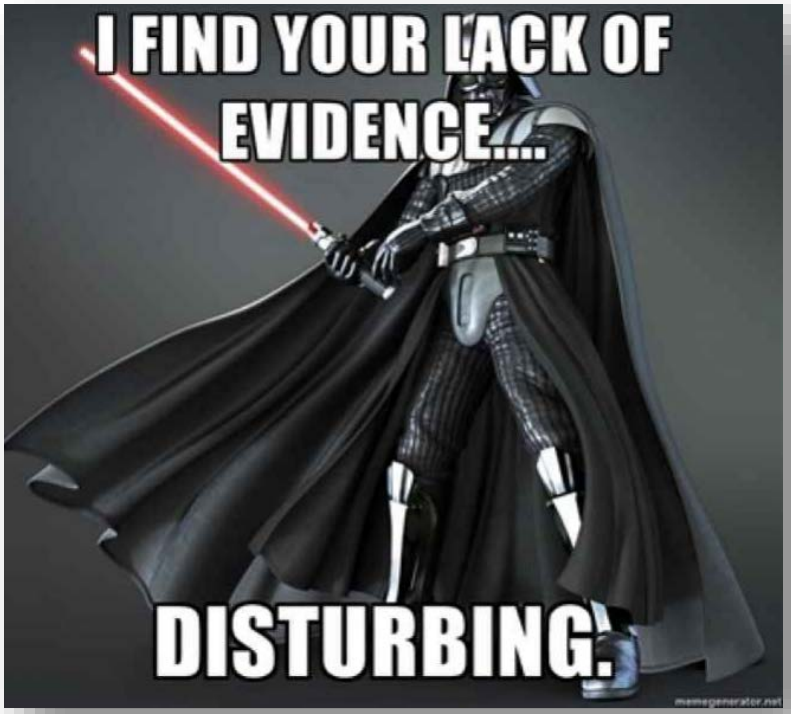
Differential Selection NVP Resistance Mutations in Breast Milk and Plasma Samples

		Breast Milk	
Patient	Plasma	Left	Right
1	Wt	Wt	Wt
2	Wt	Wt	Wt
3	Wt	Wt	Wt
4	Wt	Wt	Wt
5	Wt	Wt	-
6	Wt	Wt	-
7	K103KN	K103KN	K103KN
8	K103KN	K103KN	K103KN
9	K103KN	K103KN	K103KN
10	K103KN, G190GA	K103KN, G190GA	K103KN, G190GA
11	Wt	Wt	K103KN
12	Wt	-	K103KN
13	Wt	K103KN	-
14	Wt	K103KN	-
15	K103KN	-	Wt
16	K103KN	K103N, Y188YC	K103N, Y188YC
17	K103KN, Y188YC	Wt	K103KN
18	K103KN, Y181YC	Wt	K103KN
19	K103KN, V106IM	V106VA	Wt
20	Y181YC	K103KN	Wt

- 10 plasma-BM pairs had *same* pattern in plasma and milk
  - 6 had wild type
  - 4 same mutation pattern

- 10 plasma-BM pairs had *different* patterns in plasma and milk
  - 4 wild type in plasma but K103N in milk
  - 6 divergent patterns including between breasts

Summary



- The lack of data on drugs needed to treat important illnesses in pregnant and breastfeeding women – and if it is studied, the long period it takes to obtain such data after a drug is first approved - is unacceptable.

- TDF approved in 2001, recommended 1st line for adults in 2004.
- First PK data in pregnancy 2011(10 years later) and sufficient data on breast milk penetration in 2016 (15 years later).

Summary: When A Drug is Needed in Pregnancy…

- As new agents are being developed that will be important for treatment and prevention of HIV (and other diseases that can occur in pregnancy), studies in pregnant women and breastfeeding are critical.

Thank You For Your Attention!