Dolutegravir in Pregnancy: An overview

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Overview

Thinking about ARVs in pregnancy

- Risks vs benefits
- Limited data on ARV safety in pregnancy
- Timing of in utero exposures

Dolutegravir: risks and benefits

- Maternal health
- Pregnancy outcomes
- Neural tube defects: state of evidence

Balancing evidence

Drug Therapy

Balancing act

Benefits

Risks

Drug Therapy in Pregnancy

Balancing act

Benefit of Maternal Treatment

Risk of Adverse Fetal Effects

Drug Therapy in Pregnancy

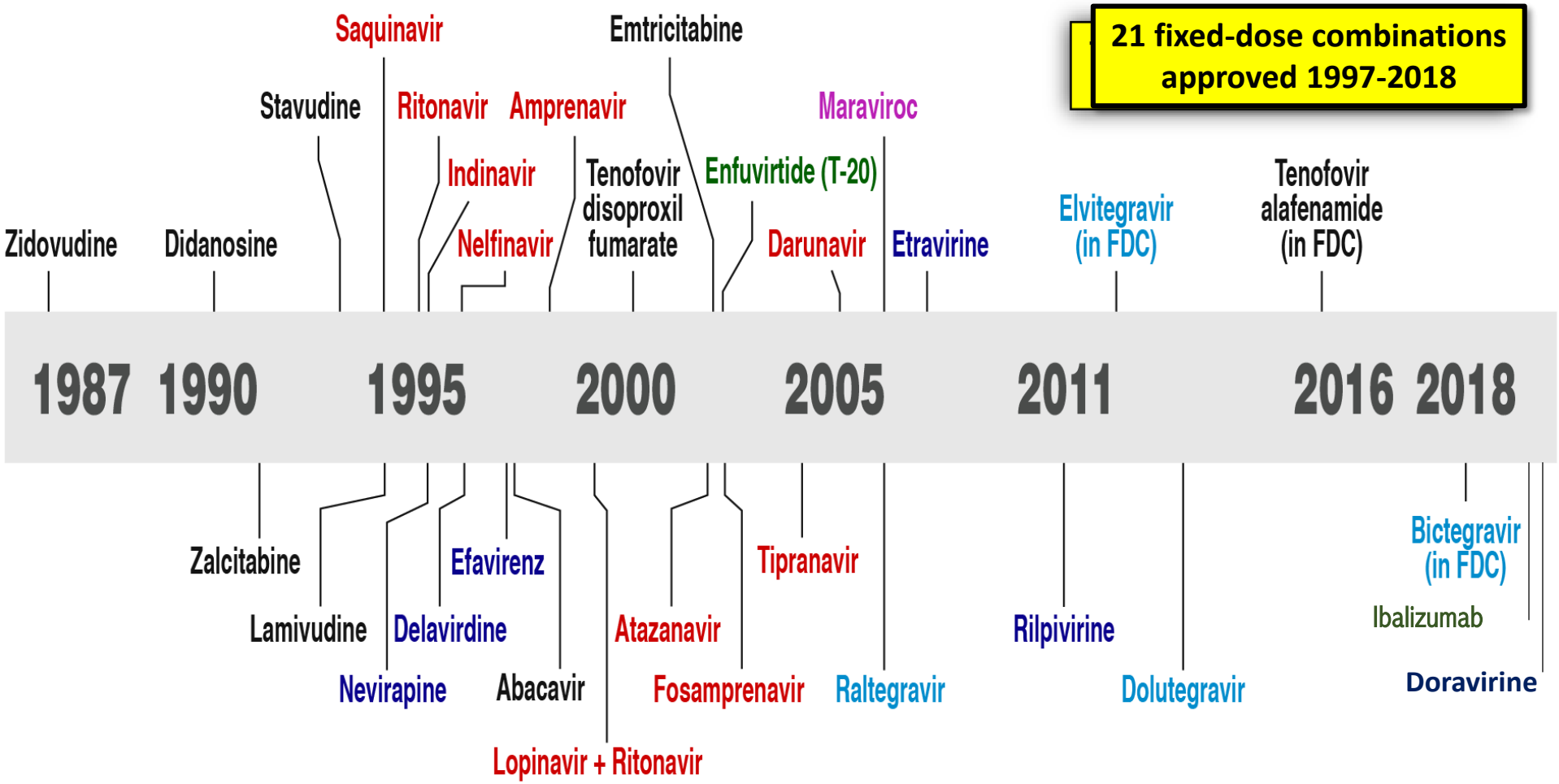
Balancing act

Benefit of Maternal Treatment

Risk of Adverse Fetal Effects

Unfortunately data on risks are (usually) very limited

Antiretroviral Drugs Approved by FDA, 1987-2018



Source: FDA

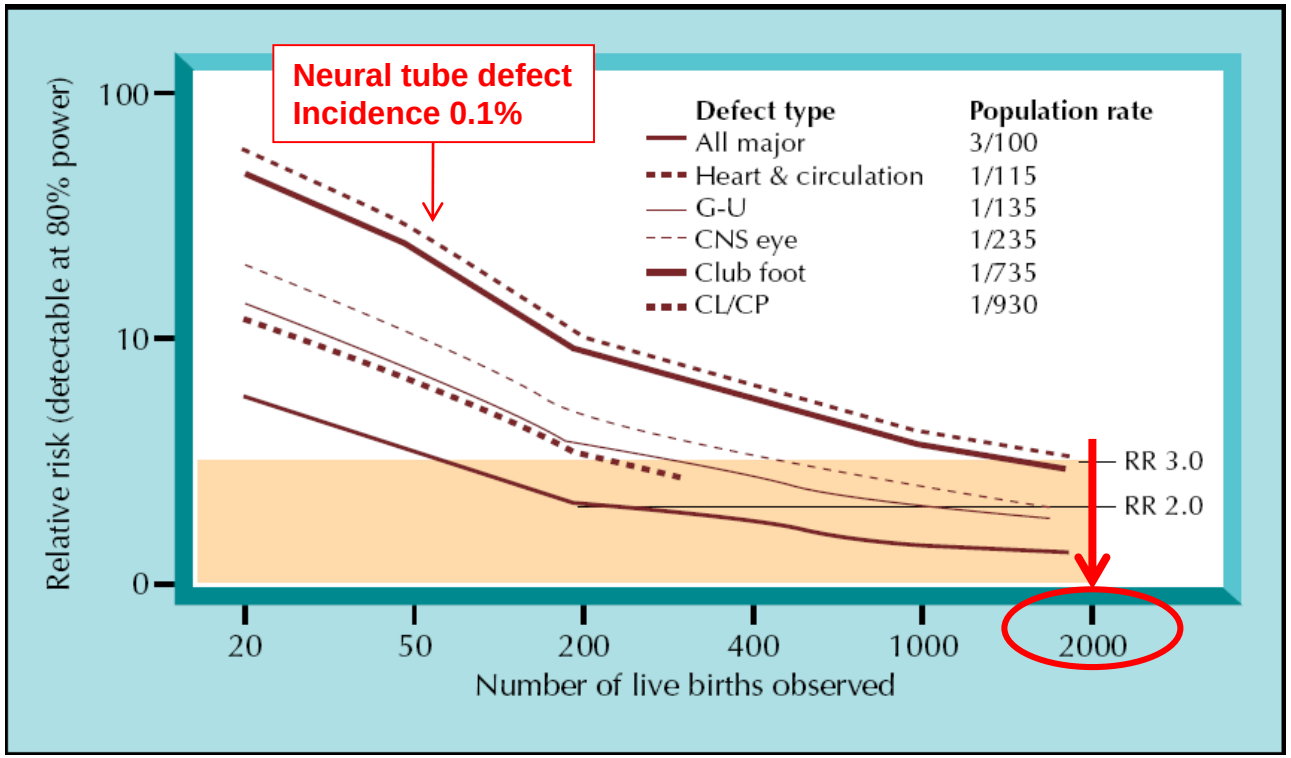
Limited Data on Pregnancy for Approved Antiretroviral Drugs

- Of the 32 ARVs approved in adults, only **one (AZT)** has indication in pregnancy by FDA (for prevention of perinatal transmission)
- Generally, drug label language is "**use in pregnancy only if potential benefit exceeds potential risk**" and prohibits use during breastfeeding
- Of the 32 drugs:
  - N=26 had significant delay between FDA approval and data in pregnancy (mean 5 years)
  - N=5, including newest drugs, have no pregnancy data

Studying rare adverse events is difficult

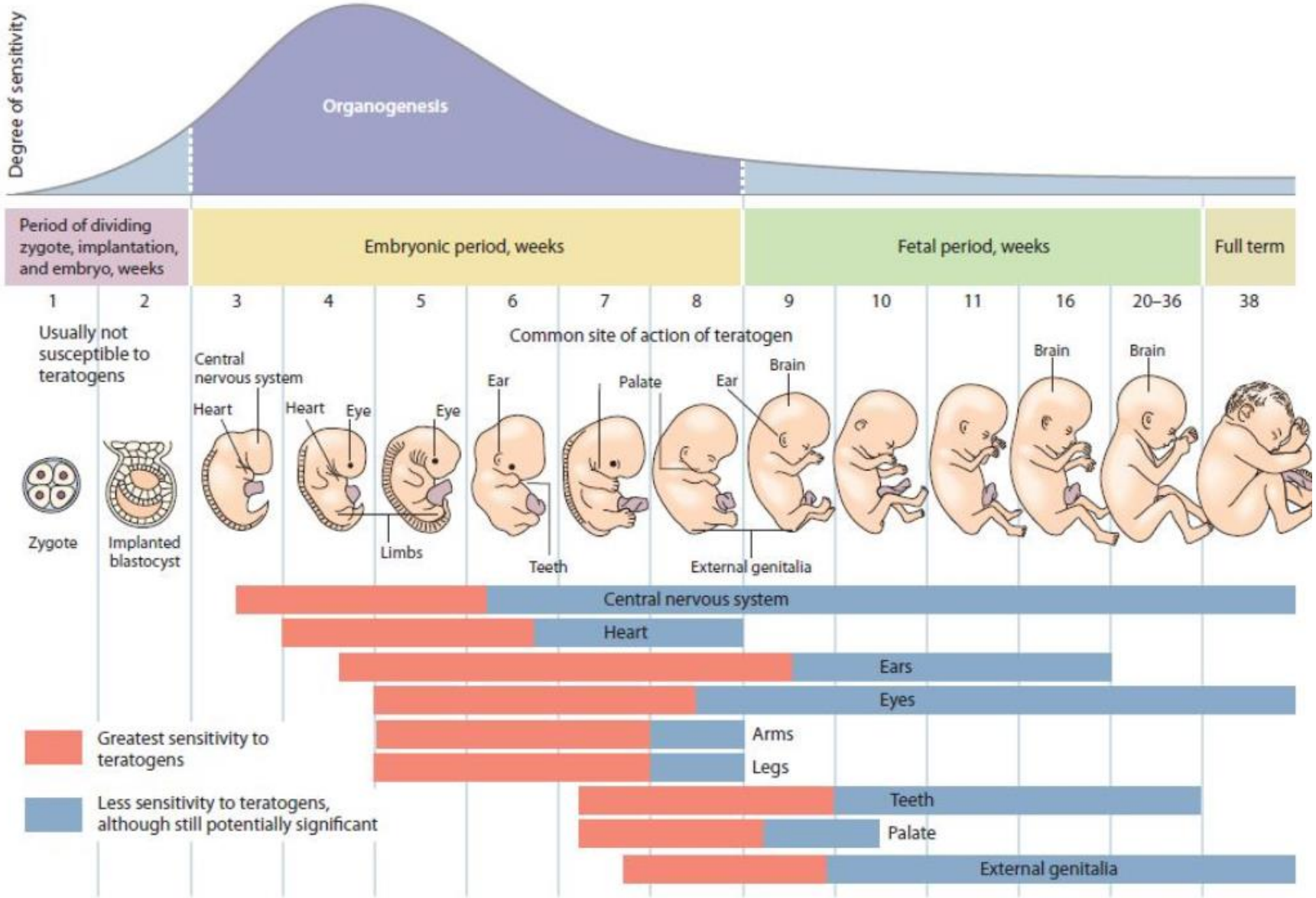
To rule-out a 3-fold increase in a relatively rare event like Neural Tube Defects (NTD, incidence 0.1%), need >2000 exposures

….>4000 to rule out a 2-fold increase



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

Timing of *In Utero* ARV Exposure and Fetal Risk



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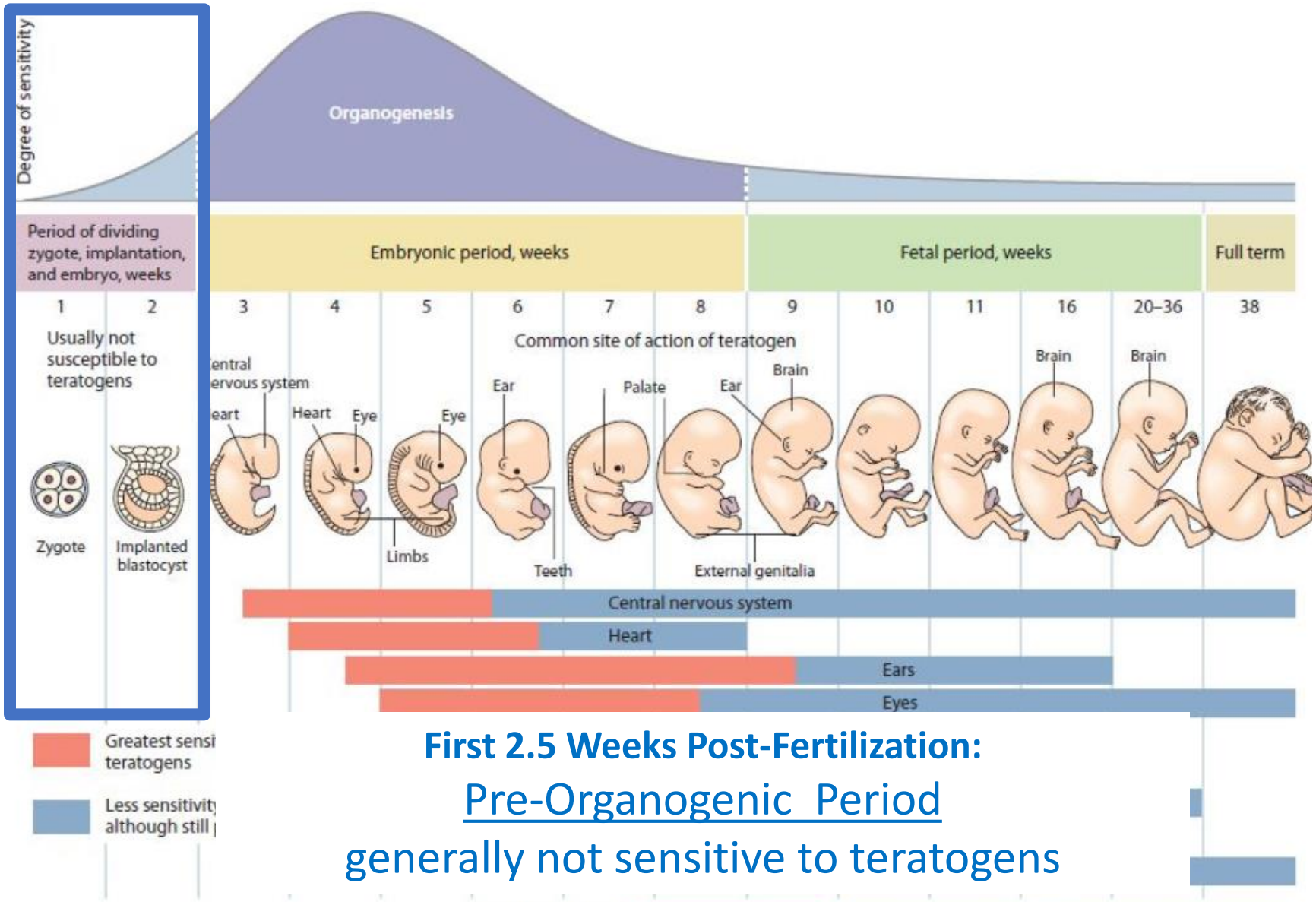
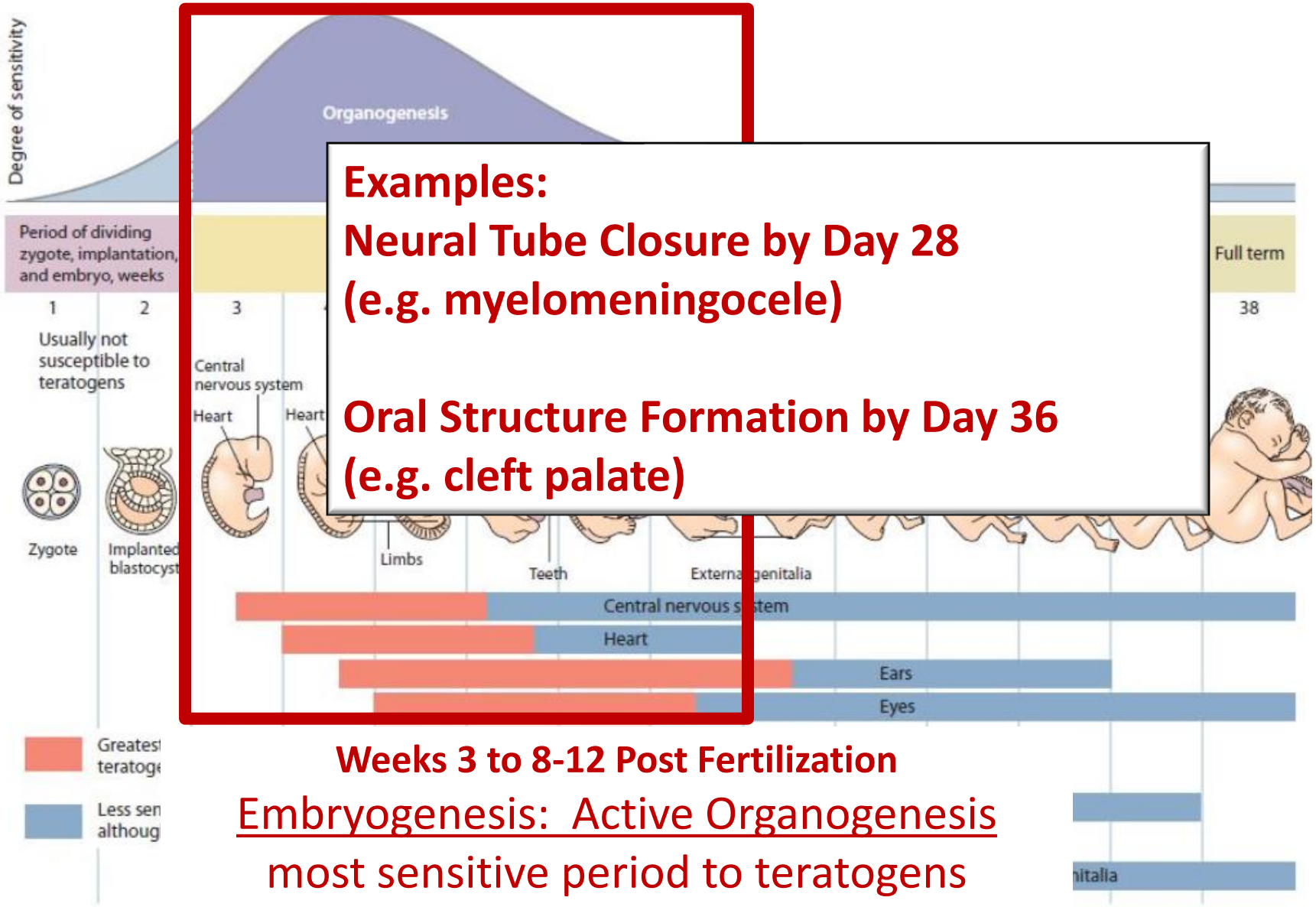


First 2.5 Weeks Post-Fertilization:

Pre-Organogenic Period

generally not sensitive to teratogens

Timing of *In Utero* ARV Exposure and Fetal Risk

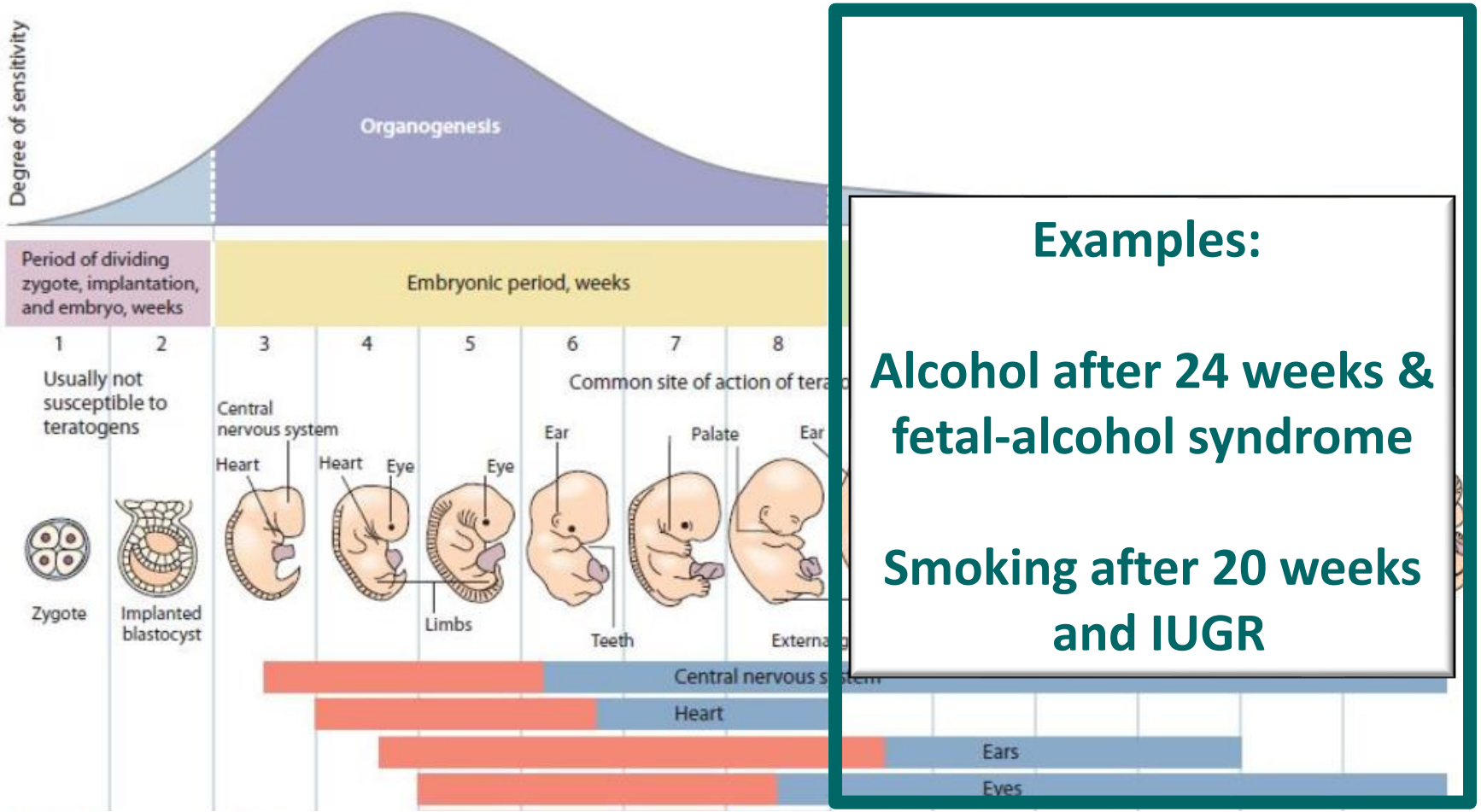


Weeks 3 to 8-12 Post Fertilization

Embryogenesis: Active Organogenesis

most sensitive period to teratogens

Timing of *In Utero* ARV Exposure and Fetal Risk



Examples:

Alcohol after 24 weeks & fetal-alcohol syndrome

Smoking after 20 weeks and IUGR

After 8-12 Weeks Post-Fertilization

Fetal Development Period

Fetal growth; teeth; external genitalia; continued brain develop

Dolutegravir: benefits in pregnancy (and for maternal health)

ARV Drug Optimization: Key Principles

- ✓ Reduce toxicity
- ✓ Improve palatability/pill burden
- ✓ Increase resistance barrier
- ✓ Reduce drug interactions
- ✓ Safe use across different age groups and populations
- ✓ Reduce cost

Dolutegravir: Why Make the Switch?

ARV Drug Optimization: Key Principles	Dolutegravir
✓ Reduce toxicity	✓ Significantly less toxicity vs EFV
✓ Improve palatability/pill burden	✓ Single tablet regimen, small size
✓ Increase resistance barrier	✓ Very high barrier to resistance
✓ Reduce drug interactions	✓ DDI with rifampin
✓ Safe use across different age groups and populations	✓ ??????????
✓ Reduce cost	✓ STR TDF-3TC-DTG $75 USD ppy

Safety and Efficacy of DTG and EFV600 in 1st line ART

(summary 2018 WHO Systematic Review)

Major outcomes	DTG vs EFV_{600}	QUALITY OF EVIDENCE
Viral suppression (96 weeks)[1]	**DTG better**	moderate
Treatment discontinuation[2]	**DTG better**	high
CD4 recovery (96 weeks)[3]	**DTG better**	moderate
Mortality	comparable	low
AIDS progression	comparable	low
SAE	comparable	low

Reference: Steve Kanters, For WHO ARV GDG, 16-18 May 2018

WHO, 2018

SINGLE TRIAL is only randomized comparison DTG and EFV (Walmsky JAIDS 2015)

[1] Difference viral suppression btn DTG and EFV driven by lower rate of discontinuation for adverse events. True viral failure (>2 VL >50) similar in the 2 groups (9% DTG & 8% EFV).

[2] Treatment discontinuation 4% with DTG, 14% with EFV.

[3] CD4 +378 with DTG, +332 with EFV at week 144.

Comparative Effectiveness of 1st Line ART in Adults, Brazil – Superior Effectiveness of DTG

Meireles MV et al. IAS, Amsterdam, July 2018 Abs. TUAB0101

DTG: <u>42%</u> increase in VS vs EFV

VS=viral suppression

			Multivariable analysis*	
ART Regimen	% use	VS <50 (%)	aOR	95% CI
3TC+TDF+DTG	**7.2**	**85.2**	**1.42**	**(1.32-1.52)**
3TC+TDF+EFV	*74.0*	*78.0*	*1.0*	
3TC+AZT+LPV/r	4.9	67.2	0.59	(0.55-0.63)
3TC+TDF+ATV/r	4.6	71.3	0.67	(0.63-0.72)
3TC+AZT+EFV	3.5	72.9	0.94	(0.87-1.02)
3TC+TDF+LPV/r	2.0	63.7	0.54	(0.49-0.60)
Others	3.7	67.9	0.67	(0.62-0.73)

*Controlled for age, sex, adherence and baseline CD4 and VL

What do we know about the benefits of DTG in pregnancy?

DTG ART *Started in Late Pregnancy* is Associated with More Rapid VL Decline than EFV

Orrell C et al. IAS, Amsterdam July 2018, Abs. THAB0307LB

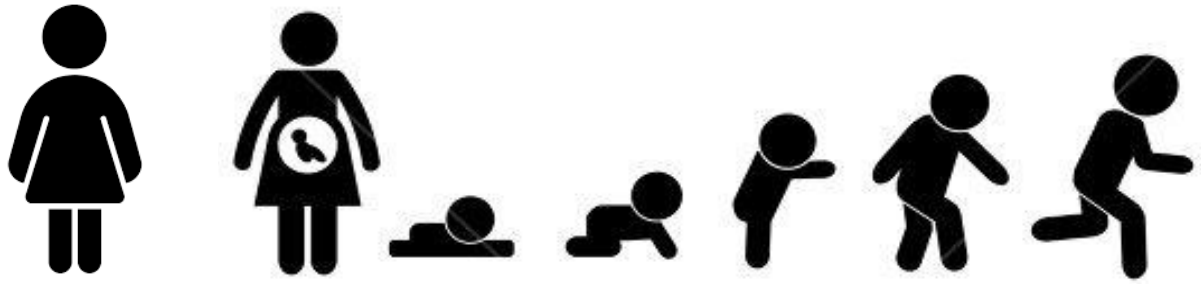
Ongoing trials:

- VESTED trial / IMPAACT 2010: Phase III Study of the Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz-Containing Antiretroviral Therapy Regimens in HIV-1-Infected Pregnant Women and their Infants (results 2019-2010)
- DolPHIN-2: Dolutegravir in Pregnant HIV Mothers and their Neonates (results early 2019)

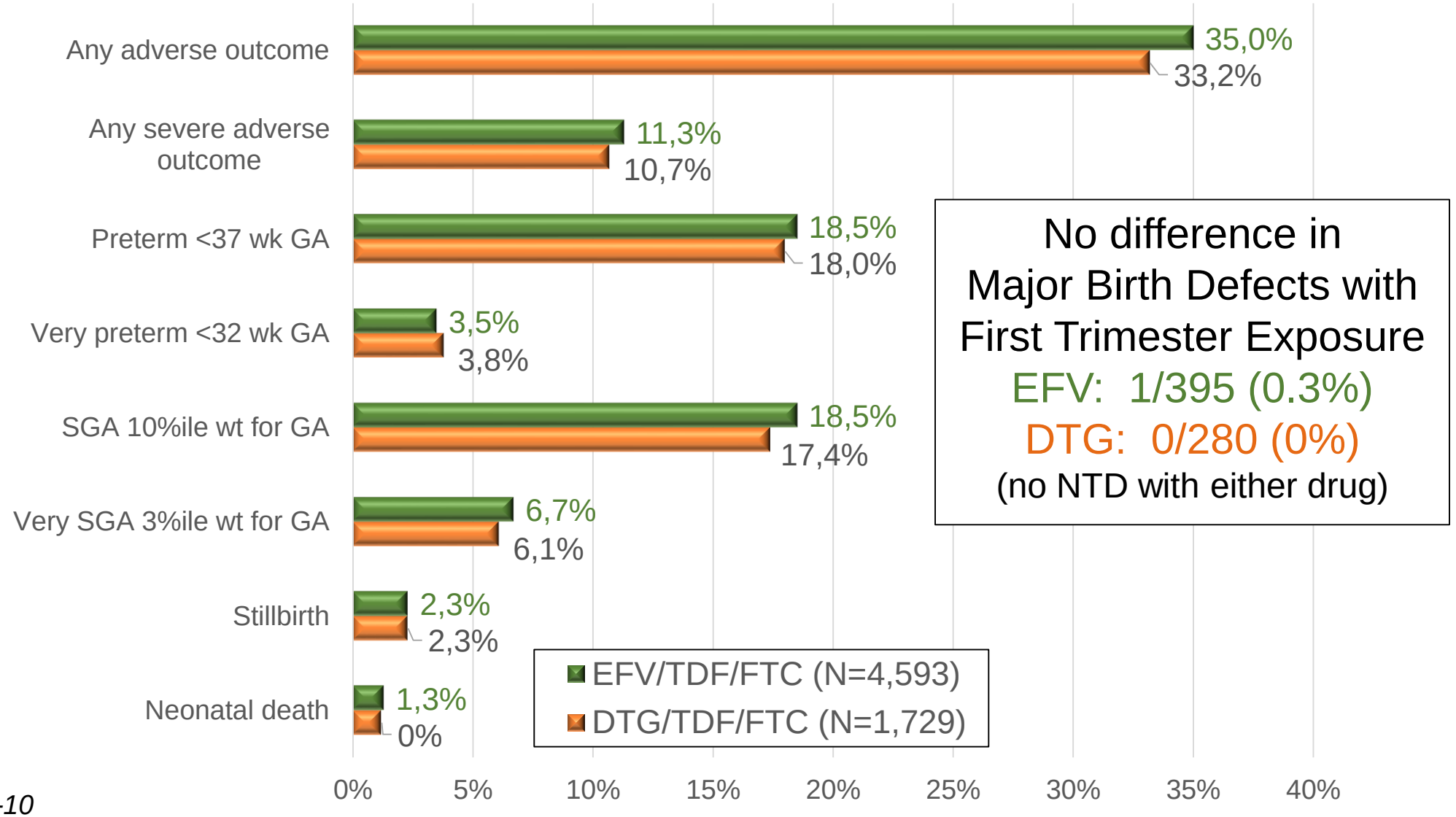
Dolutegravir: risks in pregnancy

Risks of ARVs in pregnancy: what are we looking for?

- **Congenital anomalies/birth defects** including neural tube defects (NTD)
- Fetal loss, stillbirth, neonatal and infant deaths
- Compromised birth outcomes: preterm birth (PT), small for gestational age (SGA), low birth weight (LBW)
- *Early complications*: mitochondrial disorders, hematologic abnormalities, metabolic complications, abnormal neurodevelopment and growth patterns, infectious complications
- *Late complications*: organ dysfunction, neurocognition, malignancies



When Started During Pregnancy, No Difference Pregnancy Outcomes EFV vs DTG-Based ART



No difference in Major Birth Defects with First Trimester Exposure

EFV: 1/395 (0.3%)

DTG: 0/280 (0%)

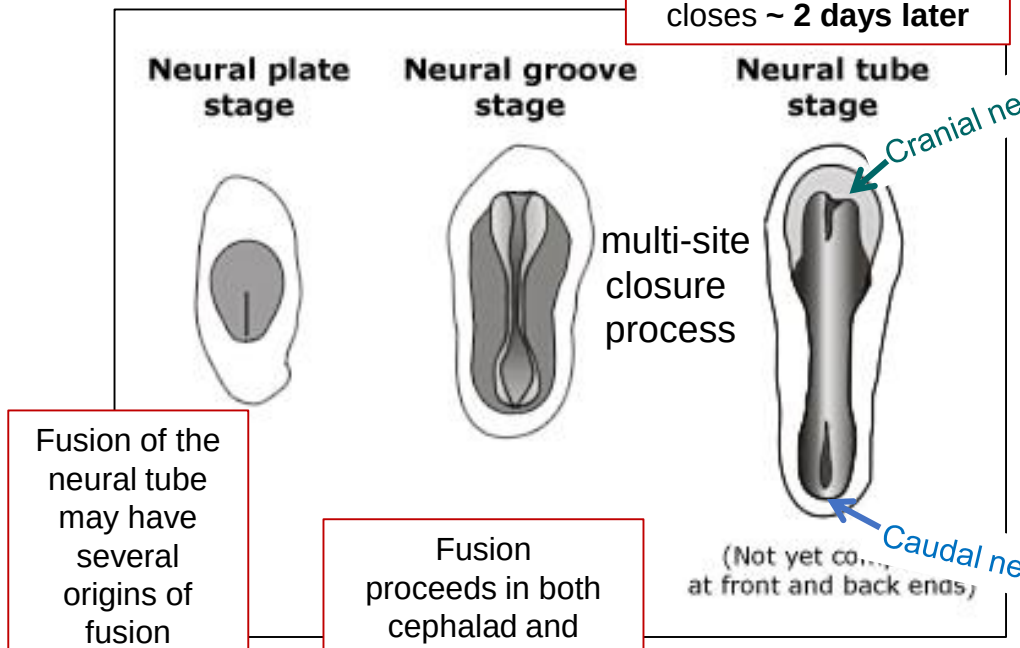
(no NTD with either drug)

Zash Lancet Global Health 2018;6:e804-10

Preconception DTG – Brief Summary on Neural Tube Development & Defects

Neural Tube Closure Normally Occurs by 28 Days Post-Conception

Cranial neuropore closes on **25th day after conception**; caudal neuropore normally closes **~ 2 days later**



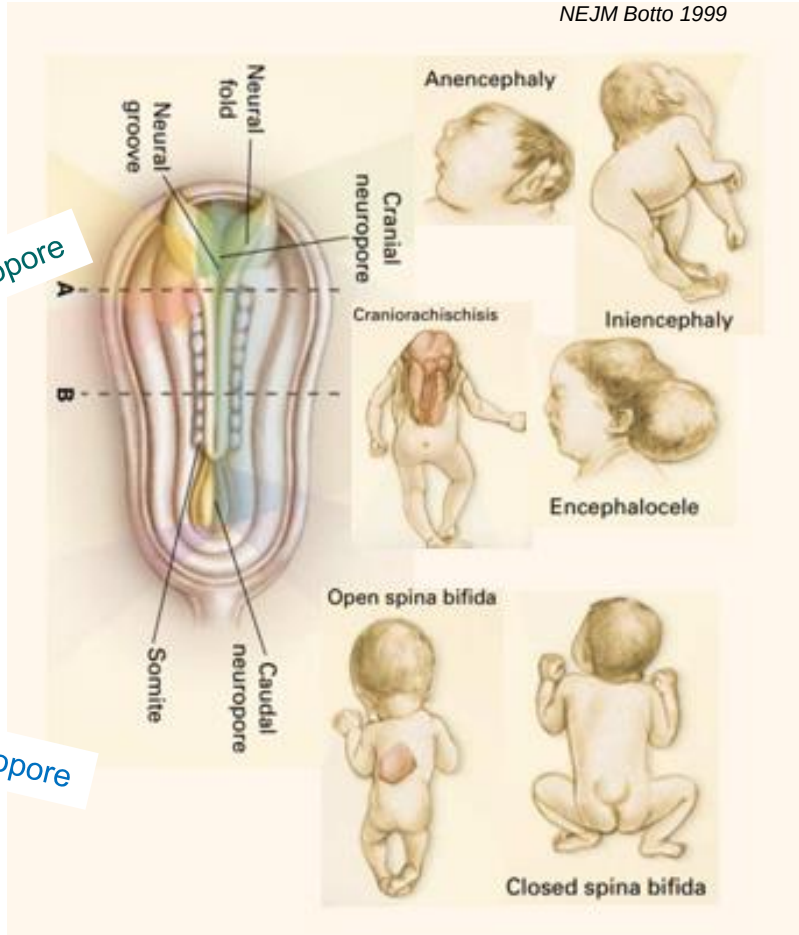
Fusion of the neural tube may have several origins of fusion

Fusion proceeds in both cephalad and caudal directions, forming anterior and posterior neuropores

UpToDate Online 17.2: McLone DG, Bowman RM

Different phenotypes of neural tube defects

NEJM Botto 1999



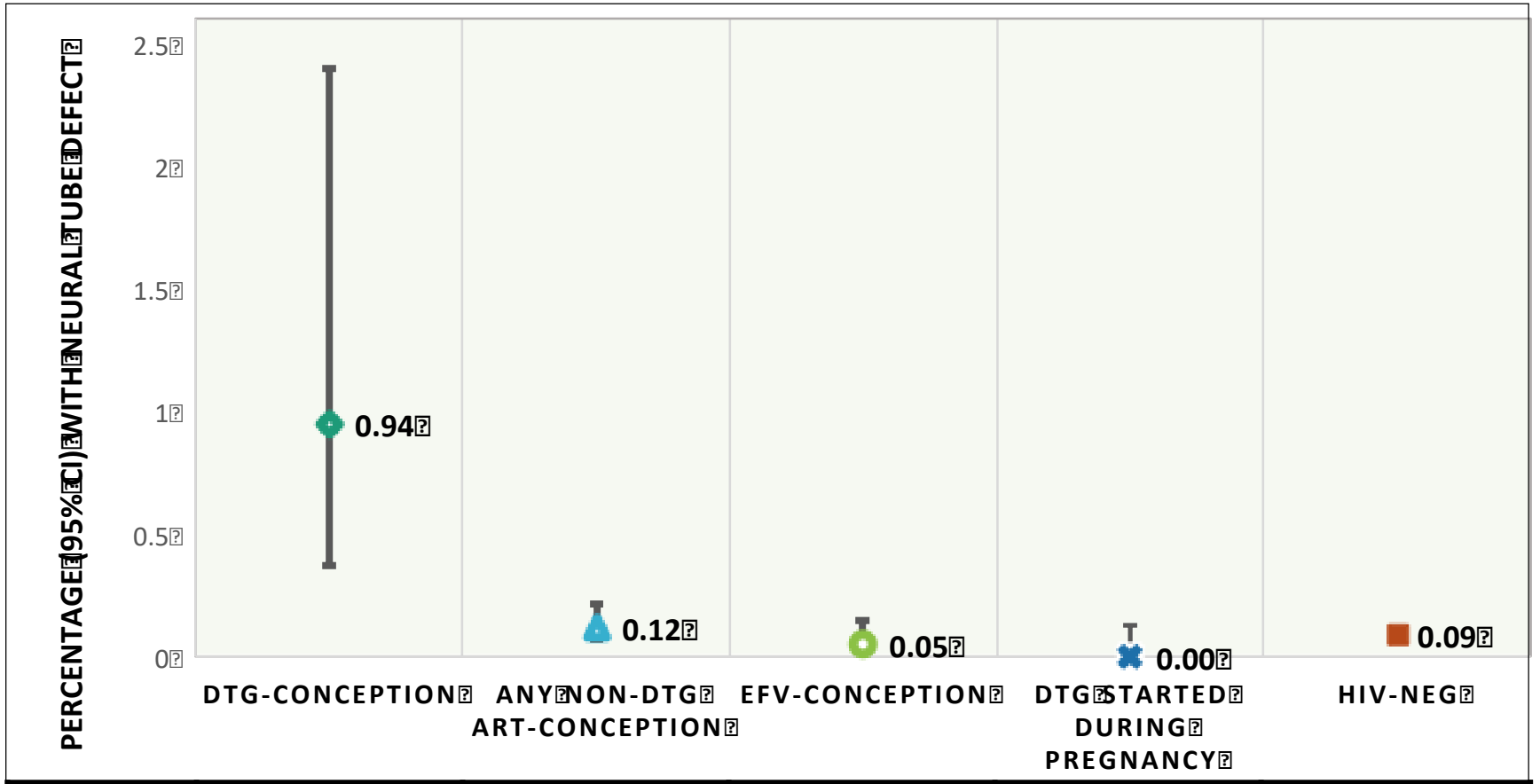
Phenotype depends on **location & level** of the defect, whether crosses CNS segmental boundaries

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, 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 blinded to exposure
- Good denominator with control groups and ability to distinguish between ARV regimens
  - HIV-uninfected
  - HIV-infected ART preconception or started in pregnancy

Zash IAS, Amsterdam July 2018 Late Breaker
Zash N Engl J Med 2018 July 24 epub

Tsepamo Study: NTD Prevalence by Exposure

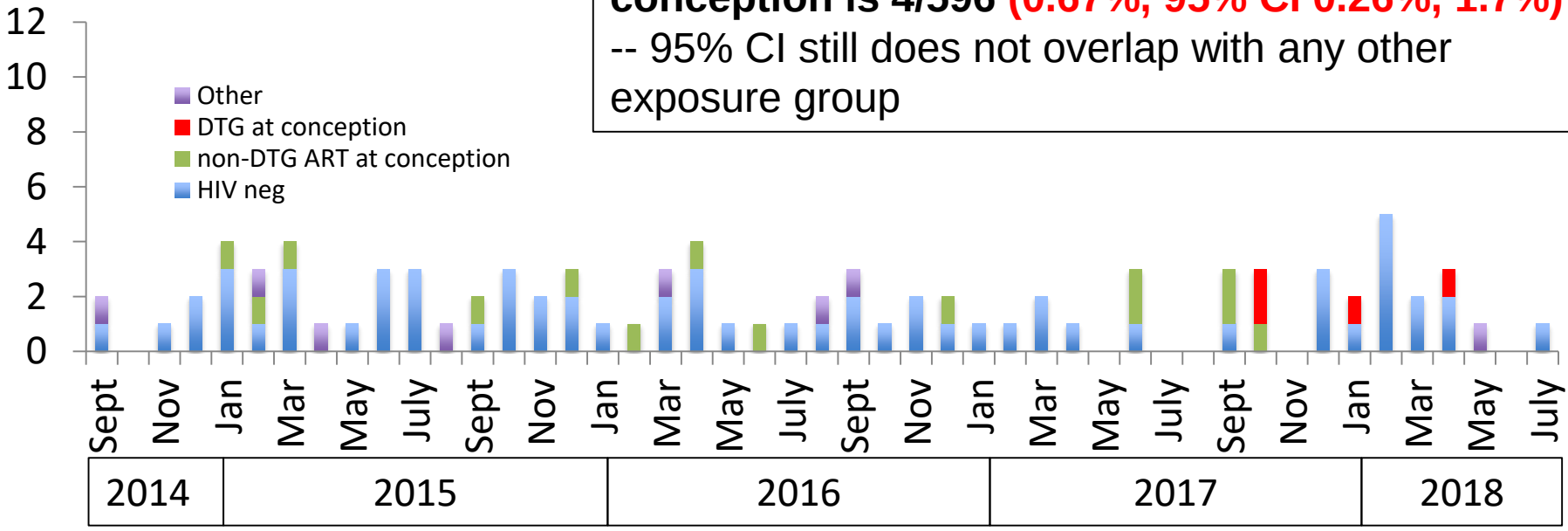


NTDs/Exposures	4/426	14/11,300	3/5,787	0/2.812	61/66,057
% with NTD (95% CI)	0.94% (0.37%, 2.4%)	0.12% (0.07%, 0.21%)	0.05% (0.02%, 0.15%)	0.00% (0.00%, 0.13%)	0.09% (0.07%, 0.12%)
Prevalence Difference (95% CI)	**ref**	**-0.82% (-0.24%, -2.3%)**	**-0.89% (-0.31%,- 2.3%)**	**-0.94% (-0.35%, -2.4%)**	**-0.85% (-0.27%, -2.3%)**

Tsepamo Study: Update since 1 May 2018

- From 1 May-15 July, there were **2 more NTDs;** 1 in an infant exposed to **DTG *started during pregnancy*** (8 weeks GA) and 1 birth to an **HIV-uninfected** woman:
  - NTDs in DTG started during pregnancy: 1/3104 (0.03%, 95% CI 0.01%, 0.18%)

Updated prevalence of DTG exposure at conception is 4/596 (0.67%, 95% CI 0.26%, 1.7%)
-- 95% CI still does not overlap with any other exposure group



Tsepamo Study: Projections for 2019

- With expanded surveillance to 18 sites, estimate ~ 1226 births with exposure to DTG from conception by end of March 2019

With 0 more NTDs, the lower CI overlaps with the upper CI for other ART at conception (0.21%), EFV at conception (0.15%) and with HIV-uninfected (0.13%)

With 1 more NTD, the lower CI overlaps with the upper CI for other ART at conception (0.21%)

Number of total NTDs	Prevalence	95% Confidence Interval
4 in 1226	0.33%	0.13%, 0.84%
5 in 1226	0.41%	0.18%,0.95%
6 in 1226	0.49%	0.22%, 1.1%
7 in 1226	0.57%	0.28%, 1.2%
8 in 1226	0.65%	0.33%,1.3%
9 in 1226	0.73%	0.38%, 1.4%
10 in 1226	0.82%	0.45%,1.5%

Data on pregnancies among women on DTG from Brazil

- From Jan 2017 - Mar 2018, >100,000 persons started DTG; 28% are women; pregnant women not eligible for DTG
- To date, 363 women have become pregnant on DTG. It is recommended when pregnancy is recognized to switch to EFV-based regimen
  - 275 still pregnant (75%)
  - 78 live birth (22%)
  - 2 stillbirth (<1%)
  - 8 terminations (2%)
- No birth defects have been reported in live births

Not clear if there are data on defects with stillbirth and elective terminations

Antiretroviral Pregnancy Registry (APR): outcomes with birth defects by trimester of earliest exposure to INSTI (as of 01-2018)

	Earliest Trimester of Exposure		
	Preconception	1st Trimester	2nd/3rd Trimester
	Defects/live birth	Defect/live birth	Defects/live birth
Exposure to any ART	215/7785 (2.8%)	40/1551 (2.6%)	259/9322 (2.8%)
Exposure to INSTI	13/507 (2.6%)	4/111 (3.6%)	14/403 (3.5%)
DTG *	3/121 (2.5%)	2/40 (5.0%)	2/94 (2.1%)
EVG	5/155 (3.2%)	0/25	0/52
RAL	5/231 (2.2%)	4/60 (6.6%)	12/278 (4.3%)

*Includes 0 NTD with INSTI exposure

Balancing risks vs benefits

Drug Therapy in Pregnancy

Balancing act

Benefit of Maternal Treatment

Risk of Adverse Fetal Effects

Drug Therapy in Pregnancy

Balancing act

Benefit of Maternal Treatment

DTG:

- *Rapid VL decline*
- *Better tolerated*
- *Effective in the face of NNRTI resistance*
- *High barrier to resistance*

Risk of Adverse Fetal Effects

DTG:

- *Potential signal for neural tube defect with preconception exposure (? ~0.6% ?)*

Drug Therapy in Pregnancy

Balancing act

Benefit of Maternal Treatment

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How do we balance risks vs benefits?

DTG:

- *Potential signal for neural tube defect with preconception exposure (?0.67%)*

How do we balance risks vs benefits?

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How do we balance risks vs benefits?

Pause *– don't rush into major decisions if there is concern*

Search *systematically for all available information – what else is out there?*

Solicit inputs *from diverse stakeholders – especially patients (women living with HIV/AIDS) and civil society*

Consider implications *of decisions holistically – mathematical modelling benefits and costs of different decisions*

Thank you!!!

Lynne Mofenson

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