INSTIs and Pregnancy

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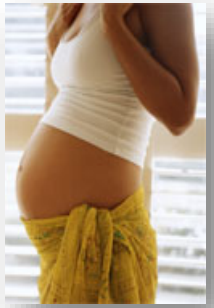


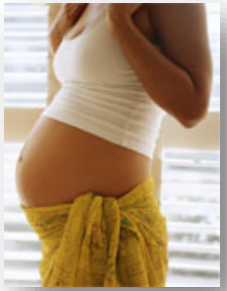
Use of Integrase Inhibitors in Pregnancy: Pharmacokinetics, Efficacy and Safety

Lynne M. Mofenson, M.D.

No conflicts to disclose

Elizabeth Glaser Pediatric AIDS Foundation

Until no child has AIDS.



InSTI Dosing: Pharmacokinetics, Placental Passage, Infant Exposure, and Breast Milk Passage

Pharmacokinetics in Pregnancy – Drug Dosing

Drug	PK Findings
DTG[1,2]	Modest ↓ total drug exposure late pregnancy (without change unbound free active drug levels). **No dose change needed.**
RAL[3]	Modest ↓ total drug exposure late pregnancy (without change unbound free active drug levels). **No dose change needed.**
EVG[4,5]	Significant ↓ in exposure 2nd/3rd trimester (peak ↓24%/44%, trough ↓81%/89%) due to ↓ cobicistat levels and pregnancy-related ↑ CYP3A4 enzyme metabolism; fail to reach target exposure (10%ile non-pregnant) in 50%/55%. **More frequent VL monitoring or consider switch in pregnancy.**
BIC	No data on PK in pregnancy.
CAB-LA[6]	Limited data in women who became pregnant on study, stopped IM CAB once pregnancy diagnosed; rate decline similar to non-pregnant women with levels 3x PA-IC_{90} at delivery, still detectable at 2-23 weeks postpartum in 2/3 women.

[1] Bollen P et al. Clin Infect Dis. 2020 Feb 26;ciaa006.

[2] Mulligan N et al. AIDS. 2018;32:729-37.

[3] Zheng Y et al. Antimicrobial Agents Chemother. 2020;64:e00759-20.

[4] Momper JD et al. AIDS. 2018;32:2507-16.

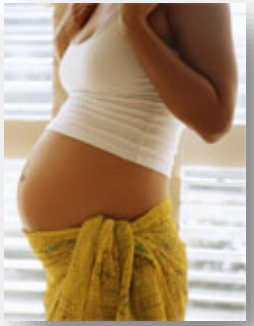
[5] Bukkems V et al. Clin Infect Dis. 2020 Apr 24;ciaa488.

[6] Patel P et al. CROI 2020, Boston. Abs. 77.

Placental Passage, Infant Wash-Out PK, Breast Milk Passage

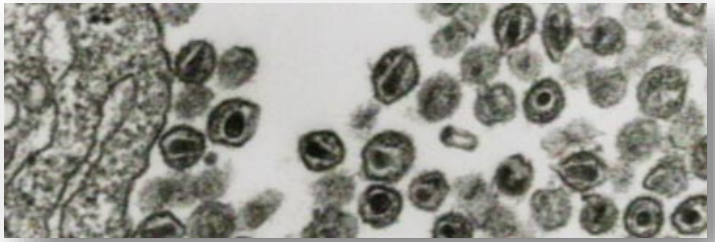
Drug	PK Findings
DTG[1,2,3]	• High placental transfer to fetus; cord:maternal blood ratio 1.2-1.3. • Prolonged half-life in newborn, 32.8 hours (immature UGT1A1). • Breast milk transfer, levels 2-3% maternal
RAL[4,5]	• High placental transfer to fetus; cord:maternal blood ratio 1.2-1.5. • Prolonged half-life newborn, 27 hours (immature UGT1A1). • No data breast milk
EVG[6]	• Good placental transfer to fetus; cord:maternal blood ratio 0.9. • Half-life in newborns similar to non-pregnant adults, 7.6 hours. • No data breast milk
BIC[7]	*Ex vivo* placental cotyledon perfusion model: low transfer, maternal to fetal ratio 0.10
CAB-LA[7]	*Ex vivo* placental cotyledon perfusion model: low transfer, maternal to fetal ratio 0.07

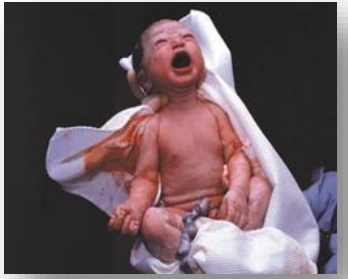
[1] Waitt C et al. PLosMed. 2019;16:e1002895
[2] Rimawi BH et al. Antimicrobial Agents Chemother. 2017;61:e00213-16
[3] Mulligan N et al. AIDS. 2018;32:729-37.
[4] Watts DH et al. JAIDS. 2014;67:375-81
[5] Clarke DF et al. JAIDS. 2014;67:310-5
[6] Momper JD et al. AIDS. 2018;32:2507-16.
[7] Pencole L et al. AIDS. 2020;34:2145-9.



Safety and Efficacy Data

Clinical Trials of DTG or RAL-Based ART in Pregnancy





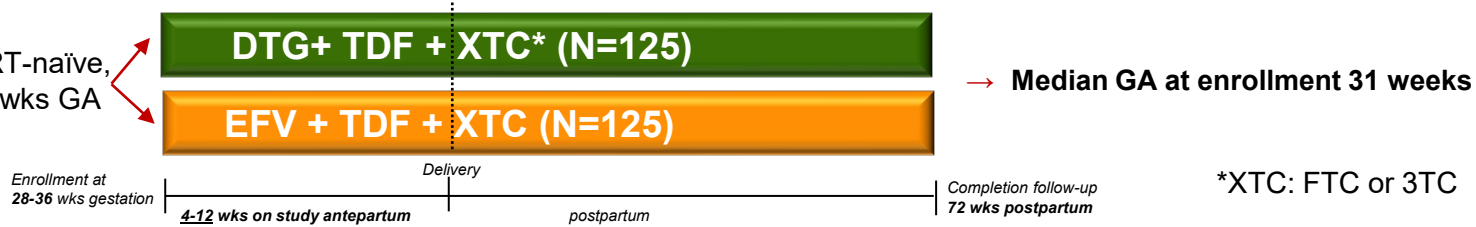
Two Trials of DTG vs EFV Started During Pregnancy

Kintu K et al. Lancet 2020;7:e332-9; Chinula L et al. CROI, 2020 Boston Abs. 130LB

- *DolPHIN-2 :* ART-naïve HIV+ pregnant women randomized at **28-36** weeks gestation. Delivery viral endpoint VL <50/1000 c/mL.

South Africa and Uganda

250 ART-naïve, 28-36 wks GA

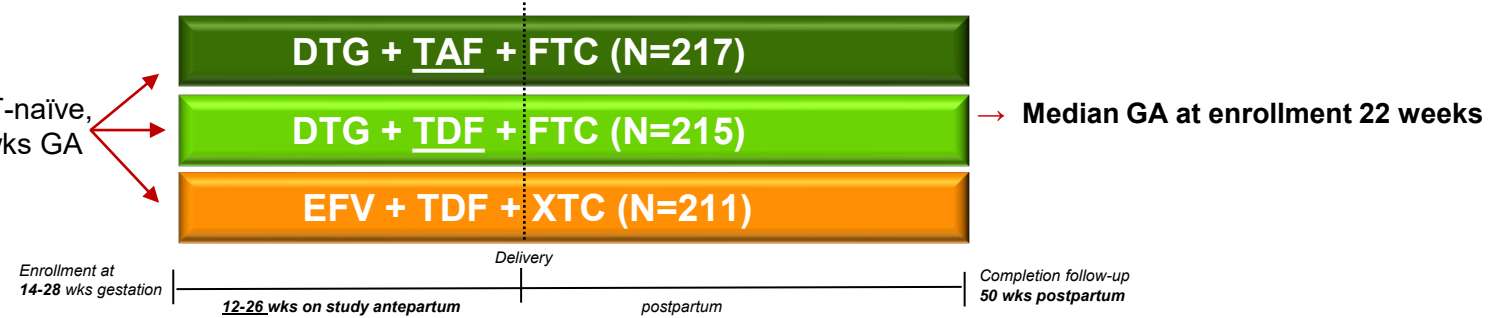


*XTC: FTC or 3TC

- *VESTED:* ART-naïve HIV+ pregnant women randomized at **14-28** weeks gestation. Delivery viral endpoint VL <200 c/mL.

22 sites in 9 countries

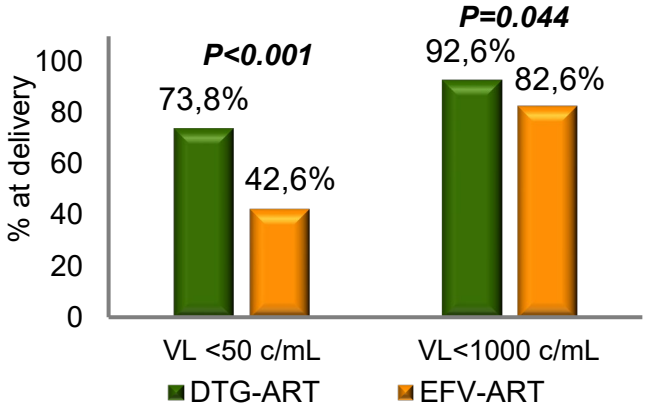
643 ART-naïve, 14-36 wks GA



More Rapid and Superior Viral Response at Delivery with DTG ART vs EFV ART in Pregnancy

DolPHIN2 *Kintu K et al. Lancet 2020;7:e332-9*

% VL <50 or <1000 copies/mL at delivery, DTG-ART vs EFV-ART

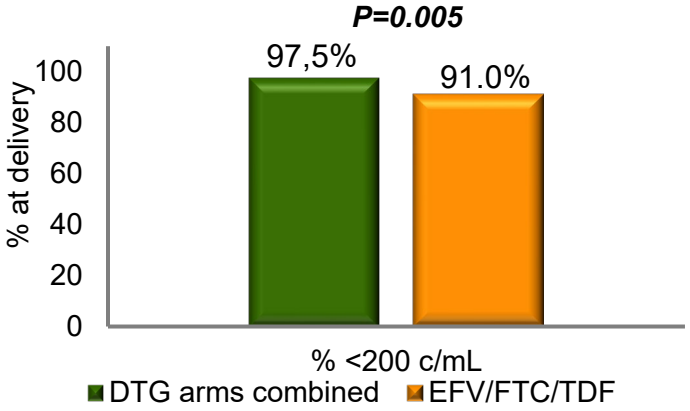


→ Both studies show superior viral efficacy at delivery with DTG.

→ Difference between studies in extent suppression related to different duration ART antepartum and differing VL endpoints.

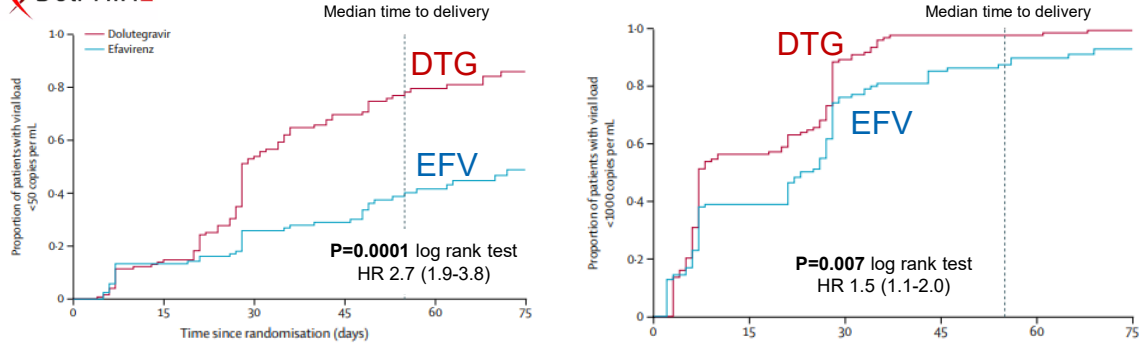
IMPAACT *Chinula L et al. CROI, 2020 Boston Abs. 130LB*

% VL <200 copies/mL at delivery, Combined DTG-ART vs EFV



DolPHIN2

Time to VL <50 or <1000 copies/mL, DTG-ART vs EFV-ART



→ In addition to superior efficacy, both studies showed significantly more rapid viral suppression with DTG than EFV (DolPHIN-2 shown, also observed in IMPAACT VESTED trial)

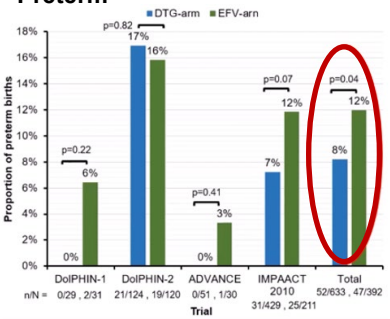
Toxicity and Pregnancy Outcome, DTG vs EFV Meta-Analysis 5 Clinical Trials

Asif SF et al. IAS Virtual July 2020 Abs.OABLB0195

- Meta-analysis 1074 pregnant women from 5 trials; 3 late pregnancy (DolPHIN 1/2, VESTED), while 2 (NAMSAL, ADVANCE) had became pregnant on study drug.

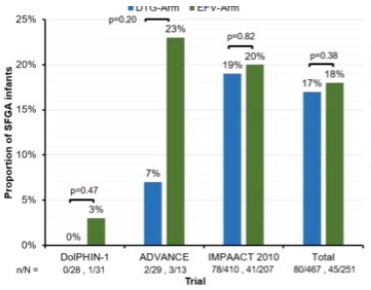
Trial	Exposure	DTG Arm	EFV arm
DolPHIN-1 (PK)	Enroll 3rd T	29	31
DolPHIN-2	Enroll 3rd T	137	131
IMPAACT 2010	Enroll 3rd T	DTG-TDF 216 DTG-TAF 213	211
ADVANCE (non-pregnant)	Conception	DTG-TDF 26 DTG-TAF 25	30
NAMSAL (non-pregnant)	Conception	13	12

Preterm



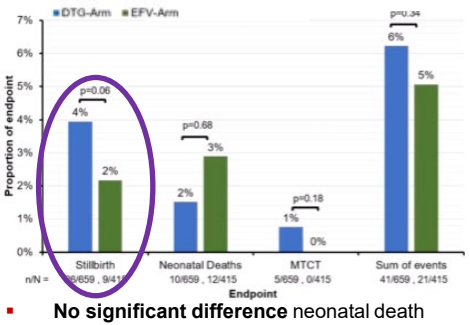
- **Higher rate PTD** with **EFV**

Small for Gestational Age



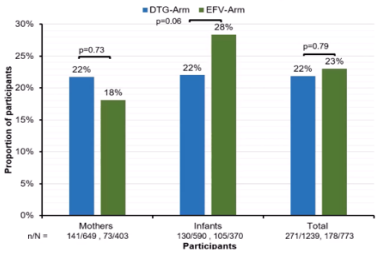
- **No difference** SGA **DTG** vs **EFV**

Stillbirth, Neonatal Death, MTCT



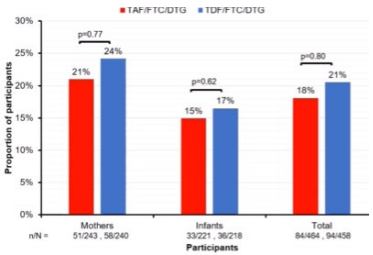
- **No significant difference** neonatal death or MTCT **DTG** vs **EFV** (despite faster suppression, all MTCT DTG arm); non-significant trend ↑ stillbirths with **DTG**

Adverse Events



- **No significant difference** AE mother/infants with **DTG** vs **EFV**

Adverse Events TAF vs TDF



- **No significant difference** AE mother/infants with TAF vs TDF

→ Short-term safety profile of DTG and EFV (and TAF and TDF) generally similar in meta-analysis; most started drugs during pregnancy as opposed to preconception (no NTD with 64 DTG preconception exposures).

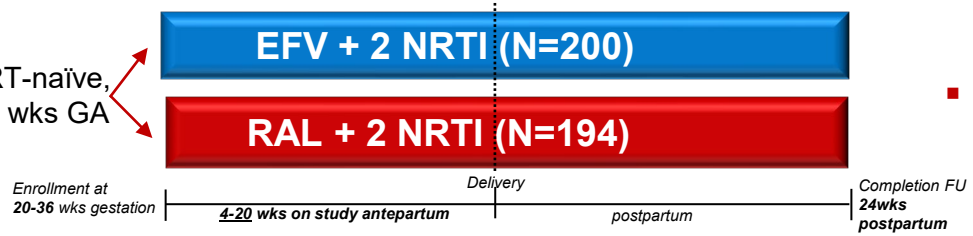
RAL vs EFV ART Started in Late Pregnancy

Joao EC et al. Lancet HIV. 2020;7:e322-31

- *NICHD/IMPAACT 1081*: ART-naïve HIV+ pregnant women randomized at 20-36 weeks gestation. Delivery viral endpoint VL <200 c/mL.

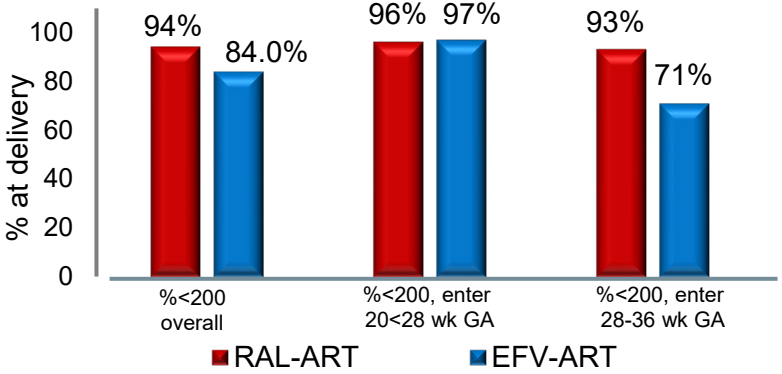
19 clinics Argentina, Brazil, South Africa, Tanzania, Thailand, and US

394 ART-naïve, ≥20-36 wks GA

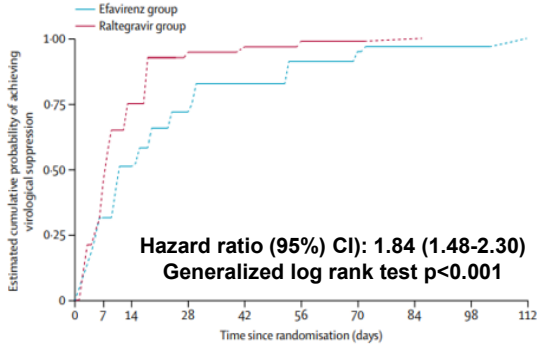


- No significant difference AE in mothers or infants
- MTCT 1/190, 1% RAL, 6/184, 3% EFV, p=0.064 (all to late presenters)

% VL <200 c/mL at delivery, RAL-ART vs EFV-ART, by entry GA



Estimated probability of viral suppression



→ RAL superior viral efficacy at delivery compared to EFV.

→ Driven by women entering at later GA, having shorter duration ART prior to delivery.

→ RAL more rapid viral suppression compared to EFV.

Lancet HIV 2020; 7: e666–76

Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial

Willem D F Venter, Sinisa Sokhela, Bryony Simmons, Michelle Moorhouse, Lee Fairlie, Nkuli Mashabane, Celicia Seemela, Godspower Akpomiemie, Mosebedi Mosenya, Amber Qavi, Nonnatemba Chandiwana, Kaitlyn McCann, Shane Norris, Matthew Cherish, Gary Maartens, Samanta Lalla-Edward, Alinda Vos, Polly Clayden, Elaine Abrams, Natasha Arulappan, Andrew Hill

DTG and Weight Gain

ORIGINAL ARTICLE

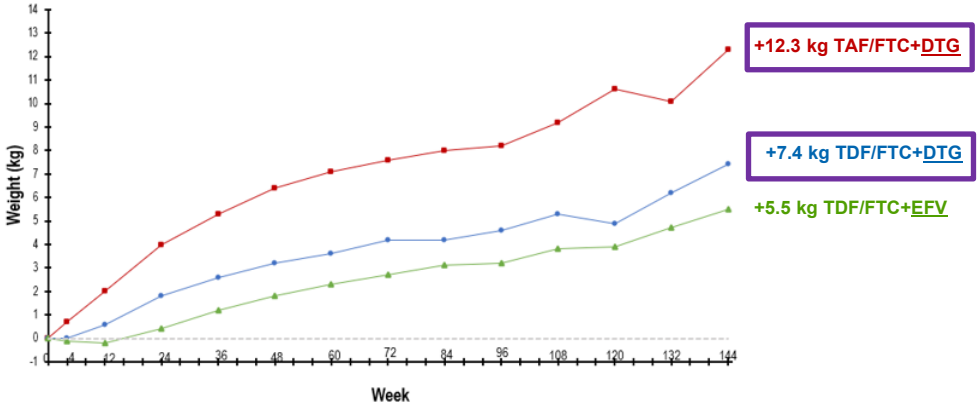
N Engl J Med 2019;381:816-26.

Dolutegravir-Based or Low-Dose Efavirenz–Based Regimen for the Treatment of HIV-1

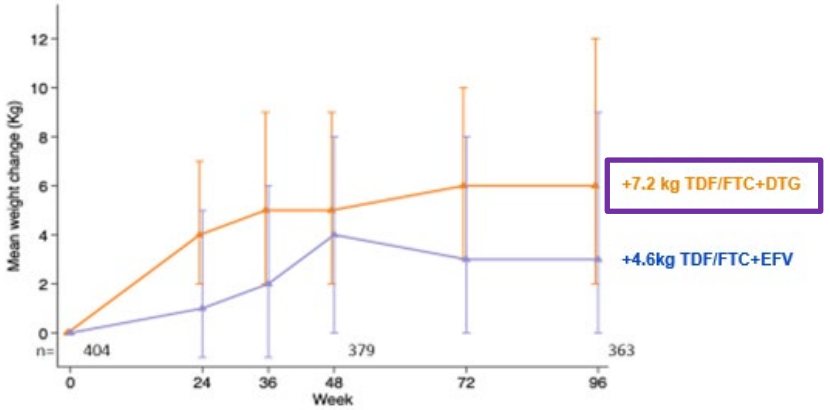
The NAMSAL ANRS 12313 Study Group*

- Data from 2 randomized trials (ADVANCE, NAMSAL) of DTG vs EFV ART in ART-naïve non-pregnant adult found excessive weight gain with DTG, highest in non-pregnant women and when given with TAF.

ADVANCE trial weight gain, to 144 weeks: Women



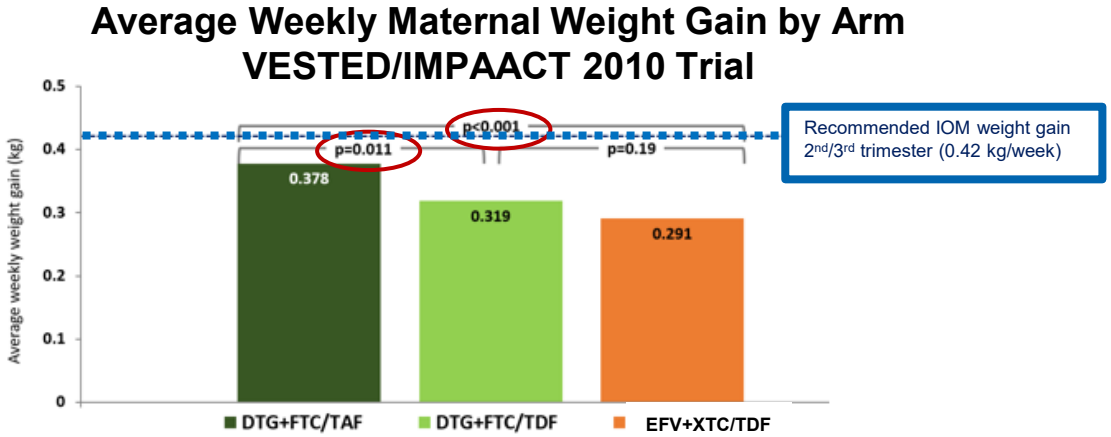
NAMSAL trial weight gain to 96 weeks: Women



- Given known association of excess weight gain in pregnancy with adverse pregnancy outcomes *(Santos S. BJOG. 2019;126:984-95)*, what do we know about weight gain in pregnancy and postpartum with DTG?

Weekly Weight Gain During Pregnancy Highest with DTG-TAF compared to DTG-TDF and EFV

Chinula L et al. CROI, 2020 Boston Abs. 130LB

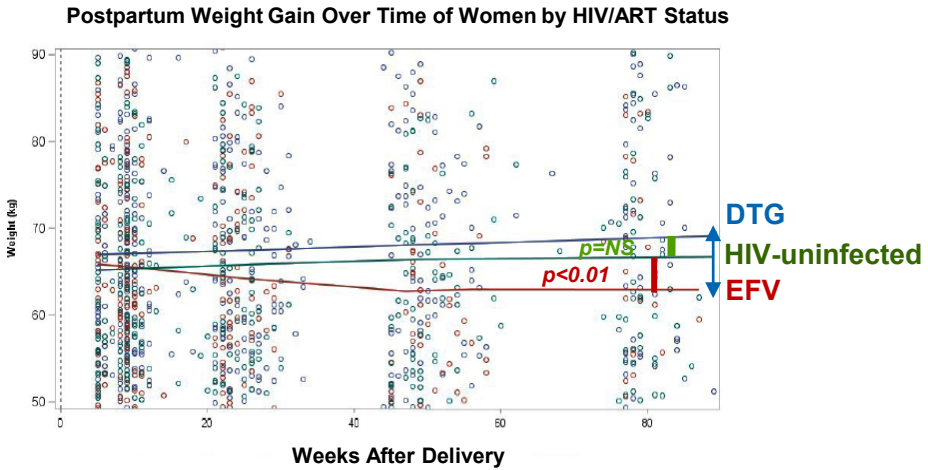


- Weekly maternal weight gain significantly higher in DTG/TAF/FTC arm than DTG/TDF/FTC or EFV/XTC/TDF arms (which were not significantly different).
- However, even with DTG/TAF, weekly weight gain was **less than recommended** for the general population.

DTG ART is Associated with Higher Postpartum (PP) Weight Gain than EFV ART, Botswana

Jao J et al. CROI, 2020 Boston Abs. 772

- Pregnant HIV+ women on DTG (n=170) or EFV (n=114) ART and HIV-uninfected (n=122) women followed in observational Tshilo Dikotla study Botswana.
- Assessed the association of DTG with PP weight over 18 mos PP comparing HIV+ women on DTG vs EFV and to HIV-uninfected women.

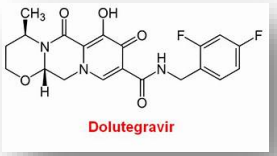


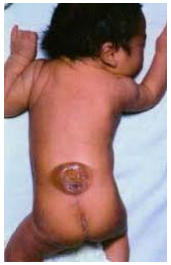
→ HIV+ women on DTG had significantly higher weight gain (~5 kg) through 18 mos PP vs those on EFV, adjusting for CD4, VL, and ART at conception.

→ However, compared to HIV-uninfected women, HIV+ women on DTG had similar PP weight gain while HIV+ women on EFV had lower weight gain vs HIV-uninfected women ($p<0.01$).

Summary - Safety/Efficacy

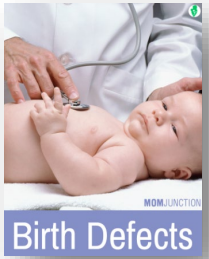
- DTG or RAL ART started in pregnancy results in more rapid and superior viral suppression by delivery than EFV ART.
- Adverse pregnancy outcomes and maternal/infant toxicity with DTG or RAL are not different than EFV.
- While DTG ART is associated with higher weight gain than EFV ART during pregnancy and postpartum, even with DTG, weight gain during pregnancy was less than recommended and weight gain postpartum similar to HIV-uninfected women.

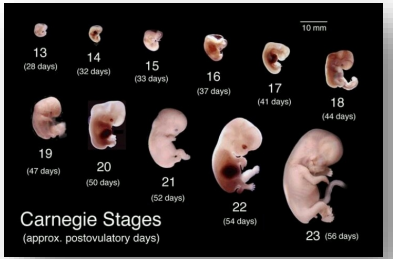




Open spinal bifida
(Copp & Greene, 2016, Encyclopedia of Life Sciences, John Wiley)

Infant Safety, Including Neural Tube Birth Defects and Preconception DTG



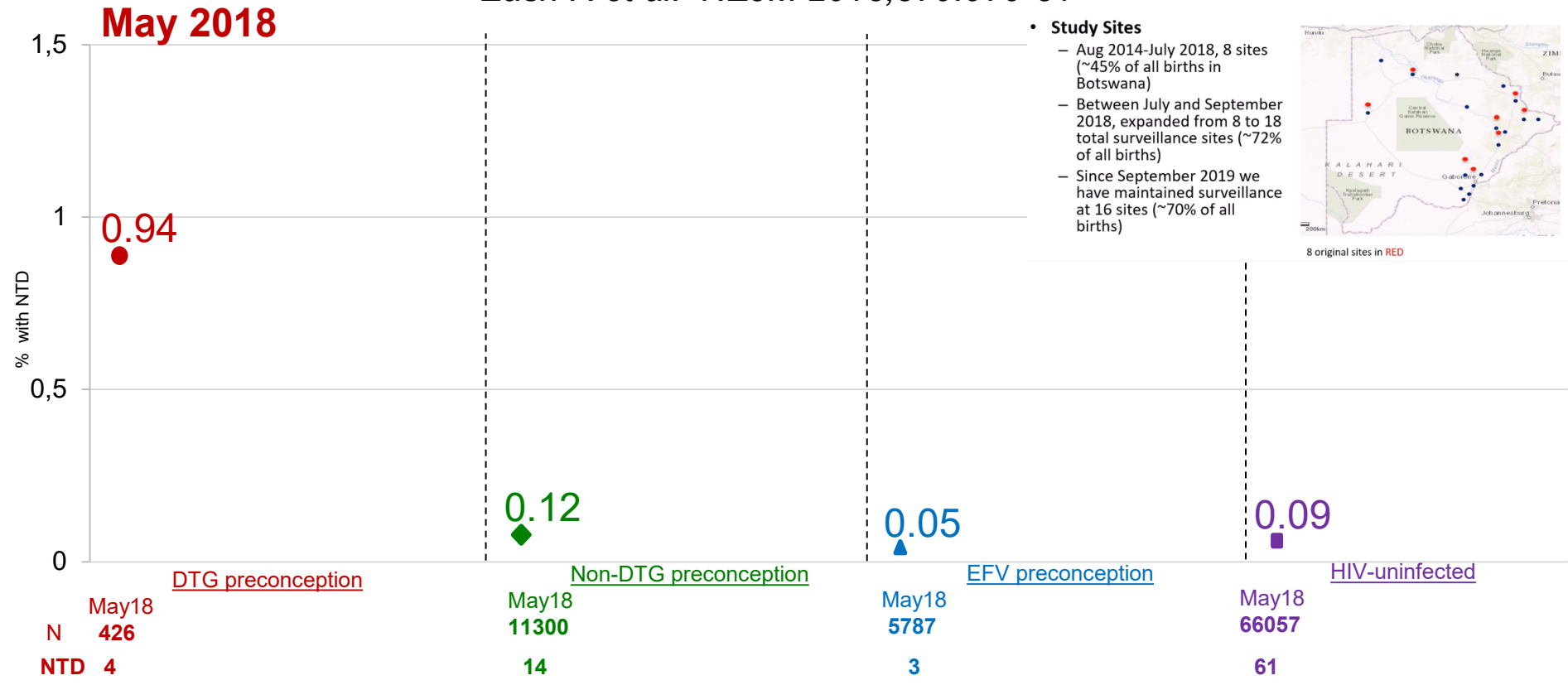


Botswana Tsepamo Study – Birth Surveillance

- Designed to evaluate the risk of neural tube defects (NTD) with *preconception EFV exposure*
- Prospective birth outcomes surveillance for major surface birth defects, initially at 8 large maternity wards, population-based (45% of Botswana births)
- Trained hospital-based midwifes surface exam
- Research assistant consent mother for photo
- Medical geneticist reviews reports blinded to exposure
- Good denominator with control groups including HIV-uninfected women, and ability to distinguish between ART regimens and ART preconception or started in pregnancy

Tsepamo: Evolution of NTD Prevalence with Preconception DTG

Zash R et al. NEJM 2018;379:979-81



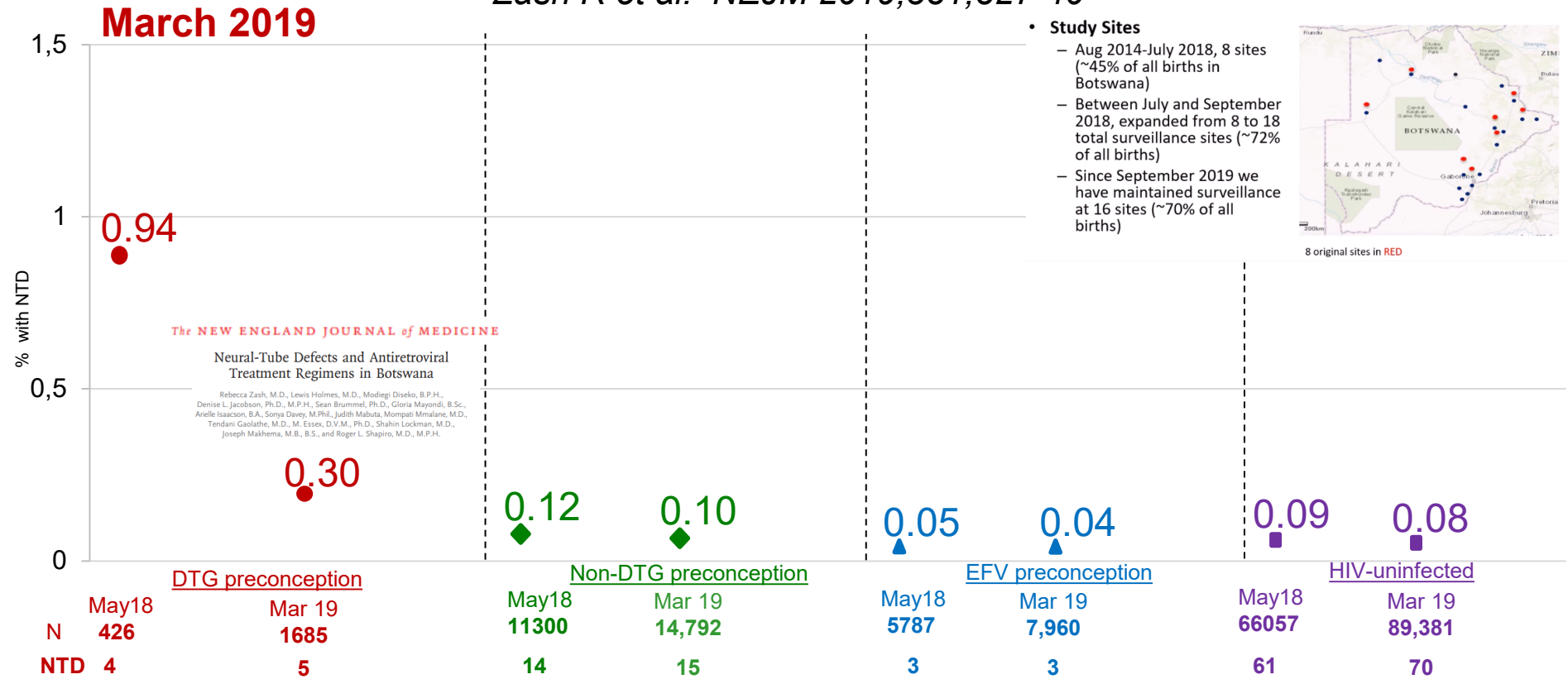
- **Study Sites**
  - Aug 2014-July 2018, 8 sites (~45% of all births in Botswana)
  - Between July and September 2018, expanded from 8 to 18 total surveillance sites (~72% of all births)
  - Since September 2019 we have maintained surveillance at 16 sites (~70% of all births)

8 original sites in RED

→ Significant prevalence difference between DTG preconception and other exposure groups (**0.82 to 0.94**)

Tsepamo: Evolution of NTD Prevalence with Preconception DTG

Zash R et al. NEJM 2019;381;827-40



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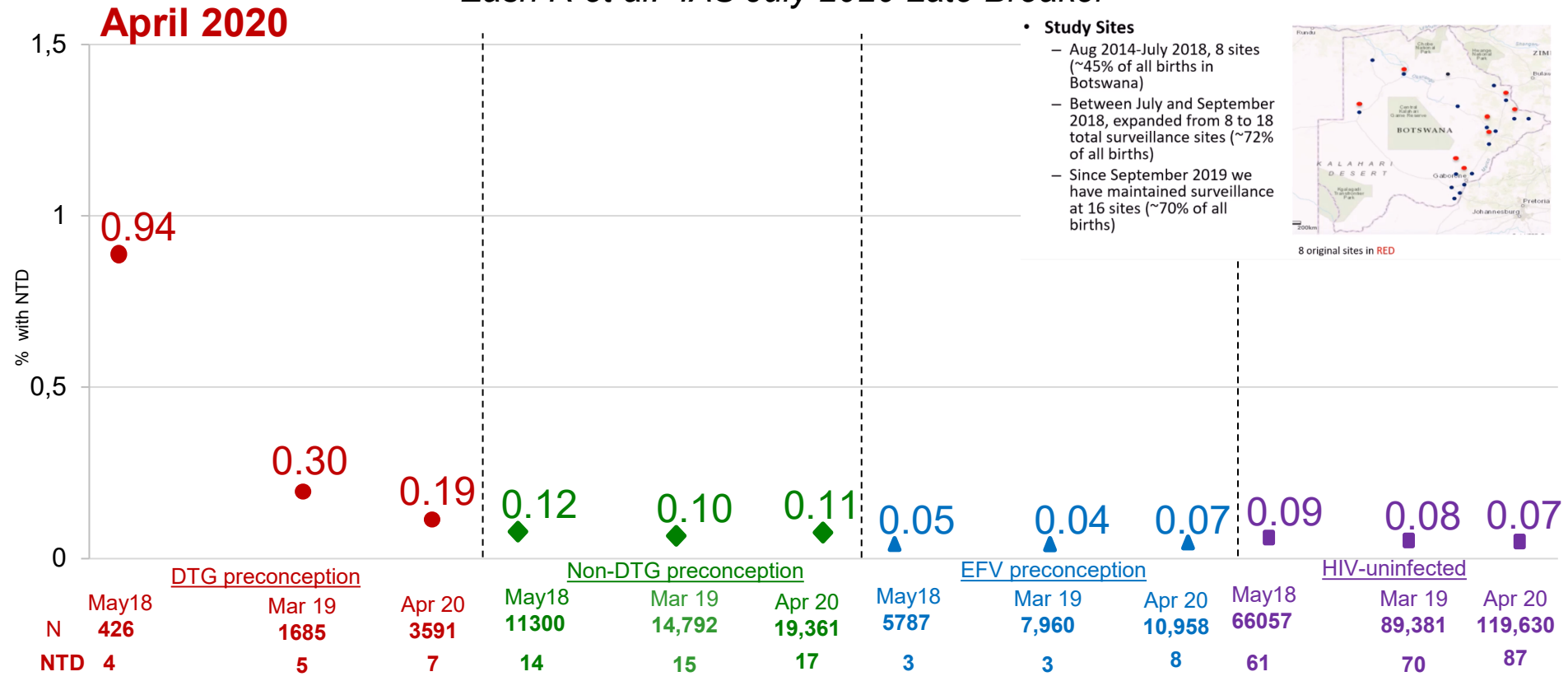
8 original sites in RED

→ Still significant prevalence difference between DTG preconception and other exposure groups (**0.20 to 0.27**)

Tsepamo: Evolution of NTD Prevalence with Preconception DTG

Zash R et al. IAS July 2020 Late Breaker



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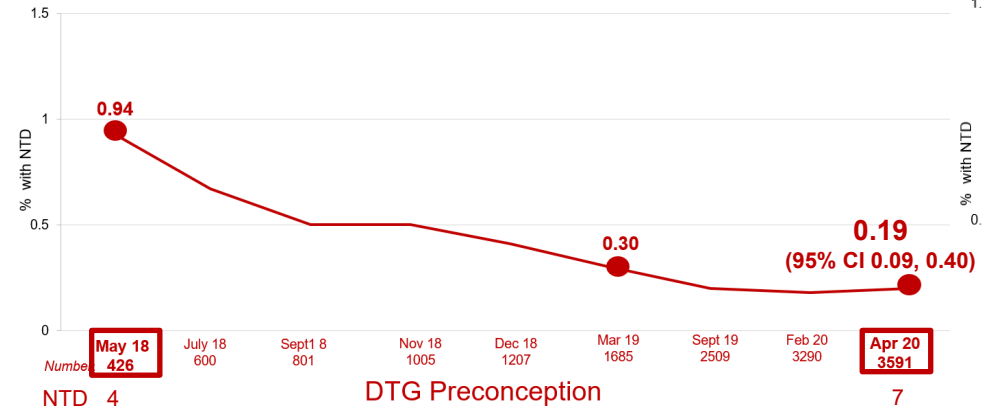
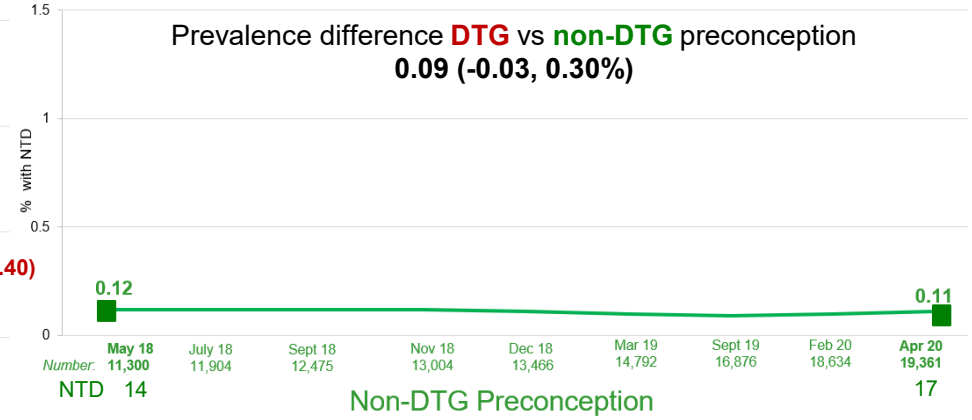
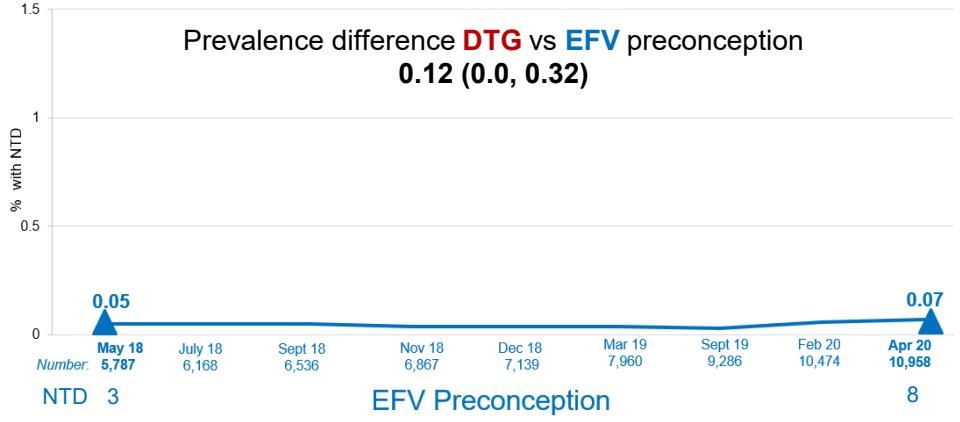
8 original sites in RED

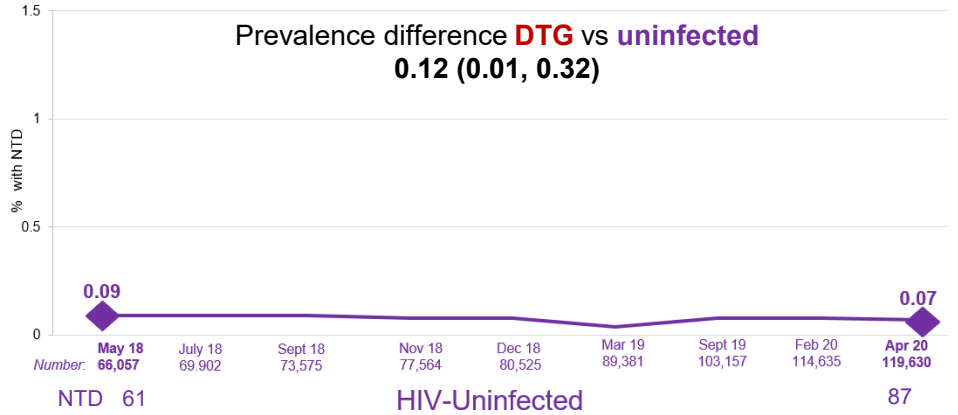
Tsepamo: Evolution of NTD Prevalence with Preconception DTG

Zash R et al. IAS Virtual July 2020 Abs. OAXLB0102





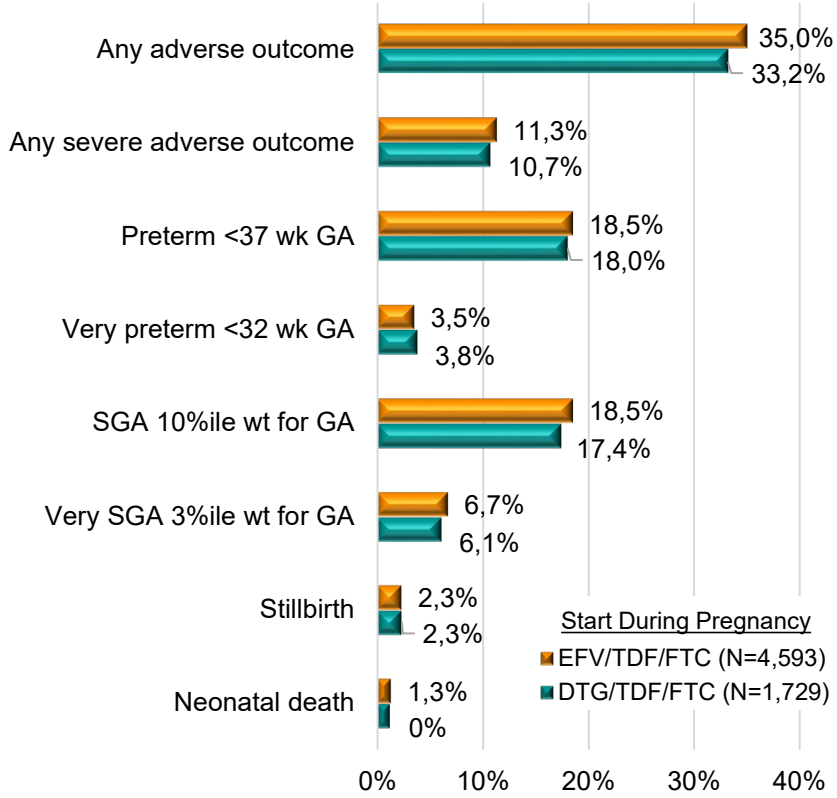




Other Pregnancy Outcomes Appear Similar with DTG vs EFV Regardless of Timing

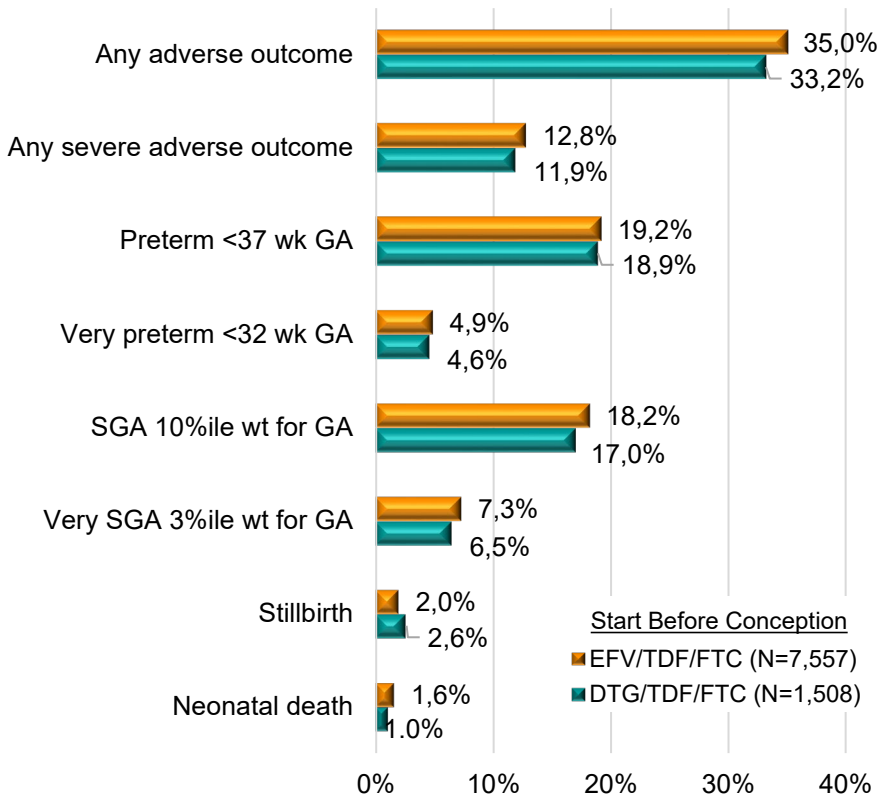
Tsepamo Study

EFV or DTG **Started During Pregnancy**



Zash R et al. Lancet Global Health 2018;6:e804-10

EFV or DTG **Started Before Conception**



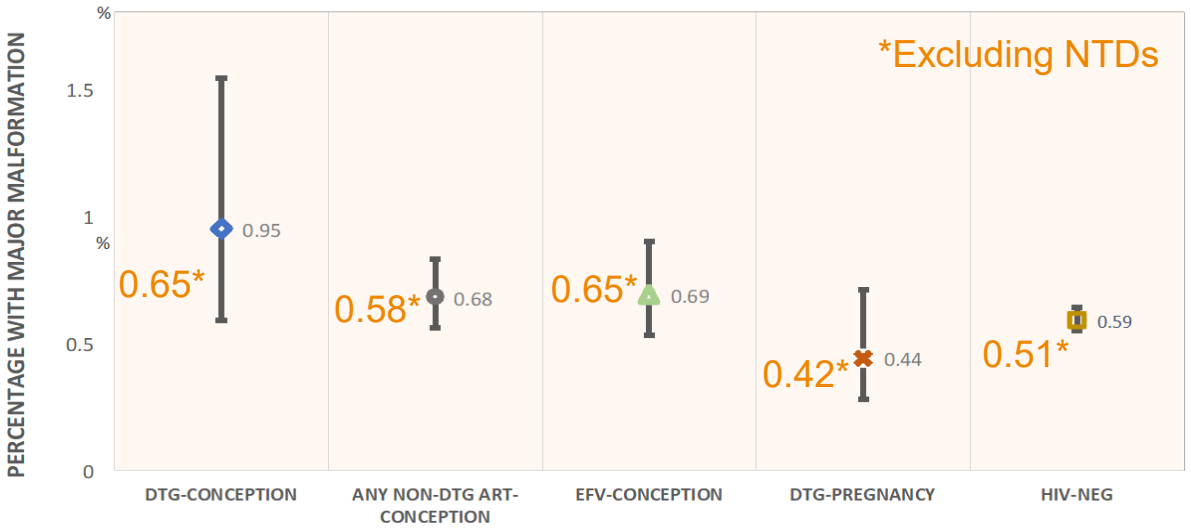
Zash R et al. N Engl J Med 2019;381:827-40

Major Structural Malformations by Exposure

Zash R et al. NEJM 2019;381;827-40

→ NTD accounted for 14% major defects

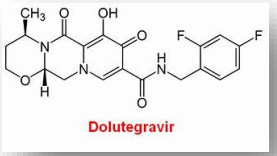
→ <u>No significant difference</u> overall major structural defects DTG vs non-DTG at conception, EFV at conception, HIV-uninfected

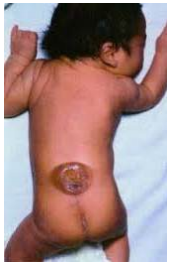


DTG at conception, major structural defects:

- neural-tube defects (5)
- presumed holoprosencephaly (1)
- omphalocele (2)
- gastroschisis (2)
- club foot (2)
- upper-limb defects (2)
- anophthalmia (1)
- skeletal dysplasia (1)
- neural-tube defects (5)

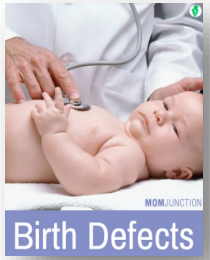
# of Major Malformations	16	101	55	17	528
Number of Exposures	1683	14792	7959	3840	89372
% with MM (95% CI)	0.95% (0.59%, 1.54%)	0.68% (0.56%, 0.83%)	0.69% (0.53%, 0.90%)	0.44% (0.28%, 0.71%)	0.59% (0.54%, 0.64%)
Prevalence Difference (95% CI)	ref	0.27% (-0.13%, 0.87%)	0.26% (-0.16%, 0.87%)	0.51% (0.06%, 1.12%)	0.36% (-0.01%, 0.95%)

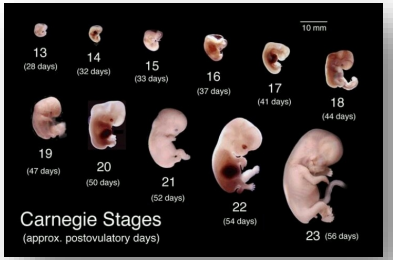




Open spinal bifida
(Copp & Greene, 2016, Encyclopedia of Life Sciences, John Wiley)

Other Data on Neural Tube Birth Defects and Preconception DTG and other InSTI

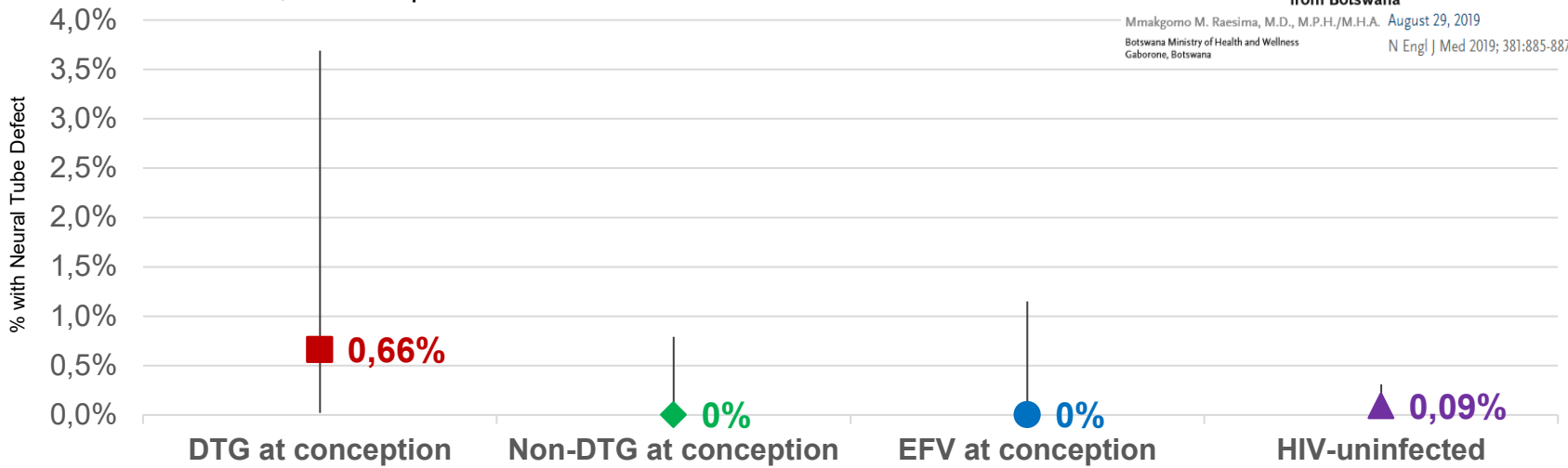




Expanded Surveillance by MOH-CDC-Botswana

Raesima MM et al. NEJM 2019;381:885-7

→MOH added 22 non-Tsepamo facilities
→With Tsepamo cover 92% all births in country
→3070 deliveries=3122 infants, 6 month period **Oct 2018-Mar 2019**



The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Dolutegravir Use at Conception — Additional Surveillance Data from Botswana

Mmakgomo M. Raesima, M.D., M.P.H./M.H.A.
Botswana Ministry of Health and Wellness
Gaborone, Botswana

August 29, 2019
N Engl J Med 2019; 381:885-887

Number of NTDs	1	0	0	2
Number of Exposures	152	381	261	2328
% with NTD (95% CI)	**0.66% (0.02%, 3.69%)**	**0 (0, 0.79%)**	**0 (0, 1.15%)**	**0.09% (0.01%, 0.31%)**
Prevalence Difference (95% CI)	ref	0.66% (-0.73%, 4.16%)	0.66% (-1.25%, 4.16%)	0.58% (-0.10%, 4.10%)

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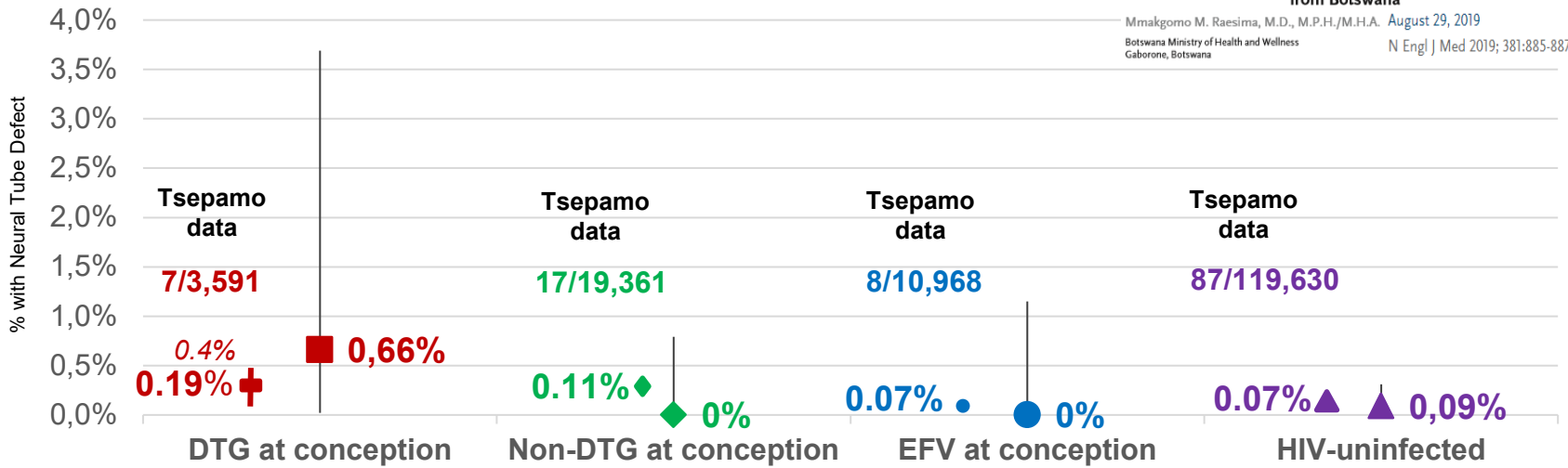

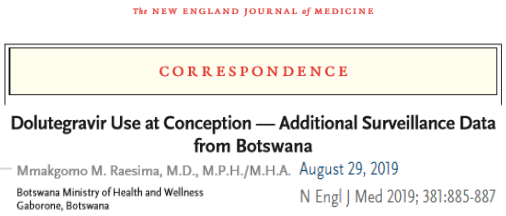
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Brazil Case-Control Study

Fonseca FF et al. IAS 2019 Abs. MOAX0104LB

- Case-control (1:3) study using registry linkage through national MoH databases to estimate NTD risk with periconception (±8 wk of estimated date conception) DTG vs non-DTG (EFV or RAL) ART.
- No NTD with periconception ART (DTG or non-DTG) live births (defects in stillbirth/abortions not routinely reported).
- NTD prevalence in Brazil, with food folate fortification, is 0.06% *(Santos LM. Bull WHO 2016)*; a 3-fold increase to 0.18% likely not be detectable with 384 exposures

	Periconception Non-DTG (EFV or RAL) ART N=1,068	Periconception DTG ART N=384	P value
Pregnancy outcome			<0.01
Live birth	1,025 (96%)	359 (93.5%)	
Stillbirth	15 (1.4%)	2 (0.5%)	
Abortions (spontaneous miscarriage)	28 (2.6%)	**23 (6.0%)**	
Birth defect			
Any birth defect	62 (5.6%)	18 (4.7%)	0.50
NTD	**0/1,068**	**0/384**	-
Primary outcome: NTD, stillbirth or abortion	43 (4.0%)	25 (6.5%)	0.07

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Pre			01
Birt			
			0
Primary outcome: NTD, stillbirth or abortion	43 (4.0%)	25 (6.5%)	0.07

After database closure, 2 NTD with preconception DTG identified (estimated 1,084 preconception DTG pregnancies, 0.18%)


THE ANTIRETROVIRAL PREGNANCY REGISTRY
INTERIM REPORT
1 JANUARY 1989 THROUGH 31 JANUARY 2020

Update: Prospective Antiretroviral Pregnancy Registry InSTI and Neural Tube Defects through **July 2020**

1 Jan 1989 - 31 July 2020

Overall Birth Defects/Neural Tube Defects and Timing Earliest InSTI Exposure

	(0%)Earliest Trimester of Exposure – Prospective Cases		
	Periconception	**Later 1st Trimester**	**2nd/3rd Trimester**
Overall birth defects	Defects/outcomes	Defect/outcomes	Defects/outcomes
Exposure to any InSTI	***34/1127 (3.0%)***	***3/180 (1.7%)***	***31/741 (4.2%)***
DTG	**13/420 (3.1%)** **1/420 NTD (0.24%)**	**2/88 (2.3%)**	**16/330 (4.8%)**
EVG	11/331(3.3%) 0 NTD	0/27(0%)	1/70 (1.4%)
RAL	11/350 (3.1%) 0 NTD	3/108 (2.8%)	16/430 (3.7%%)
BIC	2/51 (3.9%) 0 NTD	0/6 (0%)	0/28 (0%)

→ One NTD in prospective APR with periconception DTG, rate 0.24%

Published/Presented Data on NTD with Preconception DTG

Study	Food Folate Fortification	#NTD/# PC Exposures
Tsepamo 2019 (NEJM 2019)	No	**7/3,591 (0.19%)**
CDC-MOH Botswana 2019 (NEJM 2019)	No	**1/152 (0.66%)**
Sibiude, France (AIDS 2020 epub)	No	0/57
Chouchana, France (JAIDS 2019)	No	0/49
Thorne, EPPICC 2020	No	0/325
Weissmann, Germany (Glasgow 2018)	No	0/3
Kowalska, eastern Europe (Glasgow 2018)	No	0/24
Bornhede, Sweden (Eur J ID 2018)	No	0/14
Orrell, multicountry ARIA (Lancet HIV 2017)	No	0/1
Bollen, Europe (CID 2020)	No	0/8
APR July 2019	International registry (most)	**1/420 (0.24%)**
Brazil case-control	Yes	2/1,084 (0.18%)
Advance, S Africa (IAS 2019)	Yes	0/54
Money, Canada (BJOG 2019)	Yes	0/69
Grayhack, US (AIDS 2018)	Yes	0/28

Published/Presented Data on NTD with Preconception DTG

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Thorne, EPPICC 2020	No	0/325

No folate food fortification, preconception DTG NTD prevalence
8 NTD / 4,224 = 0.19%

NTD pooled prevalence, general population without food folate fortification ~0.10%

Bollen, Europe (CID 2020)	No	0/8

With folate food fortification, preconception DTG NTD prevalence
3 NTD / 1,655 = 0.18%

NTD pooled prevalence general population with food folate fortification ~ 0.06%

Grayhack, US (AIDS 2018)	Yes	0/28

Perinatal Outcomes and Birth Defects with InSTI in Pregnancy

Sibiude J et al for French Perinatal Cohort. AIDS. 2020 Oct 8 (epub ahead print)

- French Perinatal Cohort is national multicenter prospective study of pregnant HIV+ women delivering in 90 centers in France.
- Evaluated birth defects in 808 InSTI-exposed mother-infant pairs (703 RAL, 57 DTG, 48 EVG), 301 exposed at conception; compared to matched InSTI-unexposed group (receiving DRV/r).

Perinatal Outcome	Exposed at Conception		P value
	InSTI-Exposed (N=246)	InSTI-Unexposed (N=246)	
Birth defect*	14, 5.7%	7, 2.9%	0.13
Stillbirth	6, 2.4%	6, 2.4%	1.0
Preterm birth	41, 16.8%	39, 16.1%	0.71

*__No NTD__ reported

NTD With Other InSTI- Prospective Preconception Exposures

	#NTD/# Preconception
Raltegravir	
Merck review* (*Shamsuddin H. JAIDS 2019;81:247-50*) (includes clinical trials, APR, NSHPC, French Perinatal Cohort)	0/456
Other new reports in literature: *Ramos MI. Med Clin (Barc) 2020 May 27 (n=22); Ganter P. PLosOne. 2019;14:e0216010 (n=33)*	0/55
Elvitegravir	
Gilead review* (*Farrow T. Glasgow HIV Conf 2019 Abs P030*) (includes APR, post-marketing, lit review)	0/155
Other new reports in literature *Badell ML et al, Open Forum Infect Dis 2019*	0/82
Total	0/237
Bictegravir	
Gilead review* (*Farrow T. Glasgow HIV Conf 2019 Abs P030*) (includes clinical trials, APR, post-marketing, literature review)	0/18

Lancet HIV 2020; 7: e193-200

Updated assessment of risks and benefits of dolutegravir versus efavirenz in new antiretroviral treatment initiators in sub-Saharan Africa: modelling to inform treatment guidelines

Andrew N Phillips, Loveleen Bansi-Matharu, Francois Venter, Diane Havlir, Anton Pozniak, Daniel R Kuritzkes, Annemarie Wensing, Jens D Lundgren, Deenan Pillay, John Mellors, Valentina Cambiano, Andreas Jahn, Tsitsi Apollo, Owen Mugurungi, David Ripin, Juliana Da Silva, Elliot Raizes, Nathan Ford, George K Siberry, Ravindra K Gupta, Ruanne Barnabas, Paul Revill, Jennifer Cohn, Alexandra Calmy, Silvia Bertagnolio

Risk vs Benefits of DTG at Population Level Including Women of Childbearing-Potential

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

- Individual model looking at HIV transmission and progression in adults starting DTG vs EFV over 20 years (2019-2039) updated to include:
  - Used data **NTD risk** in women on DTG at conception, Mar 2019, 0.3% (benefits will be even greater using current rate 0.19%).
  - Included effects of DTG on **weight gain**, including effects on conditions such as diabetes and mortality/morbidity, as well as possible effects of potential increases in bodyweight on babies of pregnant women.
- In a range of modelled scenarios in sub-Saharan Africa, ART initiation with DTG-based ART **including in women intending pregnancy** was predicted to bring most population health benefits and be cost-effective.

Summary

- DTG/RAL highly effective and generally safe for mother in pregnancy.
- Adverse pregnancy outcomes (miscarriage, stillbirth, fetal growth, PTD, SGA, neonatal mortality) do not appear to be increased with preconception InSTI use.
- After a period of decline since the original safety signal, prevalence of NTD among infants born to women on DTG at conception appears to be stabilizing at a low prevalence level of 0.19%; it is no longer significantly higher than preconception non-DTG, although remains statistically significantly higher than preconception EFV and uninfected women.
- In literature review, the prevalence of NTD in countries with and without food folate fortification is similar to Tseampo, 0.18-0.19%.

Summary

- No NTD reported in prospective reports of other preconception InSTI in pregnancy, but numbers remain small.
- NTD risk, if remains with continued follow-up (Tsepamo and APR continuing, and other surveillance with DTG roll-out in Africa), appears to be significantly under 1% (a potential excess of only 1 NTD per 1,000 DTG exposures compared to general population prevalence).
- With risk/benefit analyses showing substantial DTG benefit in women childbearing potential, WHO now recommends DTG as preferred for all individuals.

Thank You For Your Attention!