

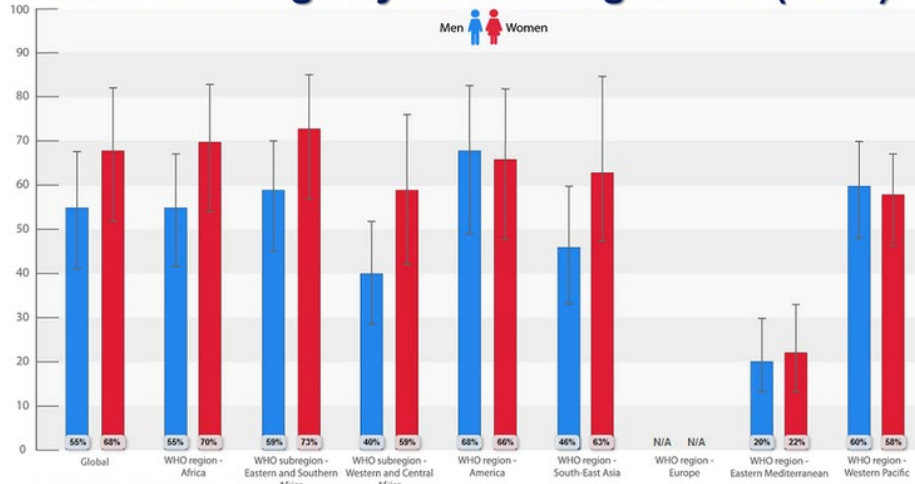
# No conflicts of interest



# Women, HIV and ART

- **Women represent more than half of the global population of people living with HIV (PLWHIV)**

**ART coverage by sex among adults (2018)**

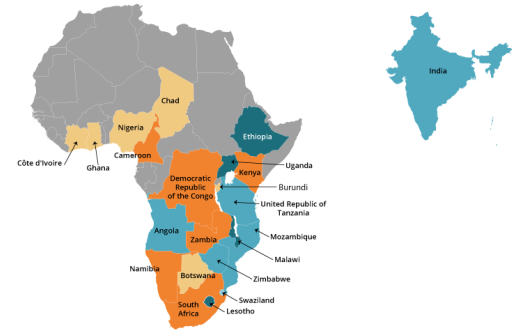


Source: UNAIDS/WHO estimates

- ART coverage is approaching 70% for women globally (55% for men)

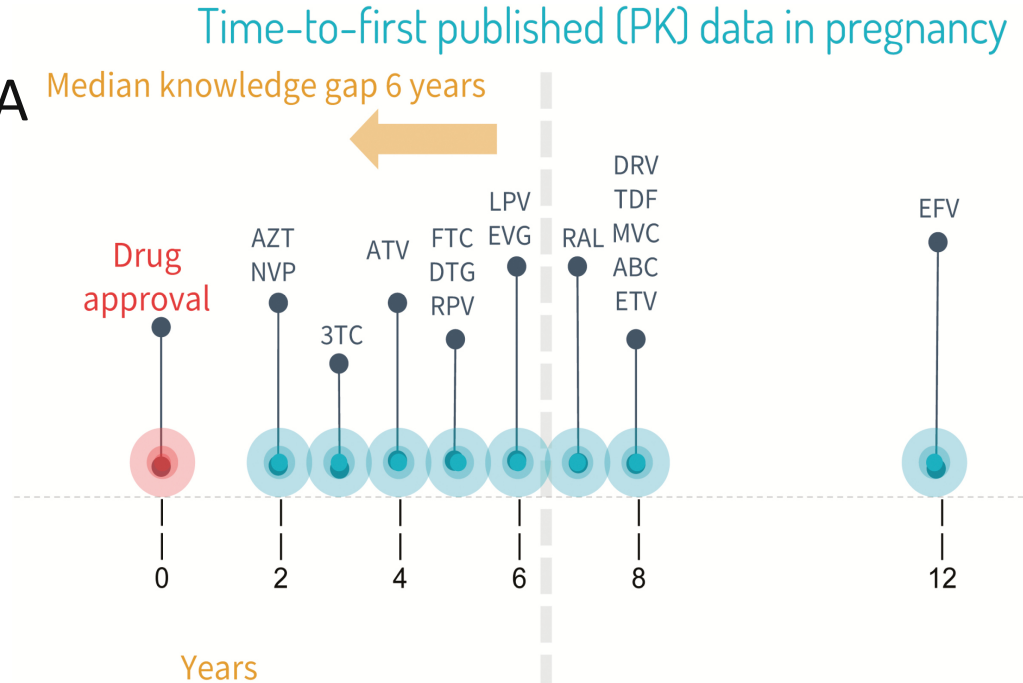
# HIV, ART and Pregnancy

- **HIV disproportionately impacts young, sexually active women**
  - ~2 million women living with HIV become pregnant every year
  - Taking ART in pregnancy is critical-- improves maternal health, prevents pediatric HIV infection, decreases transmission to partners without HIV
  - ART pregnancy safety data is necessary to HIV treatment programs worldwide to maintain gender equity in HIV treatment outcomes



# What is (are) the best ART regimen(s) for Women?

- Median delay between FDA approval of an ARV for adults and pregnancy PK data is 6 years



**What *is* the best ART regimen for women of reproductive potential????**

**Is *Dolutegravir* the best ART regimen for women of reproductive potential????**

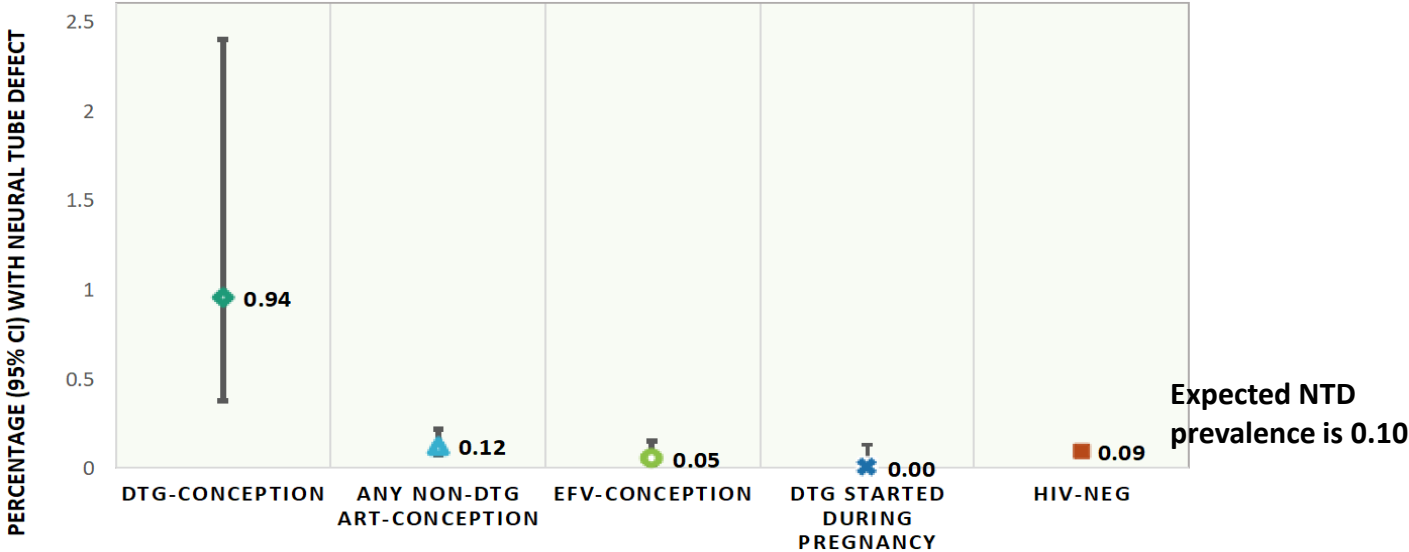
# DTG and Pregnancy

## **Two major safety questions about the use of DTG in pregnancy**

1. Is there increased risk of neural tube defects with DTG at conception?
2. Does DTG-associated weight gain impact pregnancy outcomes?

# Tsepamo Study Preliminary NTD Results: May 2018

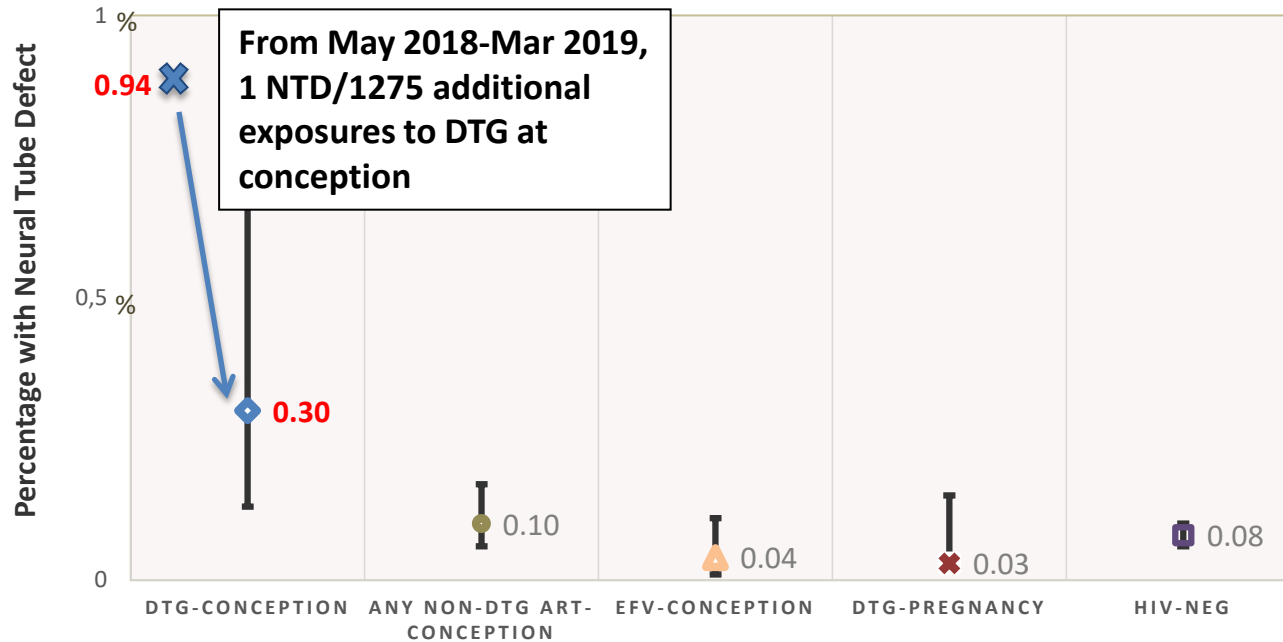
Unplanned, interim analysis (requested by WHO)



NTDs/Exposures	4/426	14/11,300	3/5,787	0/2,812	61/66,057
% with NTD (95% CI)	0.94% (0.37%, 2.4%)	0.12% (0.07%, 0.21%)	0.05% (0.02%, 0.15%)	0% (0%, 0.13%)	0.09% (0.07%, 0.12%)
Prevalence Difference (95% CI)	ref	0.82% (0.24%, 2.3%)	0.89% (0.31%, 2.3%)	0.94% (0.35%, 2.4%)	0.85% (0.27%, 2.3%)



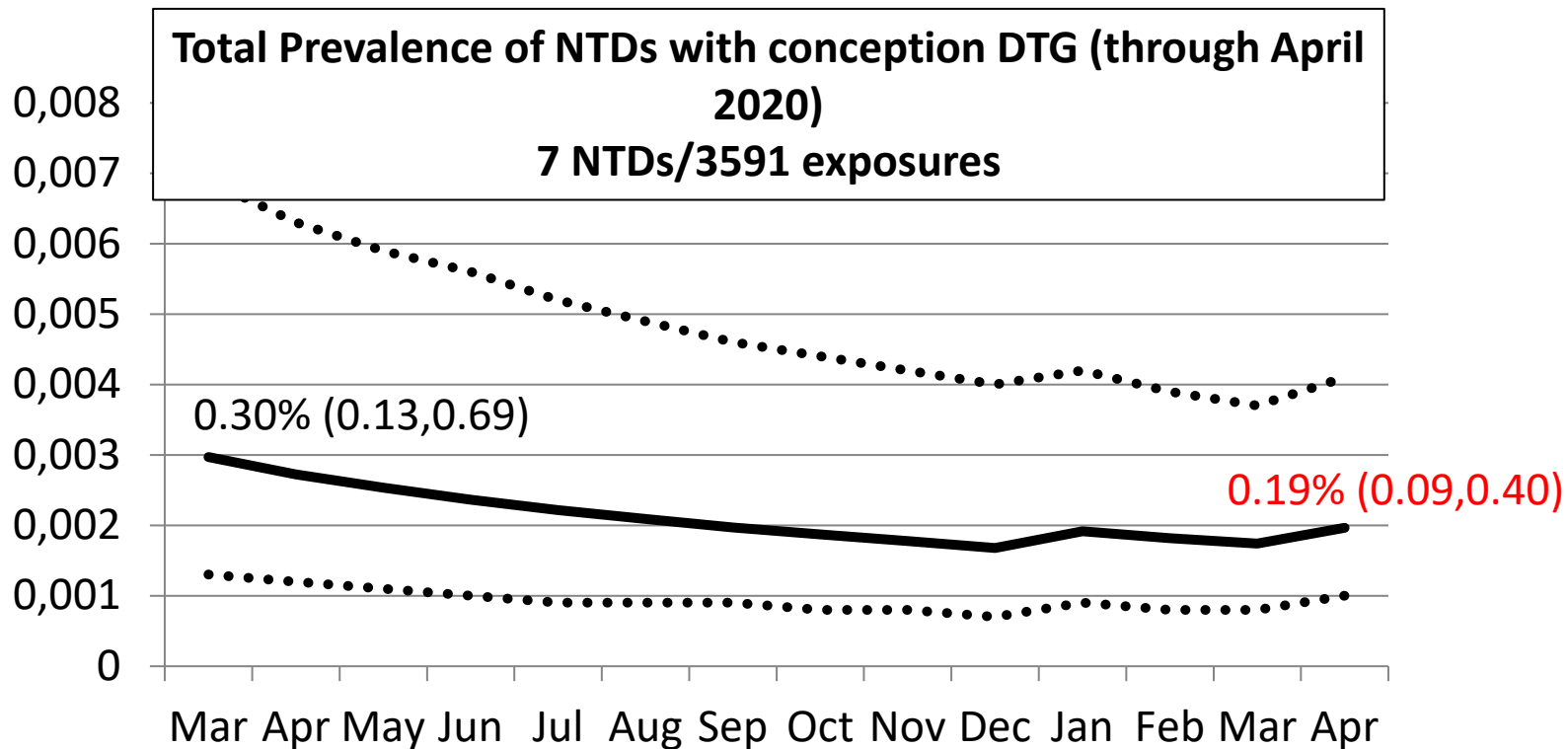
# Tsepamo Results as of March 2019



NTDs/Exposures	5/1683	15/14792	3/7959	1/3840	70/89372
% with NTD (95% CI)	0.30% (0.13, 0.69)	0.10% (0.06, 0.17)	0.04% (0.01, 0.11)	0.03% (0.0, 0.15)	0.08% (0.06, 0.10)
Prevalence Difference (95% CI)	ref	0.20% (0.01, 0.59)	0.26% (0.07, 0.66)	0.27% (0.06, 0.67)	0.22% (0.05, 0.62)

# Tsepamo: Birth Defects and Antiretroviral Exposures in Botswana

AIDS2020 Abstract: Zash et al, OAXLB0102

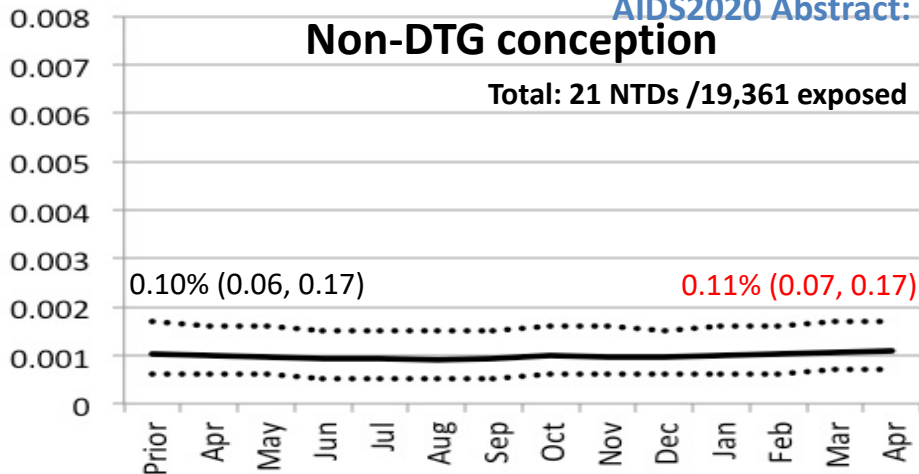


# Tsepamo: Birth Defects and Antiretroviral Exposures in Botswana

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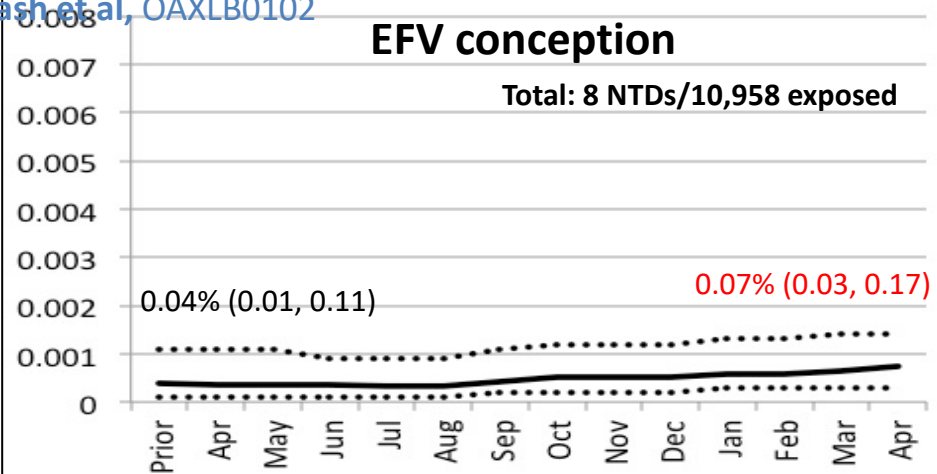
## Non-DTG conception

Total: 21 NTDs /19,361 exposed



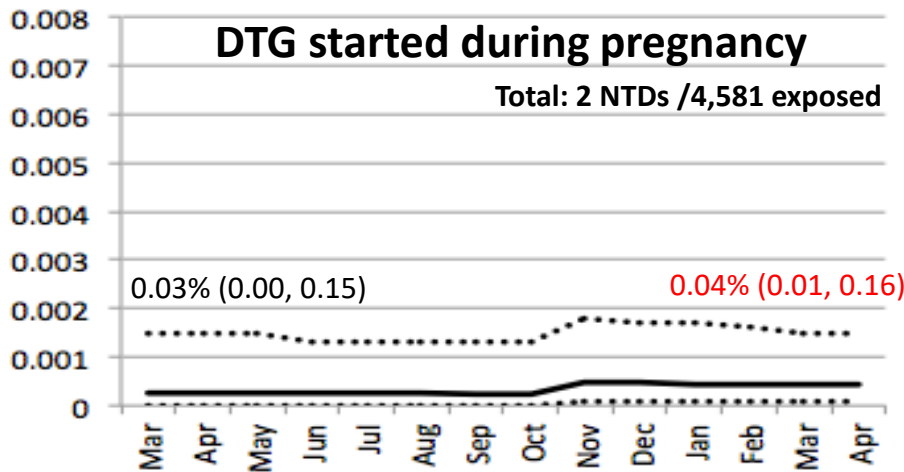
## EFV conception

Total: 8 NTDs/10,958 exposed



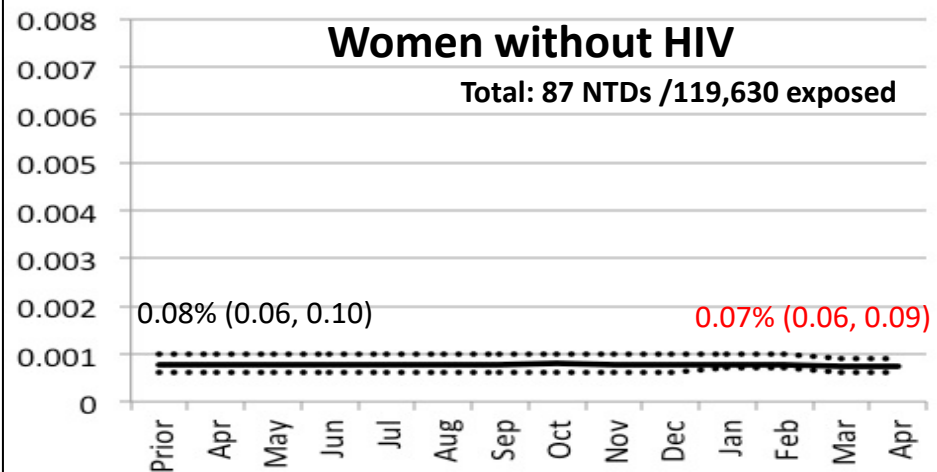
## DTG started during pregnancy

Total: 2 NTDs /4,581 exposed

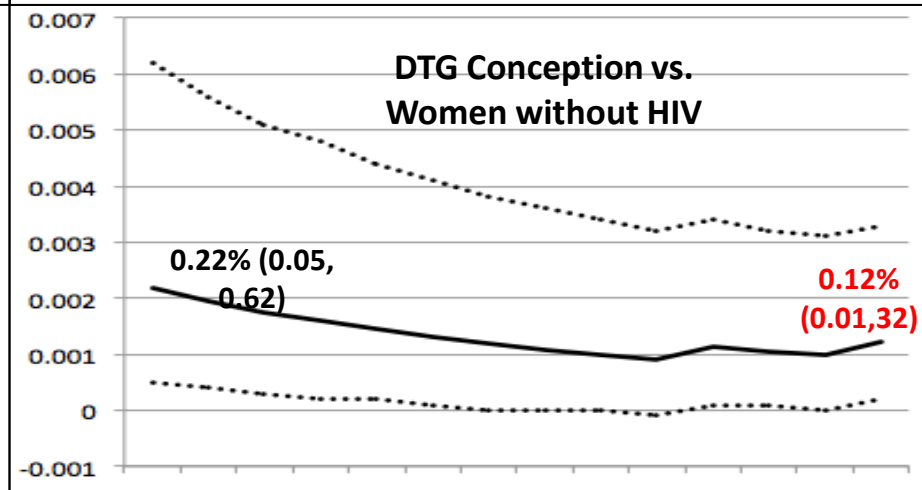
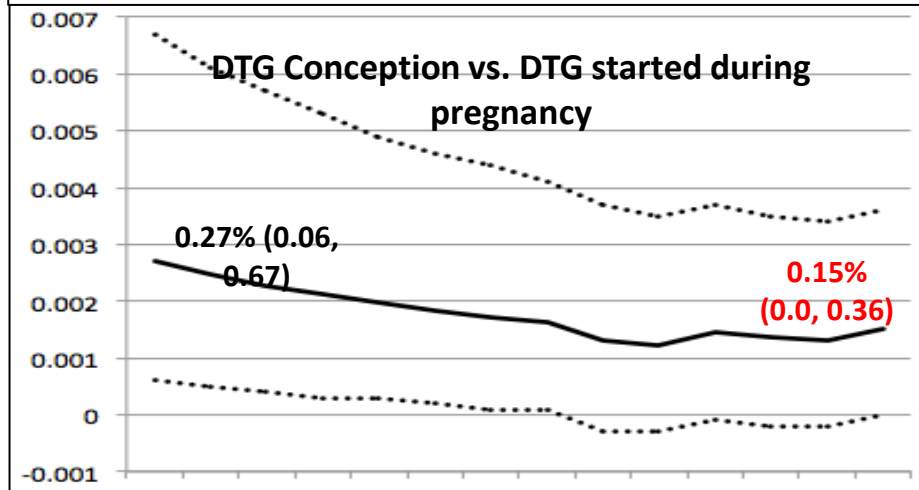
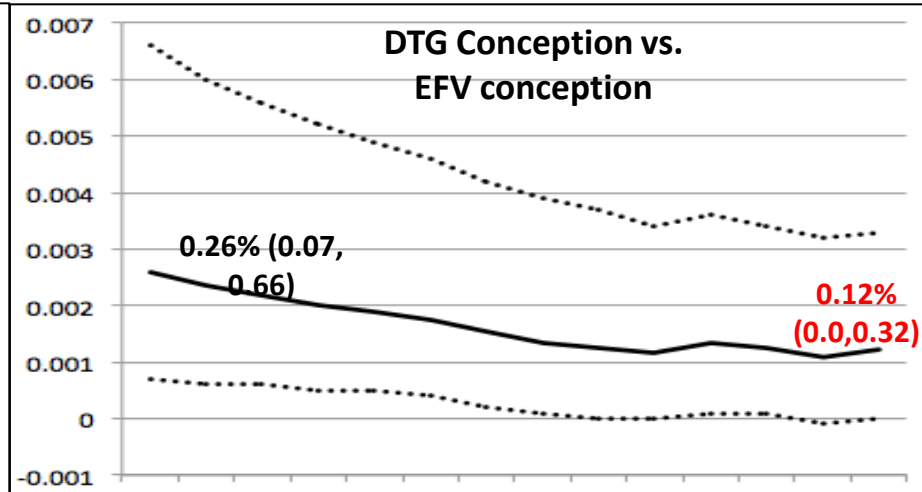
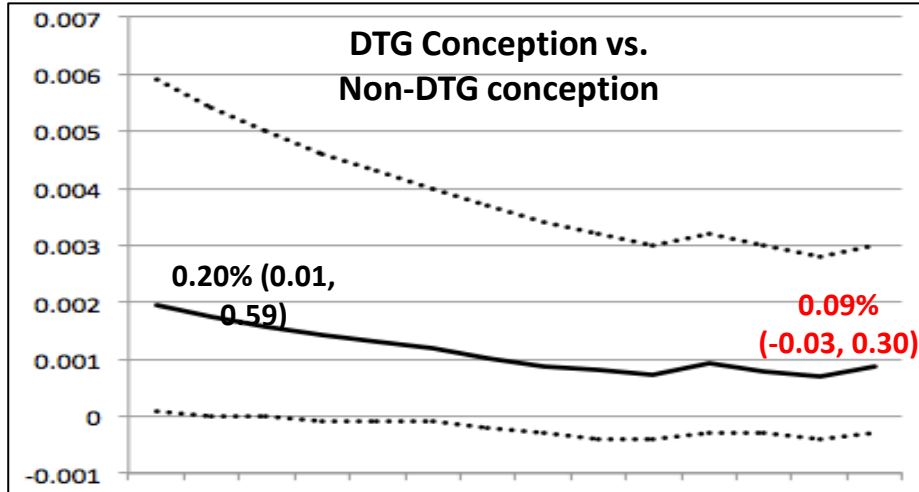


## Women without HIV

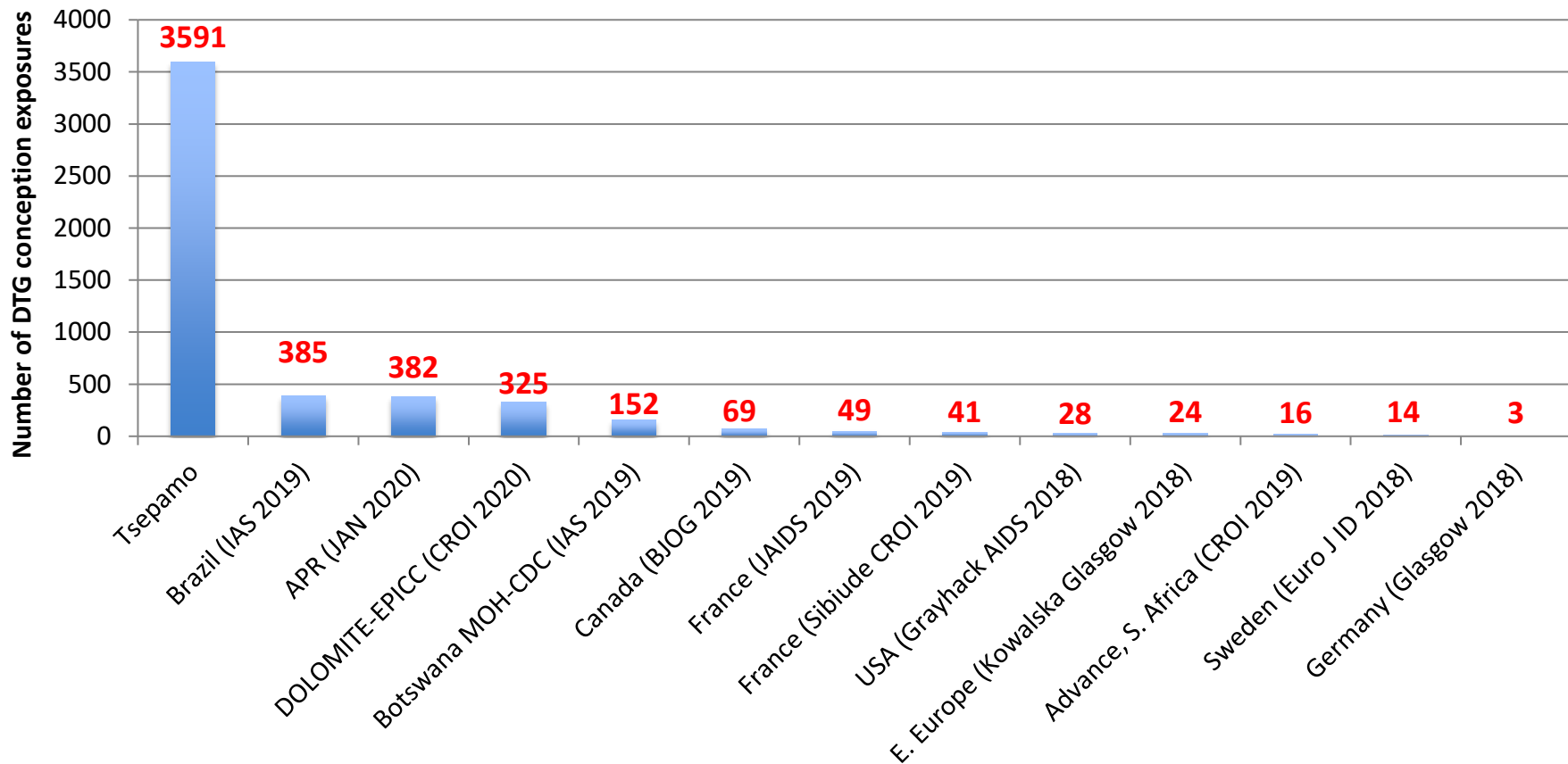
Total: 87 NTDs /119,630 exposed



# Prevalence Difference (95% CI)



# What About Other Data Sources?



## Other new DTG Data

Antiretroviral Pregnancy Registry (through 31 January 2020)

- **1 NTD/382 (0.26%)** peri-conception DTG exposures

Botswana MOH-CDC (non-Tsepamo sites)

- **1 NTD in 152 (0.66%)** periconception DTG exposures

DOLOMITE-EPICC (UK and Europe)

- **0 NTDs in 325 DTG (0%)** conception exposures (1 neural migration disorder with severe microcephaly induced abortion)

Brazilian MOH Case-Control Study (only live births)

- **0 NTDs in 384 (0%)** periconception DTG exposures but 2 NTDs reported to MOH with DTG conception exposure after study completed (?2 of ~900 exposures)

## Still lack similar birth defects data for....

- Raltegravir, Bictegravir, Elvitegravir
- Atazanavir, Darunavir
- Rilpivarinine

# ART Treatment Considerations in Pregnancy: It's not just birth defects...

Conception

Birth

Year 1

Year 2

Year 3

Year 4

Year 5

## Pregnancy complications

- HTN/Pre-e
- Anemia
- Weight gain
- miscarriage
- intrauterine MTCT

## Adverse Birth Outcomes

- birth defects
- preterm
- SGA/LBW
- stillbirth
- early NND
- intrapartum MTCT

## Childhood morbidity and mortality

- neonatal death
- under5 death
- postpartum MTCT
- pediatric HIV infection

## Long-term pediatric outcomes

- neurodevelopment
- malignancy
- immune dysfunction



# Risk vs. Benefit from Public Health Perspective

## A computer model

If DTG instead of EFV for all, over 20 years, for every 1000 women of childbearing potential starting DTG, there would be:

**2 more NTDs**

**1 more neonatal death**

BUT

**29 fewer MTCTs**

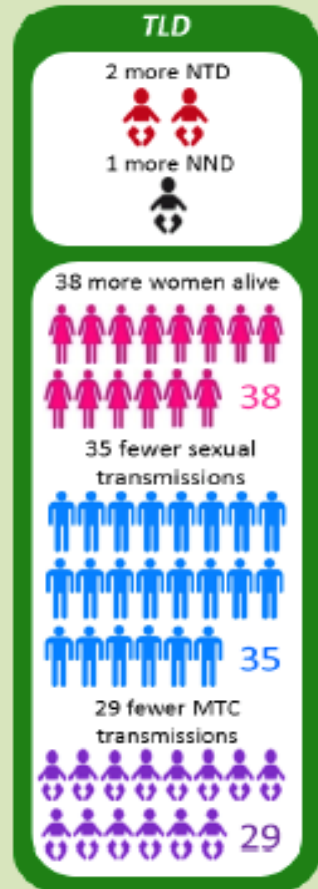
**38 more women alive**

**35 fewer transmissions to male partners**

**SYNTHESIS: May 2019 Tsepamo**

**Incl. NAMSAL/ADVANCE, PDR 9%**

For every 1000 WCP wanting more children starting ART, per year, compared with **TLE (average over 20 years)**:



## DTG-NTD Conclusions

**Conclusion:** Even in countries without mandated folate fortification of food, the increased risk of NTDs is very small (~1 excess NTD per 1000 births) compared to potential large public health benefits of DTG

# DTG and Pregnancy

Two major safety questions about the use of DTG in pregnancy

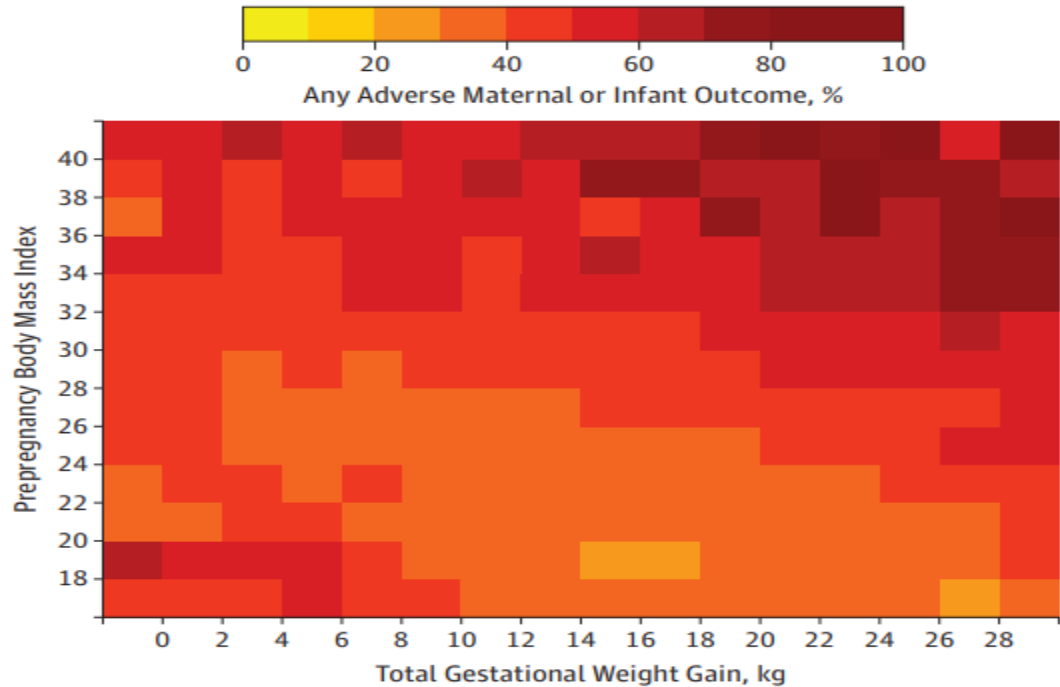
1. Is there increased risk of neural tube defects with DTG at conception?
2. Does DTG-associated weight gain impact pregnancy outcomes?

# Weight gain, pregnancy and DTG

- **High maternal pre-pregnancy weight and inappropriately high gestational weight gain** are associated with adverse maternal and birth outcomes:
  - Gestational hypertension and diabetes, preterm birth, macrosomia and obstructed labor
- **Low pre-pregnancy weight and inappropriately low gestational weight gain** are also associated with adverse outcomes such
  - Preterm birth, low birthweight, SGA, IUGR

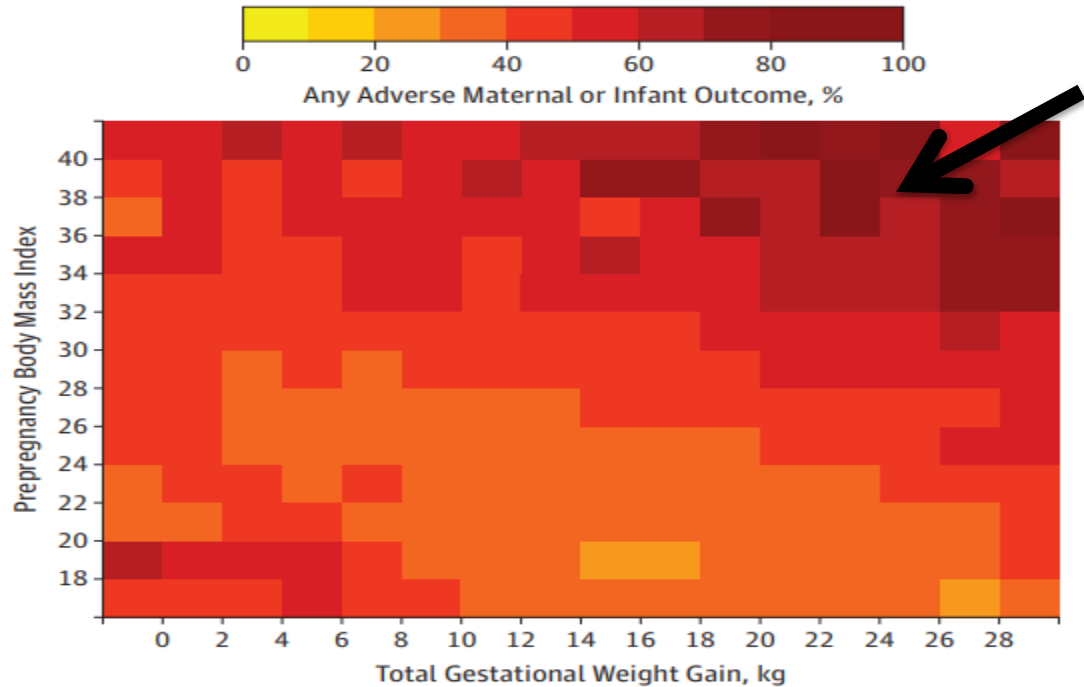
# Impact of pre-pregnancy weight and weight gain on infant outcomes

Meta-analysis of individual patient data: (N=196,670) from N. America and Europe



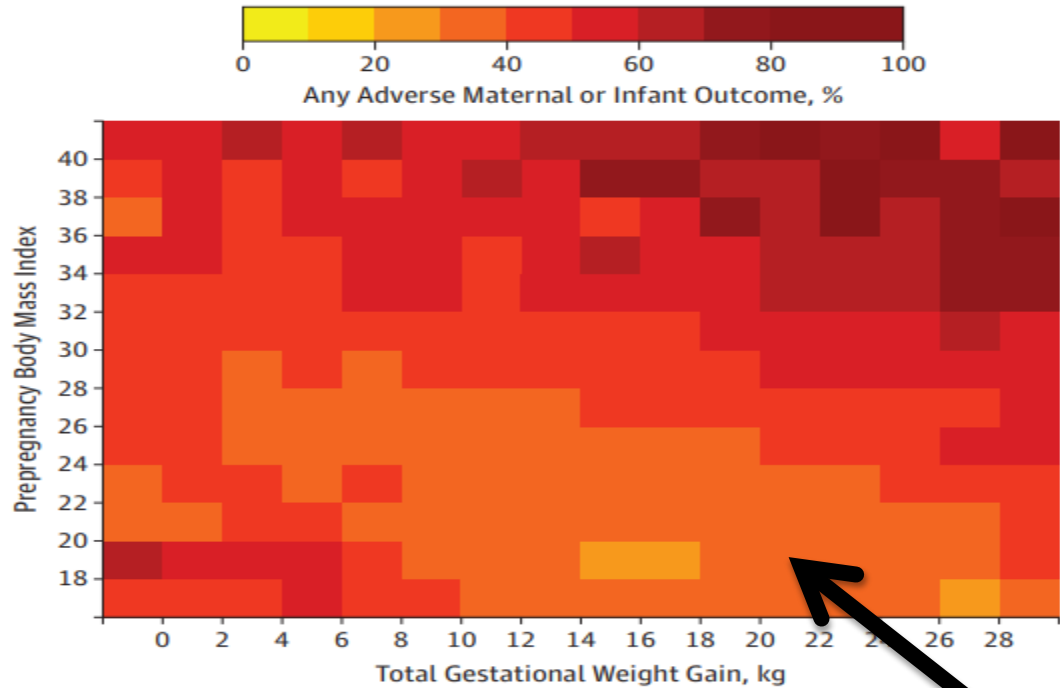
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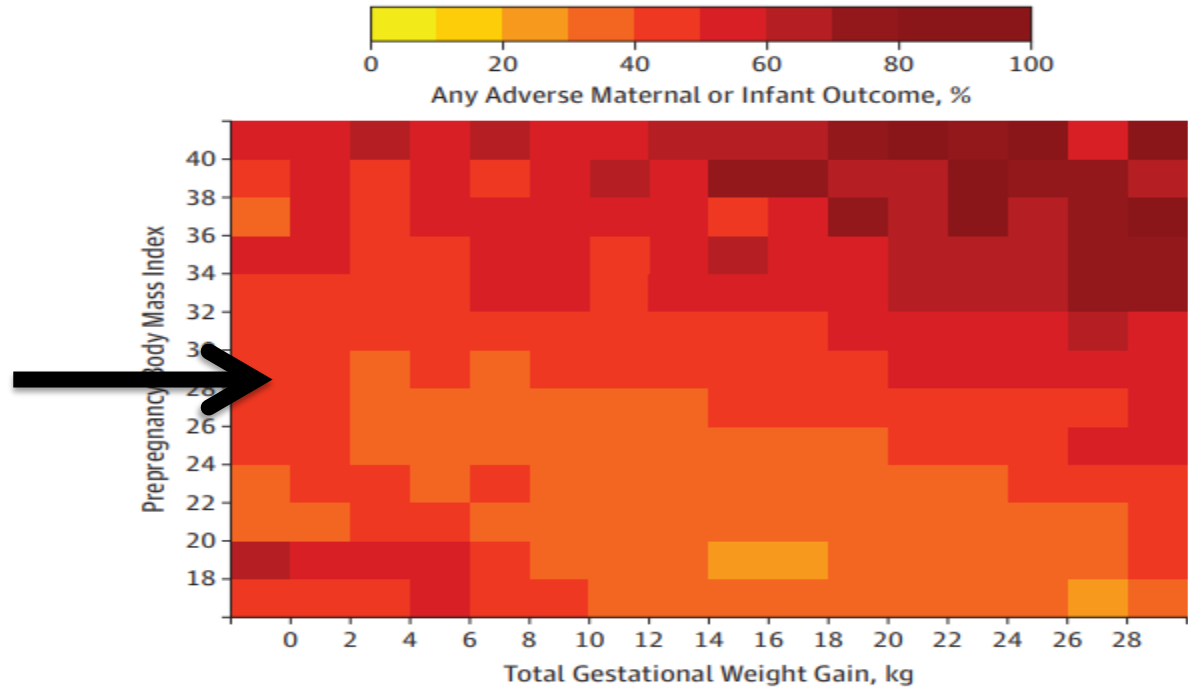
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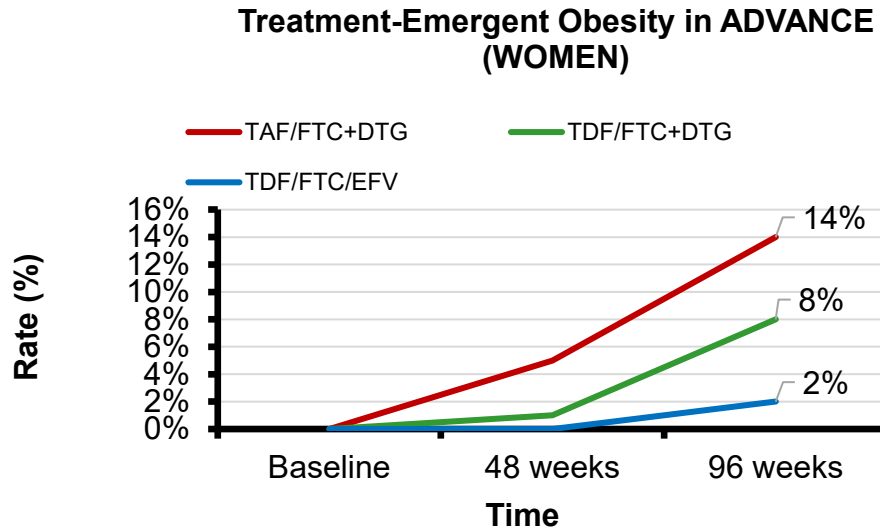
Meta-analysis of individual patient data: (N=196,670) from N. America and Europe





# Weight gain, pregnancy and DTG

## 1. Modeling the potential impact of weight gain increases on adverse maternal and infant outcomes (ADVANCE STUDY)



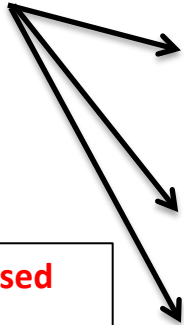
# ADVANCE: Will TAF/DTG associated weight gain impact pregnancy outcomes?

AIDS2020 Abstract: Asif et al, OABLB0103

## Adverse Outcomes per 1000 births (assuming obesity prevalence of ART regimen at 96-weeks)

Adverse Maternal Outcomes	Baseline	TAF/FTC/DTG	TDF/FTC/DTG	TDF/FTC/EFV
		96-weeks	96-weeks	96-weeks
Preterm delivery	70	73 (+3)	71 (+1)	70 (0)
Gestational hypertension	28	39 (+11)	34 (+6)	29 (+1)
Gestational diabetes	16	23 (+7)	19 (+3)	16 (0)
Pre-eclampsia	25	35 (+10)	30 (+5)	26 (+1)
Postpartum haemorrhage	112	115 (+3)	114 (+2)	112 (0)
Caesarean section	213	232 (+19)	224 (+11)	215 (+2)
Small-for-gestational-age infants	89	87 (-2)	88 (-1)	89 (0)
Large-for-gestational-age infants	134	154 (+20)	145 (+11)	137 (+3)
Macrosomia	31	37 (+6)	34 (+3)	31 (0)
Stillbirth	4	4 (0)	4 (0)	4 (0)
Neonatal death	2	2 (0)	2 (0)	2 (0)
Neural tube defect	0	0 (0)	0 (0)	0 (0)

Largest Predicted Increases



Total increased adverse outcomes ~8% with TAF/FTC/DTG

# Weight gain, pregnancy and DTG

2. **Clinical data** from IMPAACT 2010 (VESTED) and Tsepamo

# Weight Gain in Pregnancy is Higher with DTG than EFV

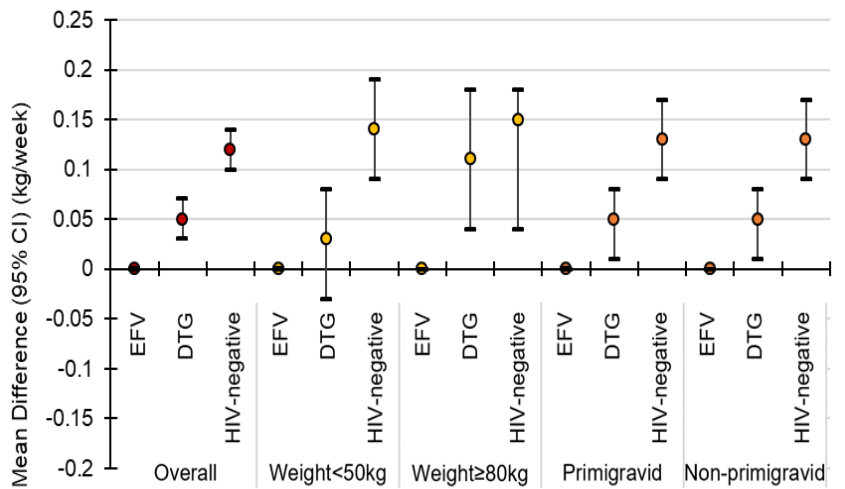
**Tsepamo (Botswana) Observational:**  
ART initiated at 1-17 weeks gestation

**TDF/FTC/DTG (N=1464)**

**TDF/FTC/EFV (N=1683)**

**Women without HIV (N=21,917)**

Adjusted mean difference (kg/week)

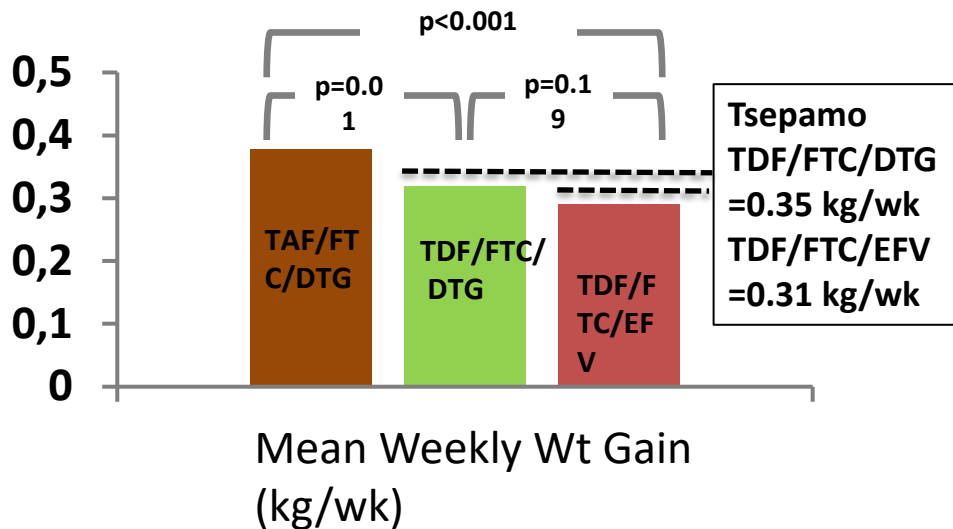


**VESTED (IMPAACT 2010) RCT**  
ART initiated at 14-28 weeks gestation

**TAF/FTC/DTG (N=217)**

**TDF/FTC/DTG (N=215)**

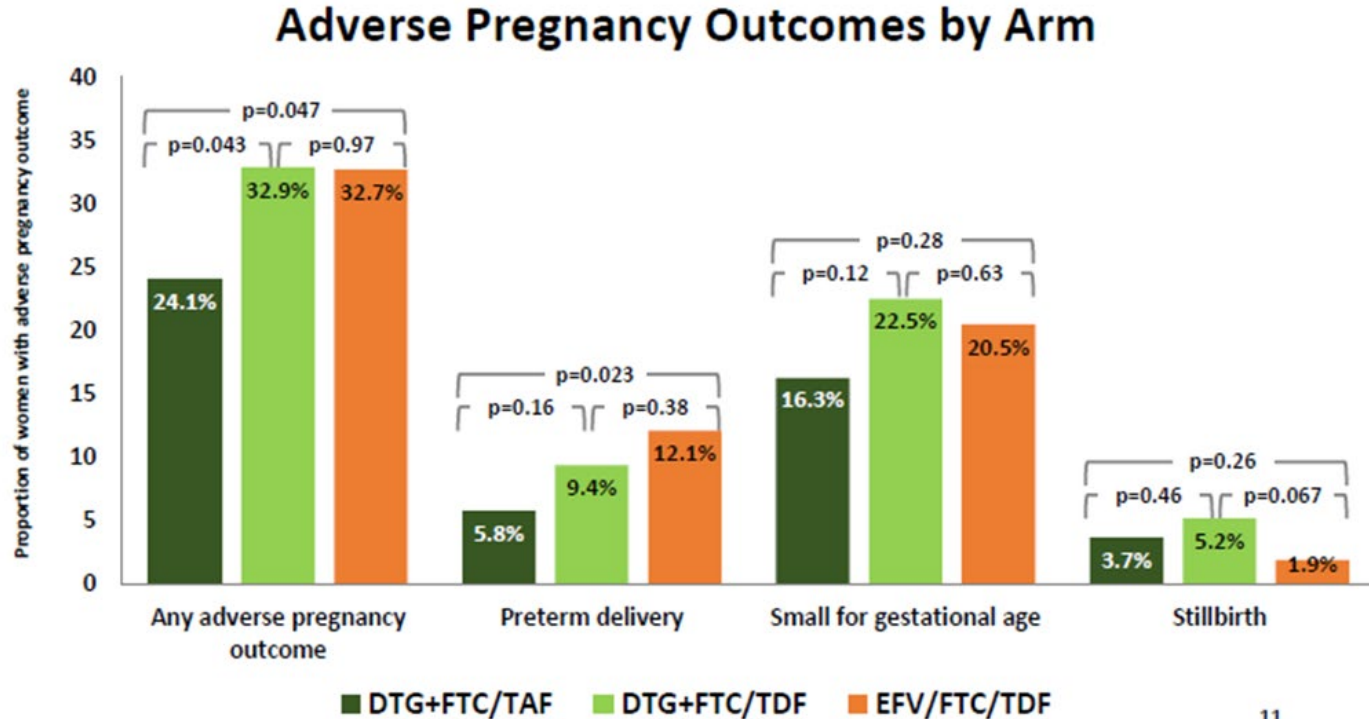
**TDF/FTC/EFV (N=211)**



## Weight Loss/Insufficient Gain is Higher with EFV than DTG

	EFV-based ART	DTG-based ART	Women without HIV
<b>Insufficient Weight Gain</b> ( $<0.18\text{kg/wk}$ , between 18+/-2 and 36 +/-2 weeks GA)			
<b>Total (%)</b>	312 (27.7%)	188 (20.2%)	1826 (11.1%)
<b>aRR</b>	1.00 (ref)	0.73 (0.63,0.99)	0.40 (0.36,0.45)
<b>Weight Loss</b> (between 18+/-2 and 36 +/-2 weeks GA)			
<b>Total (%)</b>	71 (9.4%)	27 (4.4%)	246 (2.2%)
<b>aRR</b>	1.00 (ref)	0.43 (0.28,0.67)	0.30 (0.19,0.47)

# Birth Outcomes Better for TAF/FTC/DTG from VESTED (IMPAACT 2010)



Notes: stillbirth was post-hoc analysis; and no spontaneous abortions occurred

# Weight Gain, Pregnancy and DTG: Conclusions

- **DTG may have *risks*** (excess gestational gain, increased pre-preg BMI) **but also may have *benefits*** (less inadequate weight gain and weight loss)
  - Pre-pregnancy weight is more important than gestational weight gain.
  - TAF with DTG is associated with increased weight gain but also better infant outcomes among ART naïve women starting ART in pregnancy

# Modeling Risks and Benefits of DTG in Pregnancy: Update to include NTD and Weight Gain

*Phillips A et al. Lancet HIV . 2020 Mar ;7 (3):e193-200*

Predicted Effects of Policy Option <i>over 20 years</i>	Initiate <b>TLE</b> for women intending pregnancy	Initiate <b>TLD</b> for women intending pregnancy
VL <1000 at 12m	74%	80%
Increase in CD4 at 12m	132	151
<b>HIV-related death rate</b>	<b>1.03 per 1000</b>	<b>0.65 per 1000</b>
NTDs	1	73
<b>MTCT</b>	<b>9650</b>	<b>8150</b>
Perinatal Death due to excess maternal BMI	1	43



# Is DTG the best ART for women of reproductive potential?

- We lack data to truly determine the BEST regimen
- Data support WHO guidelines for use of DTG as first-line ART, using a 'woman centered approach'
- DHHS guidelines (US) have recommendations for counseling of women starting DTG
  - <https://aidsinfo.nih.gov/guidelines/html/3/perinatal/552/appendix-d--dolutegravir-counseling-guide-for-health-care-providers>

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