The Transition to Dolutegravir-based ART Regimes: Opportunities and Challenges

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The Transition to Dolutegravir-based ART Regimes: Opportunities and Challenges

- General considerations - antiretroviral drugs, women, and children
- DTG and birth outcomes
- Update on DTG safety & efficacy
- Guidance on DTG use
- Global update on TLD roll-out
- Implementation considerations

General Considerations

Antiretroviral drugs, women, and children

ART Optimization for LMIC

Optimization criteria		DTG	EFV400	DRV/r	RAL
Efficacy and safety	High virologic potency				
	Low toxicity				
	High genetic barrier to resistance				
Simplification	Available as generic FDC				
	Low pill burden				
Harmonization	Use in pregnant women				
	Use in children				
	Use in HIV-associated TB				
	Few drug interactions				
Cost	Low price				

yes no ongoing studies

tenofovir+
lamividine+
dolutegravir =TLD

ARVs, women and children: general considerations

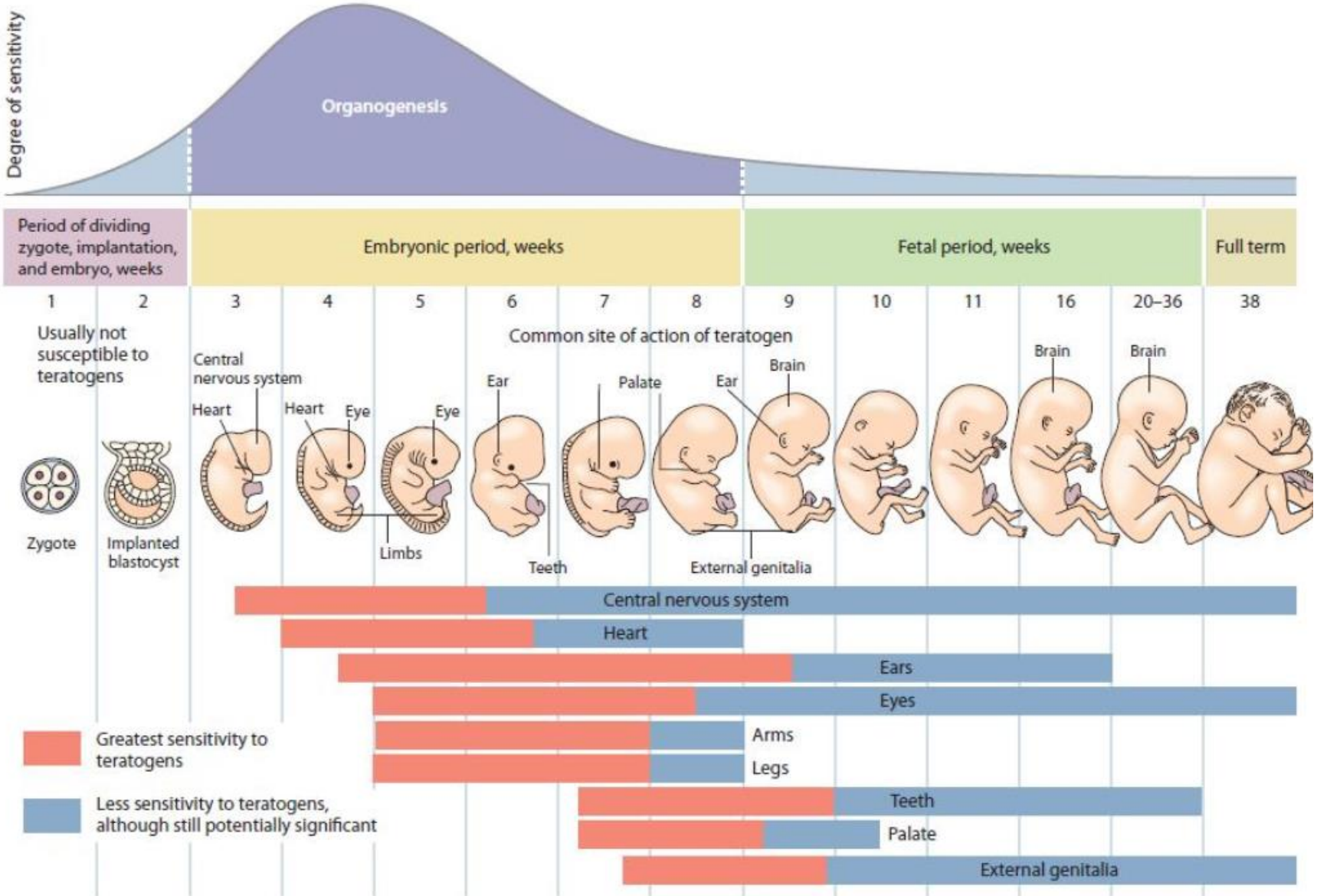
- It's all about the timing: timing of the exposure, timing of the outcome as well as the nature of the exposure
  - When the ARV exposure occurs: at conception, early pregnancy, late pregnancy, during infancy and early childhood
  - When the outcome occurs and is identified: during pregnancy, at birth, newborn period, infancy, early and late childhood, adolescence and adulthood
  - The mechanism of toxicity; the molecular basis of birth defects with drug exposure is known for only a few drugs
- Broad array of other factors that could impact child outcomes including maternal HIV infection, nutrition, environmental factors, etc.



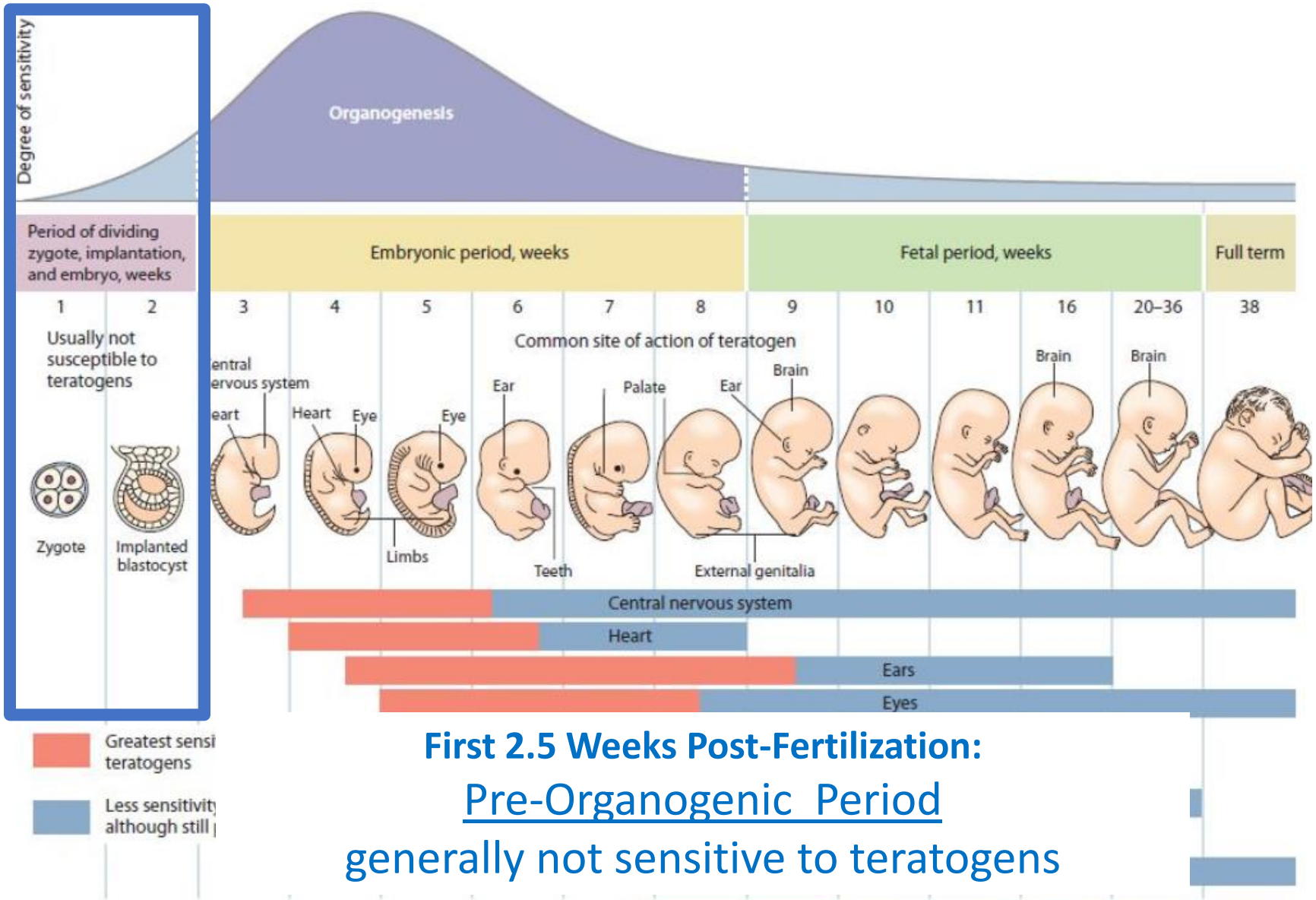

ARVs and children: what are we looking for?

- Fetal loss, stillbirth, neonatal and infant deaths
- *Congenital anomalies/birth defects including neural tube defects (NTD)*
- 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

Timing of *In Utero* ARV Exposure and Fetal Risk



Timing of *In Utero* ARV Exposure and Fetal Risk

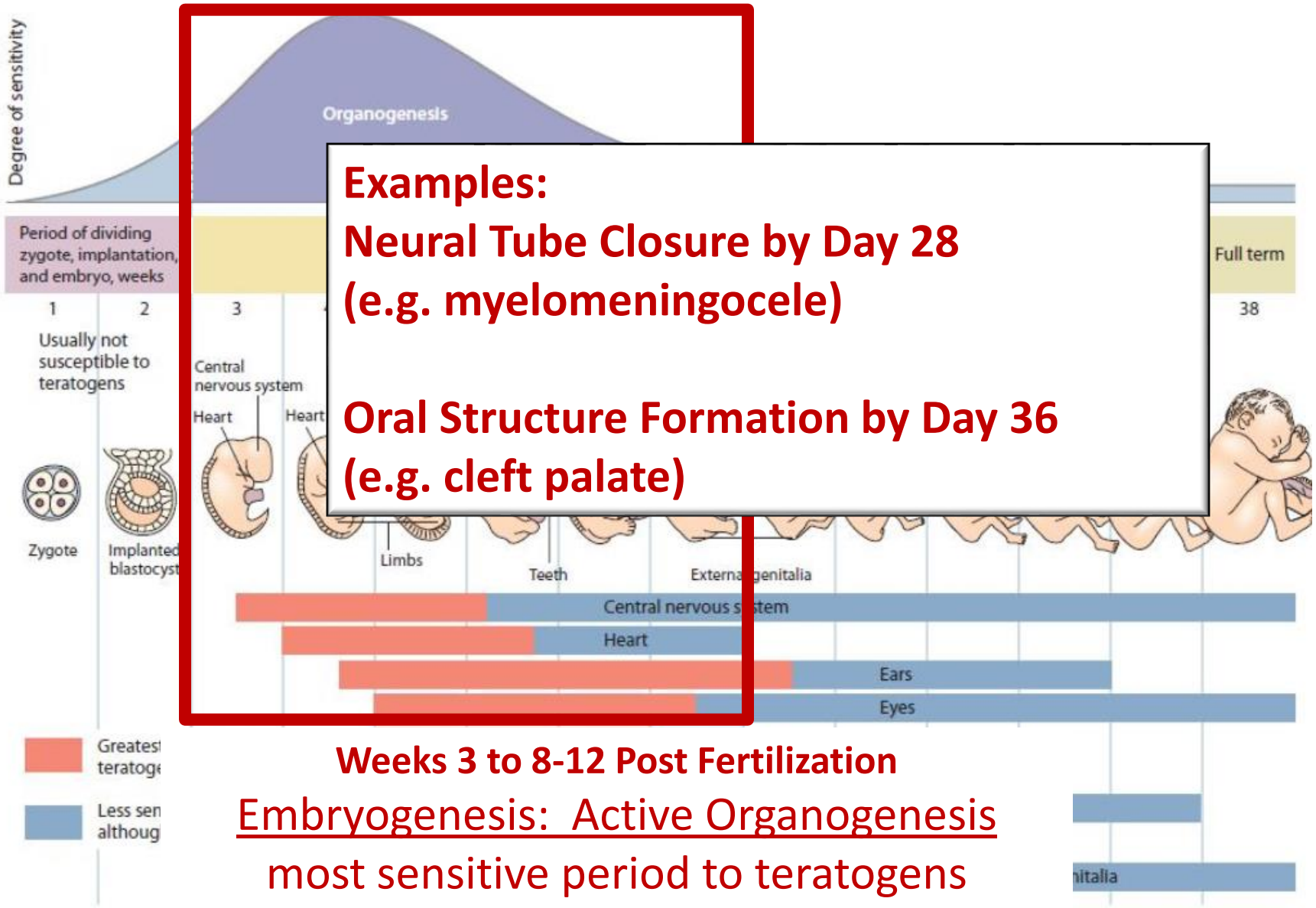


First 2.5 Weeks Post-Fertilization:

Pre-Organogenic Period

generally not sensitive to teratogens

Timing of *In Utero* ARV Exposure and Fetal Risk

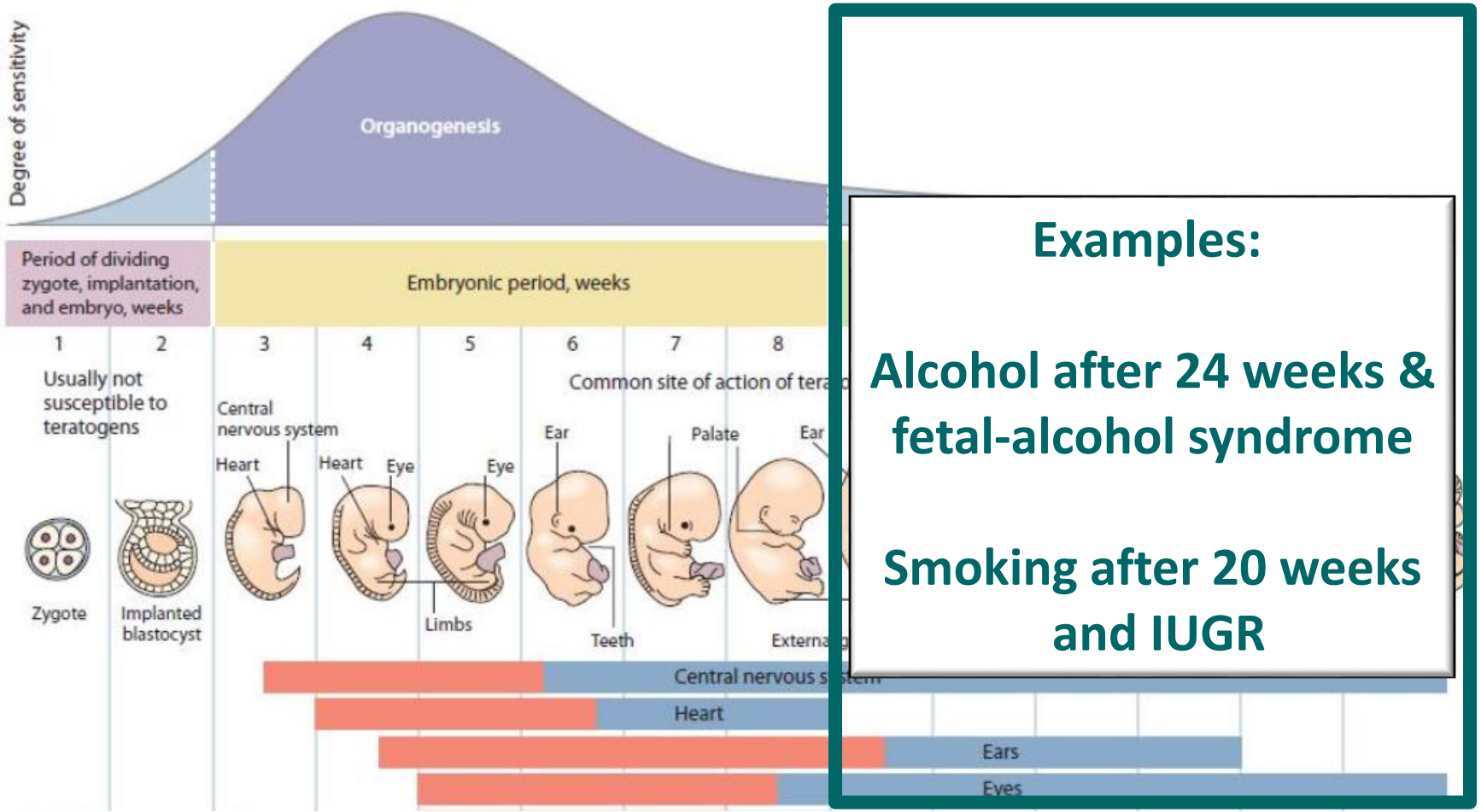


Weeks 3 to 8-12 Post Fertilization

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

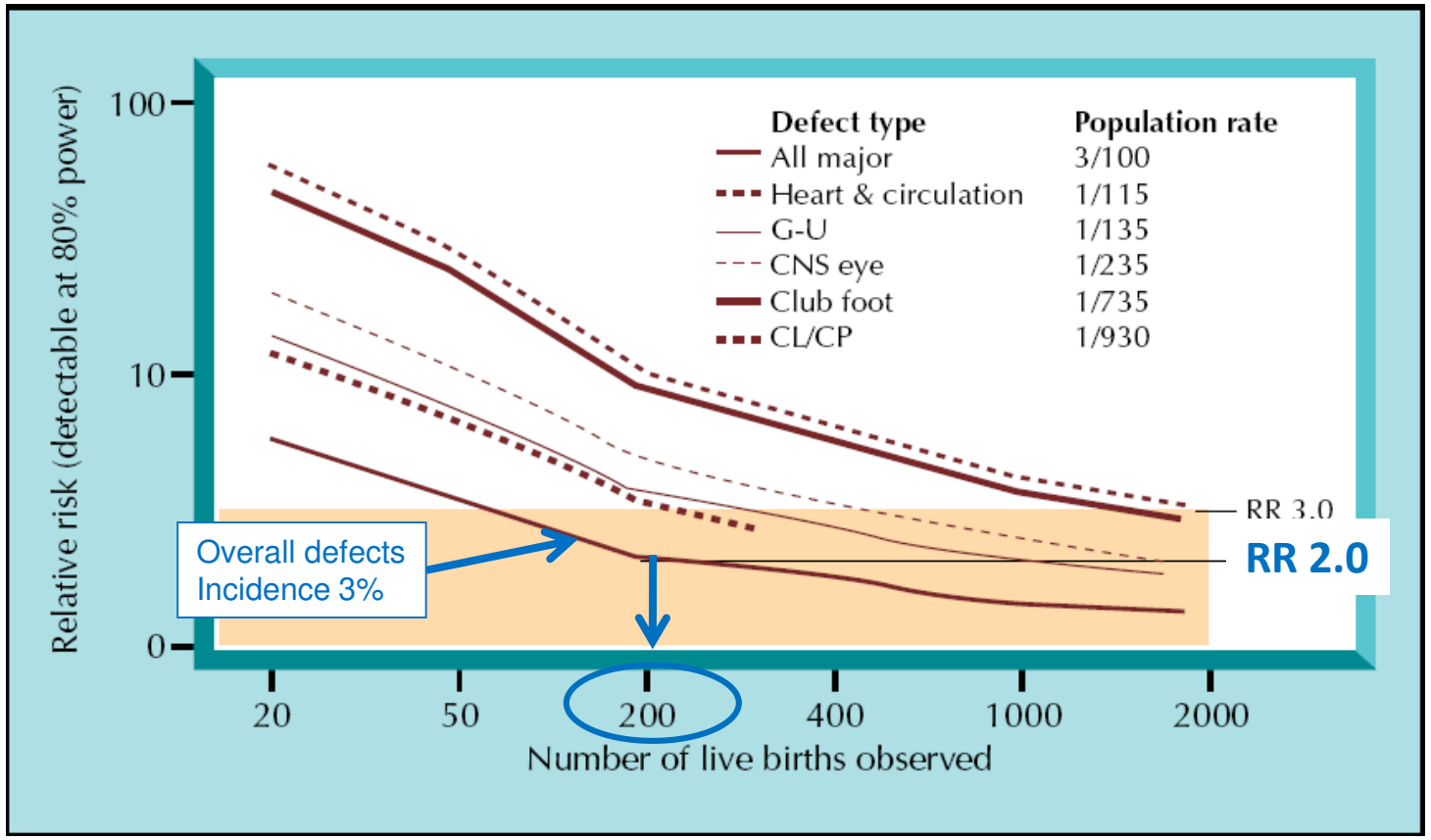
After 8-12 Weeks Post-Fertilization

Fetal Development Period

Fetal growth; teeth; external genitalia; continued brain develop

Ability to Rule-Out ↑ Birth Defect is Related to Defect Incidence and Number Observed Preconception/1st Trimester Exposures

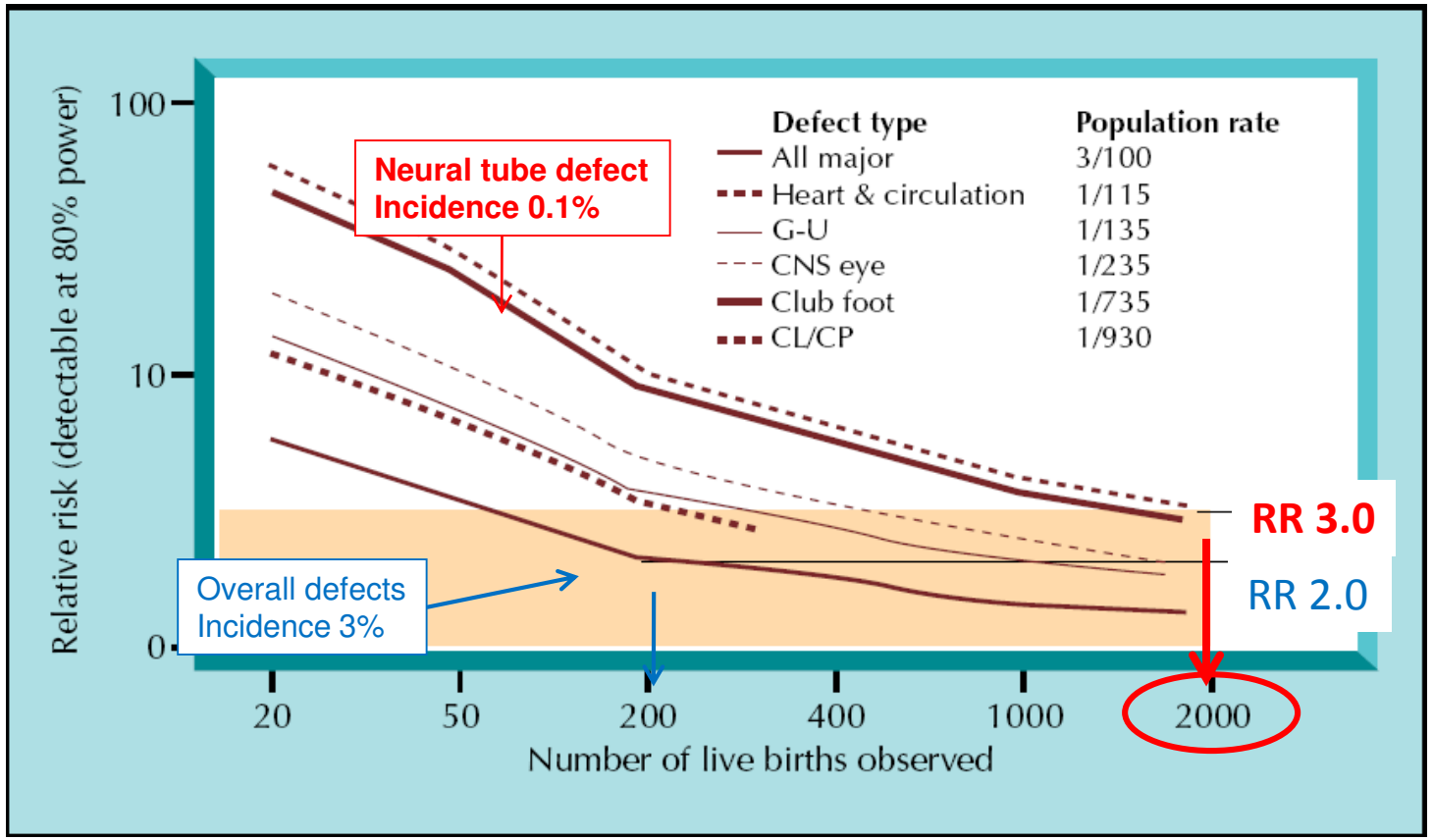
200 exposures can rule out a 2-fold ↑ in overall birth defects (incidence 3%)



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

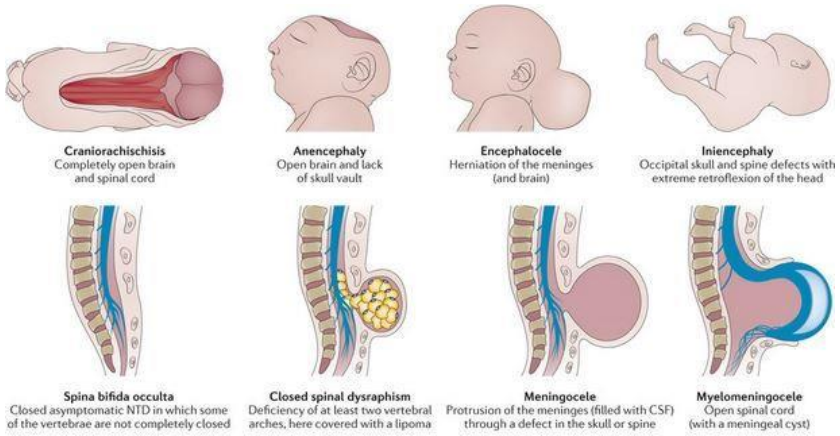
Ability to Rule-Out ↑ Birth Defect is Related to Defect Incidence and Number Observed Preconception/1st Trimester Exposures

However, to rule-out a 3-fold increase in a relatively rare event like NTD (incidence 0.1%), need about 2,000 exposures.



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

Dolutegravir, birth outcomes and birth defects

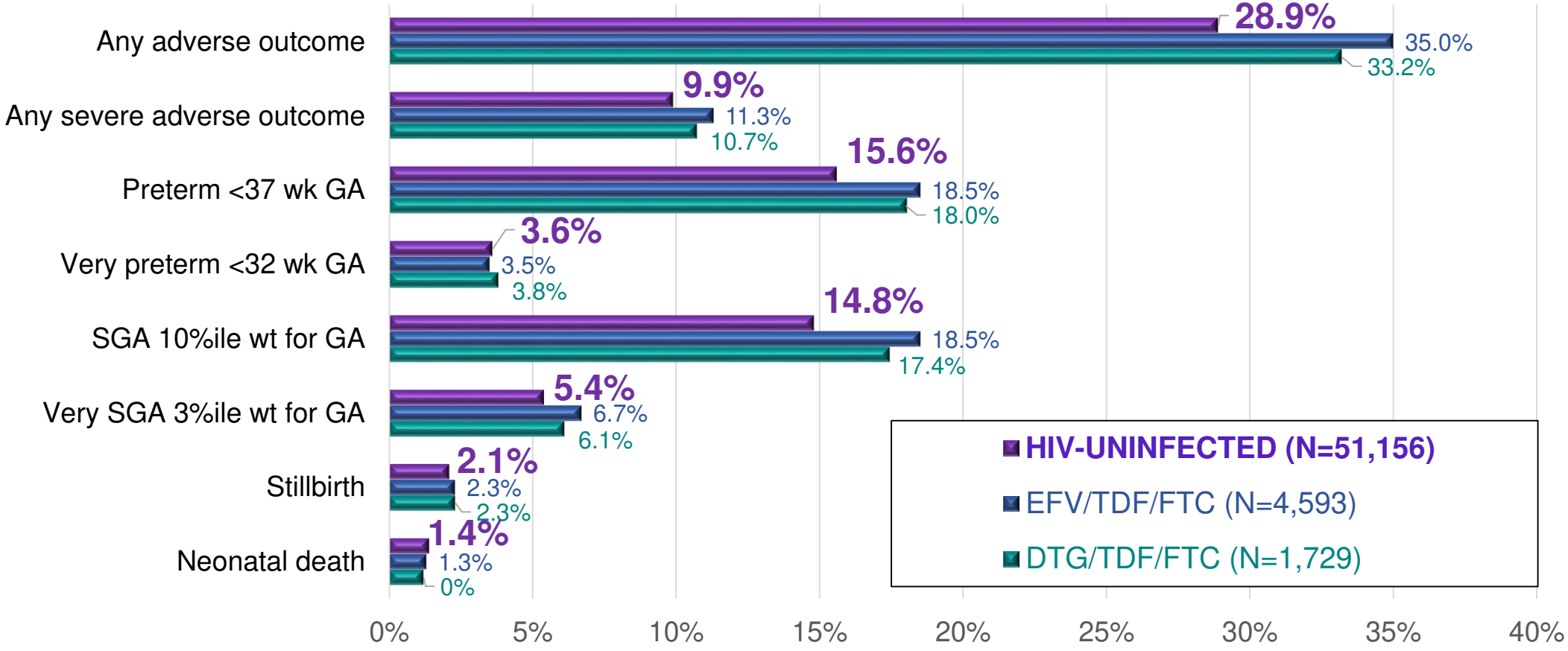


Birth surveillance and the Botswana Tsepamo Study

- *Designed to evaluate the risk of neural tube defects (NTD) with preconception EFV exposure; also examines pregnancy and birth outcomes by ARV 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
  - Clinical geneticist reviews all diagnoses
- Good denominator with control groups and ability to distinguish between ARV regimens, timing of ART initiation, infant HIV exposure status
- *In May 2016, the Botswana government shifted 1st line ART from tenofovir + lamivudine + efavirenz (TLE) to TLD*

Zash R. IAS, Amsterdam July 2018 Late Breaker; Zash R et al. N Engl J Med 2018 July 24 epub

Birth outcomes similar for women starting DTG vs EFV *during* pregnancy, Tsepamo



Zash R et al. Lancet Global Health 2018

2018 WHO Guidelines Development Group

- Convened in May 2018 to update the 2016 guidelines
- To consider whether **dolutegravir** in combination with an age appropriate backbone should be recommended as the preferred first-line as well as the preferred second-line antiretroviral agent for the treatment of HIV infection

Botswana Tsepamo Study
Reported NTD outcomes, May 2018

- **86 NTDs identified in 88,755 births -** 0.10% (95% CI 0.08%, 0.12%)
  - 42 meningocele/myelomeningocele, 30 anencephaly, 13 encephalocele and 1 iniencephaly
- 22 (25%) NTDs occurred among stillbirths
- Among live-born babies with NTDs, 25 (39%) died within 28 days, and 1 had unknown vital status
- Estimated prevalence of NTD in 2015 globally was 0.19% (95% CI 0.15% to 0.23%) [18.6 (15.3–23.0)/10,000] live births, with varied distribution geographically, ~0.09-0.14% in Sub Saharan Africa

Zash R. IAS, Amsterdam July 2018 Late Breaker; Zash R et al. N Engl J Med 2018 July 24 epub

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Deliveries up to 1 MAY 2018

- **DTG at conception:**
  - **4/426 (0.94%; 95%CI 0.37%, 2.4%)**
- Non-DTG ART at conception:
  - 14/11,300 (0.12%; 95%CI 0.07%, 0.21%)
- **EFV at conception:**
  - **3/5,787 (0.05%; 95%CI 0.02%, 0.15%)**
- DTG started during pregnancy:
  - 0/2,812 (0.00%; 95%CI 0.0%, 0.13%)
- Non-DTG ART started during pregnancy:
  - 3/5,624 (0.05%, 95% CI 0.02%, 0.16%)
- HIV-uninfected
  - 61/66,057 (0.09%, 95%CI 0.07%, 0.12%)

, 0.12%)

3

8 days, and

95% CI

varied

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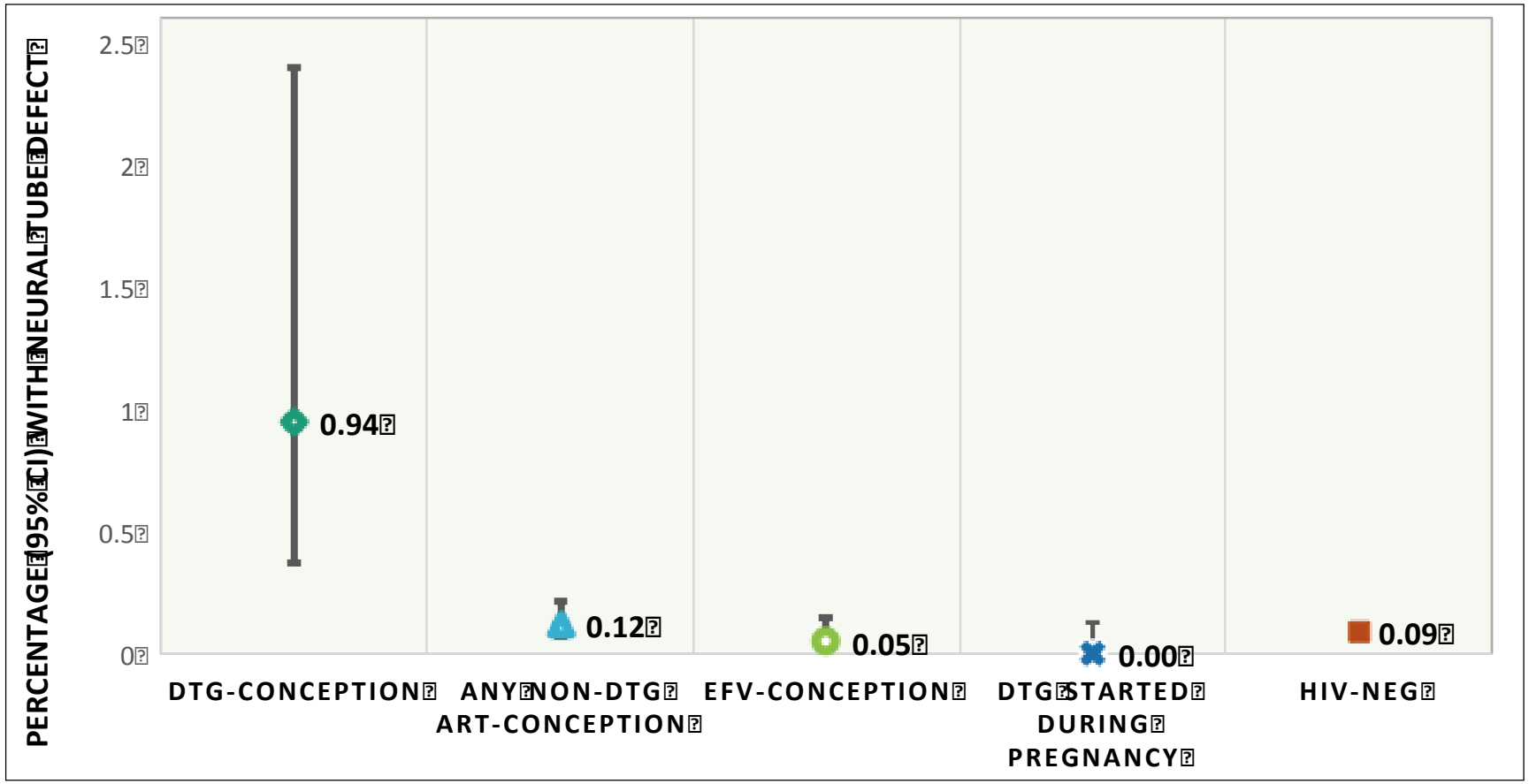
Zash R. IAS, Amsterdam July 2018 Late Breaker; Zash R et al. N Engl J Med 2018 July 24 epub

Neural Tube Defect 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%)**

Zash R. IAS, Amsterdam July 2018 Late Breaker; Zash R et al. N Engl J Med 2018 July 24 epub

WHO Statement on DTG – Geneva 18 May 2018

Potential safety issue affecting women living with HIV using dolutegravir at the time of conception

The investigator of an independent NIH-funded study has identified a potential safety issue with the HIV antiretroviral medicine dolutegravir (DTG), and reported it to the World Health Organization (WHO) and ViiV Healthcare. The potential safety issue is related to neural tube defects in infants born to women who were taking DTG at the time of conception.

The issue has been identified from a preliminary unscheduled analysis of an ongoing observational study in Botswana, which has found 4 cases of neural tube defects out of 426 women who became pregnant while taking DTG. This rate of approximately 0.9% compares to a 0.1% risk of neural tube defects in infants born to women taking other antiretroviral medicines at the time of conception.

Information on Neural Tube Defects

The neural tube is the foundation of the spinal cord, brain and the bone and tissues that surround it. Neural tube defects occur when the neural tube fails to completely form; this formation takes place between 0 and 28 days after conception. Neural tube defects may be related to folate deficiency, other medications or family history.

WHO recommends that women take daily supplements of folic acid before conception and during pregnancy to help prevent neural tube defects.

FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq)

[**05-18-2018**]

Safety Announcement

The U.S. Food and Drug Administration (FDA) is alerting the public that serious cases of neural tube birth defects involving the brain, spine, and spinal cord have been reported in babies born to women treated with dolutegravir used to treat human immunodeficiency virus (HIV). Preliminary results from an ongoing observational study in Botswana found that women who received dolutegravir at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these defects.

Neural tube defects are birth defects that can occur early in pregnancy when the spinal cord, brain, and related structures do not form properly. To date, in this observational study there are no reported cases of babies born with neural tube defects to women starting dolutegravir later in pregnancy. We are investigating this new safety issue and will update the public when we have more information.

Dolutegravir is an FDA-approved antiretroviral medicine used in combination with other antiretroviral medicines to treat HIV, the virus that can cause acquired immunodeficiency syndrome (AIDS). Dolutegravir works by blocking integrase, an HIV enzyme, to prevent the virus from multiplying and can reduce the amount of HIV in the body. Stopping dolutegravir without first talking to a prescriber can cause the HIV infection to become worse. Approved in 2013, dolutegravir has been on the market for 5 years, and is available as a single ingredient product under the brand name Tivicay and as a fixed dose combination tablet with other HIV medicines under the brand names Juluca and Triumeq.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 May 2018
EMA/295960/2018

New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir

While EMA review is ongoing, dolutegravir should not be used in women seeking to become pregnant

The European Medicines Agency (EMA) is evaluating preliminary results from a study which found 4 cases of birth defects such as spina bifida (malformed spinal cord) in babies born to mothers who became pregnant while taking dolutegravir. While EMA is assessing the new evidence it has issued the following precautionary advice:

- Dolutegravir HIV medicines should not be prescribed to women seeking to become pregnant.
- Women who can become pregnant should use effective contraception while taking dolutegravir medicines.

The study, which looked at babies born to 11 558 HIV-infected women in Botswana, showed that 0.9%

15 YEARS OF SAVING LIVES THROUGH AMERICAN GENEROSITY AND PARTNERSHIPS

PEPFAR Statement on Potential Safety Issue Affecting Women Living with HIV Using Dolutegravir at the Time of Conception

May 18, 2018

The U.S. President's Emergency Plan for AIDS Relief (PEPFAR) takes note of the May 18, 2018 statement by the World Health Organization (WHO) on "Potential safety issue affecting women living with HIV using dolutegravir at the time of conception."

CONFIDENTIAL

ViiV Healthcare SAFETY Advisory

Date: 23 May 2018

Dear Healthcare Professional

Title: Tivicay (dolutegravir): neural tube defects reported in Tsepamo Study, Botswana.

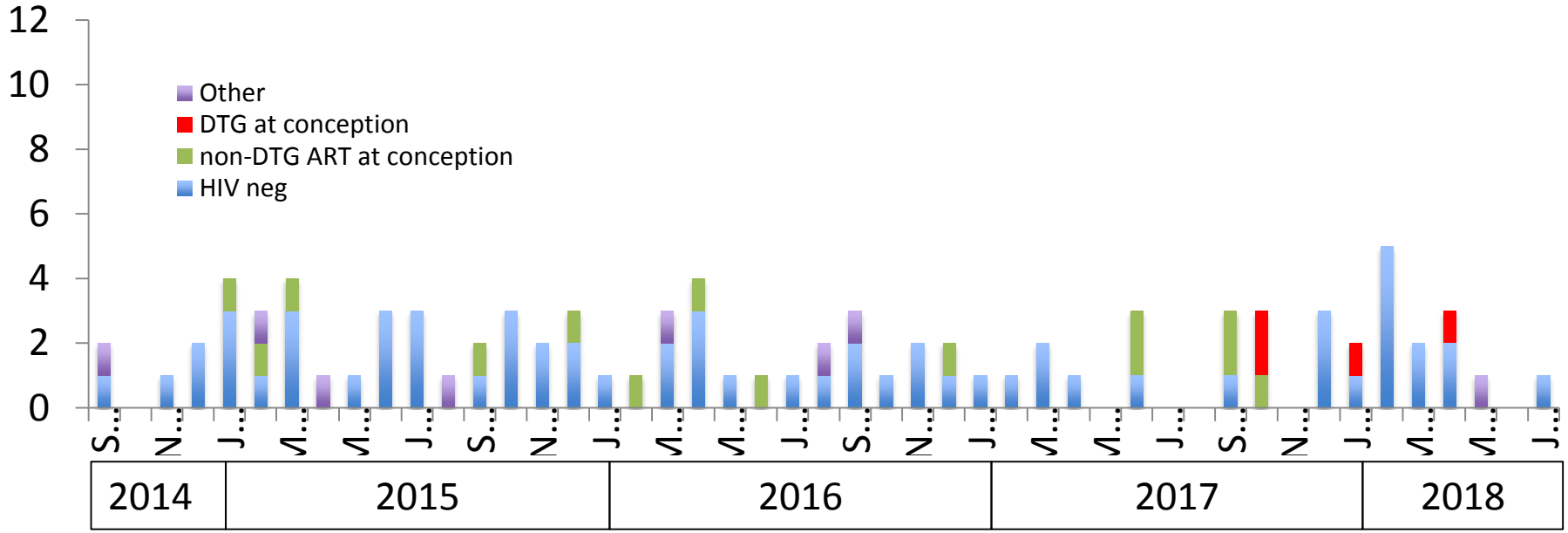
Key Messages

ViiV Healthcare would like to inform you of a potential safety issue which has been brought to our attention by the Principal Investigator of the above study conducted in Botswana. The potential safety issue is related to Neural Tube Defect (NTD) cases in infants born to women with exposure to dolutegravir-containing regimens *at the time of conception* identified from a preliminary unscheduled analysis of the Tsepamo study (4 NTD cases out of 426 pregnancies on dolutegravir). This represents an incidence of about 0.9% with an expected background rate of about 0.1%.

Tsepamo update since 1 May - 15 July 2018

- From 1 May-15 July, **2 additional NTDs;** 1 in an infant exposed to **DTG *started during pregnancy*** and 1 birth to an **HIV-uninfected** woman:

Updated prevalence of NTD among women with 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



Zash R. IAS, Amsterdam July 2018 Late Breaker; Zash R et al. N Engl J Med 2018 July 24 epub

The Botswana Tsepamo Study – more to come

- This finding may be a random event (cluster) or may be an early signal of an increased risk of NTD associated with DTG exposure at conception
- The study has expanded from 8 to 18 sites in Botswana
- *Real-time monitoring occurs every 200 DTG-conception exposures*
- Next planned analysis 31 March 2019; expected to capture about 1226 births with exposure to DTG from conception
- Limited data from other sources (APR, FDA, post-marketing surveillance) and of limited value given incomplete reporting and limited numbers.
- Brazil is undertaking a retrospective chart review of births to women with ART at conception including EFV, DTG and raltegravir

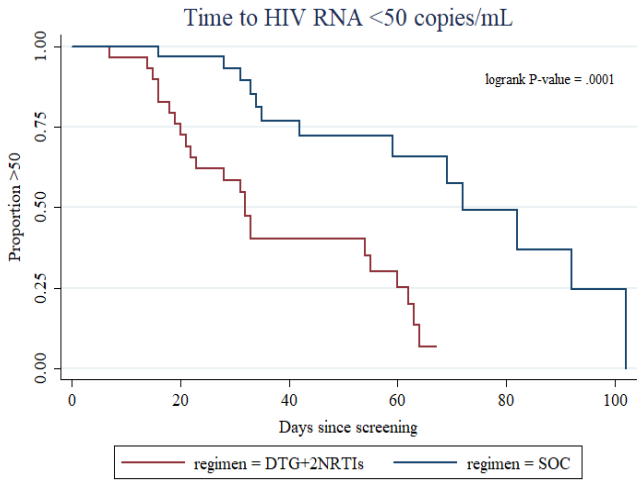
Dolutegravir safety and efficacy

Brief update

Dolphin1: DTG vs EFV when starting ART late in pregnancy

- Open-label RCT of DTG+2NRTI vs EFV+2NRTI in 60 pregnant ART-naïve women presenting late to ANC (≥28-36 weeks gestation) in Kampala and Cape Town
- Median time to RNA <50 copies was approximately halved with DTG compared to EFV (secondary endpoint)
- By ITT, significantly greater proportion of DTG than EFV subjects achieved viral suppression at 2 weeks postpartum

ITT (M=F)	DTG (N = 29)	EFV (N = 31)	P value **
HIV-1 RNA level at 2 week postpartum visit			
<50 copies/mL *	20 (69.0%)	12 (38.7%)	0.02
≥50 copies/mL	9 (31%)	19 (61.3%)	



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

Safety and Efficacy of DTG and EFV600 in 1st line ART
(summary 2018 WHO Sys Review & NMA)

major outcomes	DTG vs EFV_{600}	QUALITY OF EVIDENCE
Viral suppression (96 weeks)	DTG better	moderate
Treatment discontinuation	DTG better	high
CD4 recovery (96 weeks)	DTG better	moderate
Mortality	comparable	low
AIDS progression	comparable	low
SAE	comparable	low

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

Superior effectiveness of DTG-based 1st line ART in adults, Brazil

			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)

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

ANRS 12313 NAMSAL: TLD VS TLE400

- 616 patients (66% women, CD4 : 281/mm^3, VL 5.3 log [66% > 5 log]), three sites in Yaoundé Cameron
- Randomized 1:1 to DTG vs EFV400 + TDF/3TC, stratified by VL and site
- Primary endpoint : noninferiority of DTG vs. EFV400 by proportion with VL < 50 copies/ml at week 48 (intent to treat [ITT] snapshot analysis, 10% margin) Superiority tested if non-inferiority demonstrated

TLD is non-inferior to TLE400

	DTG N=310	EFV 400 N=303	Difference A-B IC 95%	Superiority Test p-value
HIV RNA< 50 copies/ml	231 **74.5%**	209 **69%**	5.5% (-1.6;+12.7)	0.13
HIV RNA> 50 c/mL Stop for death Stop for other reasons (LTF, withdrawn)	62 6 9	70 7 15		
HIV RNA< 100 000 c/mL	94/103 **91.3%**	86/103 **83.5%**	7.8% (-1.2;+16.8)	
HIV RNA> 100 000 c/mL	137/207 **66.2%**	123/200 **61.5%**	4.7%(-4.6;+14.0)	
HIV RNA> 500 000 c/mL	51/93 **54.8%**	55/95 **57.9%**		

Similar rates of adverse events and AIDS defining illnesses between arms; no treatment interruptions attributed to intolerance

Guidance on the use of dolutegravir

Implications and ramifications

Antiretroviral treatment for HIV infection: WHO interim guidance, July 2018

BOX 1. RECOMMENDATIONS: FIRST-LINE ARV DRUG REGIMENS

1. A DTG based regimen may be recommended as a preferred first-line regimen for people living with HIV initiating ART *(conditional recommendation)*

- Adults and adolescents *(moderate-certainty evidence)*
- Women and adolescent girls of childbearing potential[a] *(very-low-certainty evidence)*
- Infants and children with approved DTG dosing[b] *(low-certainty evidence)*

Note of caution on using DTG during the periconception period and for women and adolescent girls of childbearing potential

Antiretroviral treatment for HIV infection: WHO interim guidance, July 2018

TABLE 1. SUMMARY OF SEQUENCING OPTIONS FOR FIRST-, SECOND- AND THIRD-LINE ART REGIMENS FOR ADULTS (INCLUDING PREGNANT WOMEN AND ADOLESCENTS) AND CHILDREN

Population	First-line regimens	Second-line regimens	Third-line regimens
Adults and adolescents (including women and adolescent girls who are of childbearing potential or are pregnant)[a]	Two NRTIs + DTG[b]	Two NRTIs + (ATV/r or lopinavir/ritonavir (LPV/r))	Darunavir/ritonavir (DRV/r)[g,h] + DTG[i] + 1–2 NRTIs (if possible, consider optimization using genotyping)
	Two NRTIs + EFV[c]	Two NRTIs + DTG[b]	
Children	Two NRTIs + DTG	Two NRTIs + (ATV/r[d] or LPV/r)	
	Two NRTIs + LPV/r	Two NRTIs + DTG[e]	
	Two NRTIs + NNRTI	Two NRTIs + DTG[f]	

[b]**Women and adolescent girls of childbearing potential with consistent and reliable contraception and who are fully informed of the benefits and risks of DTG use**; [c]If population-level pretreatment resistance to EFV or NVP is ≥10%, the choice of alternative options to EFV needs to weigh the drug availability and toxicity profile, DTG (with consistent and reliable contraception among adolescent girls and women of childbearing potential) or ATV/r are drug options to be considered

Adopting a woman-centered approach

- Woman-centered health services involve an approach to health care that consciously adopts the perspectives of women and their families and communities. This means that health services see women as active participants in and beneficiaries of trusted health systems that respond to women's needs, rights and preferences in humane and holistic ways. Care is provided in ways that respect women's autonomy in decision-making about their health, and services must provide information and options to enable women to make informed choices. The needs and perspectives of women, their families and communities are central to providing care and to designing and implementing programs and services. A woman-centered approach is underpinned by two guiding principles: promoting human rights and promoting gender equality.

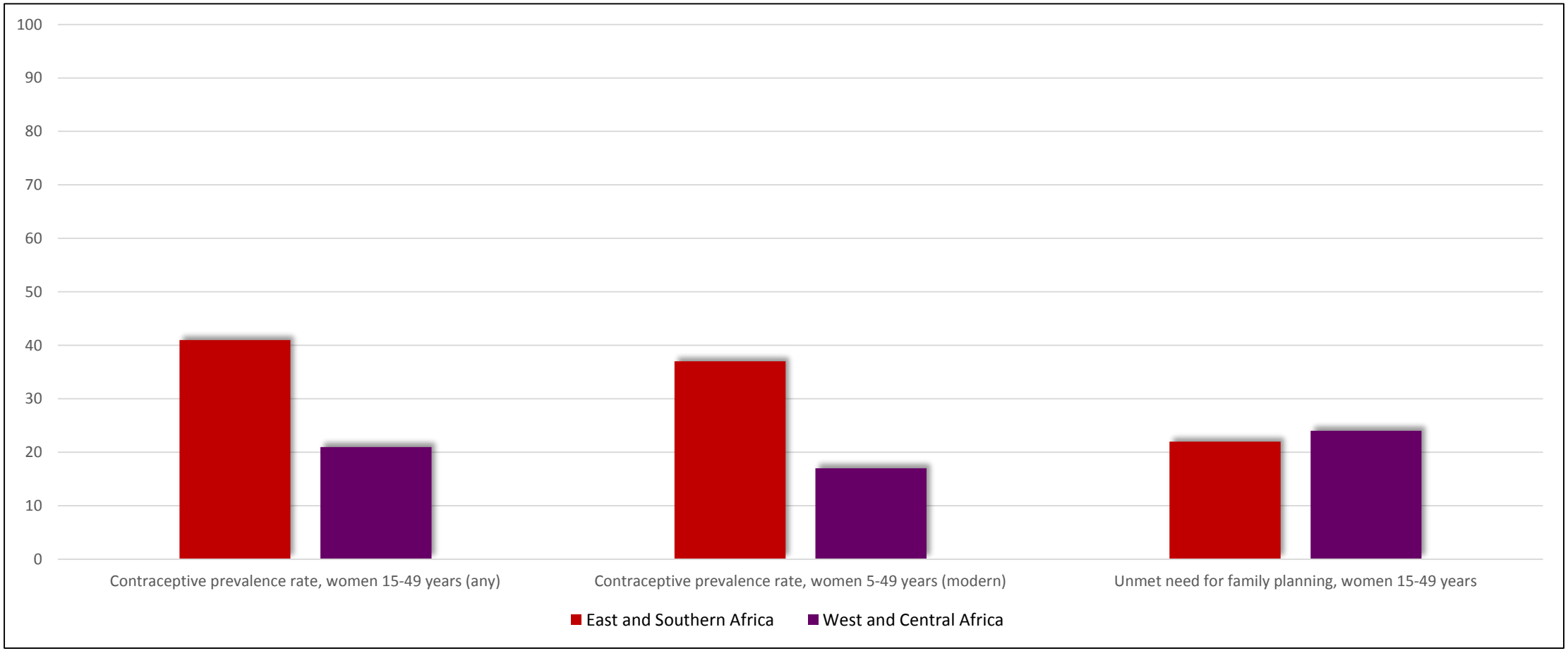
ART for HIV infection: PEPFAR guidance

- DTG-containing regimens are the preferred 1st-line antiretroviral therapy
- Programs should rapidly transition to TLD as the preferred option for ART
- Populations that are recommended to transition to TLD include:
  - All new adolescent (≥ 10 years and ≥ 30 kg) and adult 1st-line populations
  - All existing adolescent (≥ 10 years and ≥30 kg) and adult 1st-line populations
  - Patients failing an NNRTI-based 1st-line ART, or have failed an NNRTI-based ART and are currently on a PI-based 2nd-line ART in programs that can confirm virologic suppression 3-6 months after transition to TLD
  - Adults and adolescents receiving rifampicin-containing regimens for TB, with an additional 50 mg dose of DTG
  - Pregnant and breastfeeding women should be included in plans to transition to TLD
- PEPFAR recommends that **TLD counseling on the potential benefits and risks of the drug**, including NNRTI resistance, drug availability, and maternal and infant toxicity profile be provided, along with access to voluntary family planning (FP) services, **to women of reproductive potential** (WRP) to help them make informed decisions about their ARV regimen and use/non-use of FP

New guidance represents a major change in approach to ART scale-up

- Much of the success of the rapid global ART scale-up is attributed to the simplified, harmonized public health approach
- Shift from ONE 1st line regimen harmonized across populations to TWO 1st line regimens
  - Regimen determined by individual characteristics; sex, reproductive potential, choice
- Shift from public health to patient centered approach
  - Regime historically determined at national level
  - Introducing patient choice as a determinant of regimen
- WHO and PEPFAR guidance represent somewhat different approaches
  - Both speak to the importance of informed choice
- ART use now linked with sexual and reproductive health (SRH) and another commodity (contraceptives)
  - Globally contraception prevalence rates are low and unmet family planning rates are high

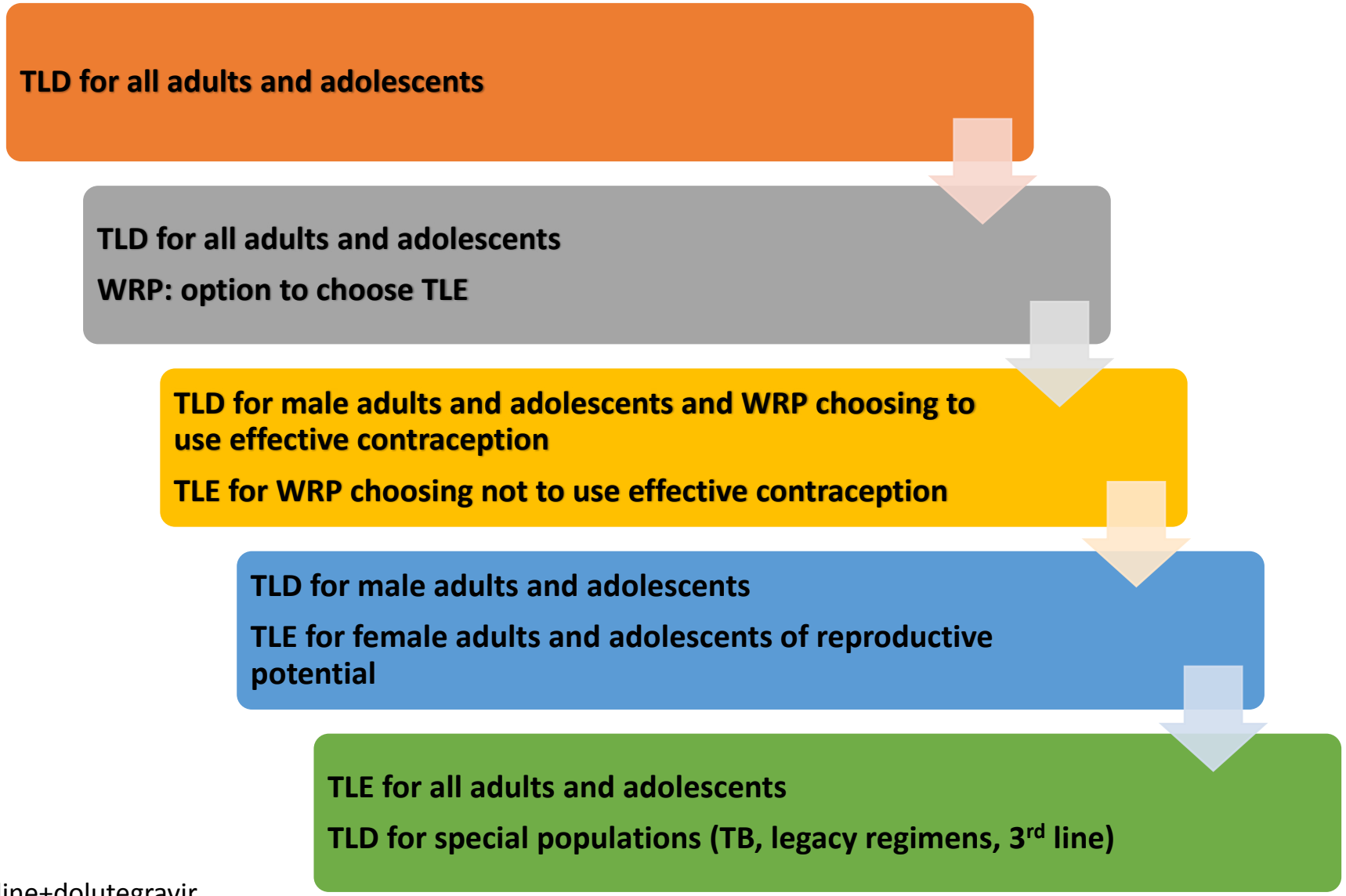
Contraceptive prevalence and unmet family planning need among women in Africa



UNFPA, 2017

Global update and implementation considerations

Approaches to introduction of DTG into national programs



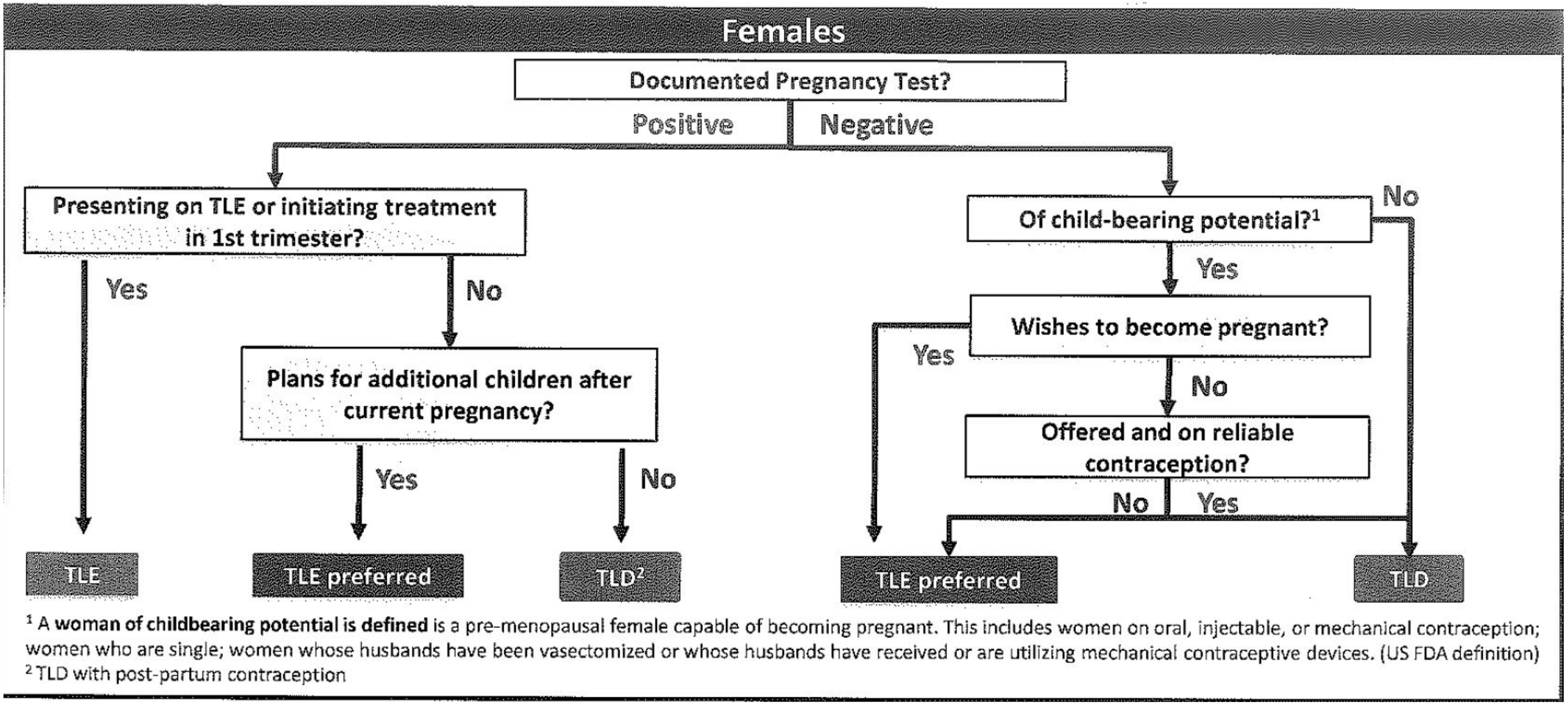
TLD – tenofovir+lamivudine+dolutegravir
WRP – women of reproductive potential

Current guidance on use of DTG based regimen for women in 20 countries (Sept-Oct 2018)

Country	Women of Childbearing Potential			Pregnant Women		
	NO DTG	Any or Long term contraception→ DTG No contraception→ NO DTG	Counselling on contraception & informed choice	NO DTG	1st trimester → NO DTG 2nd and 3rd trimester→ DTG	Counselling on ART & informed choice
Botswana		✓		✓		
Brazil		✓		✓		
Burundi	✓			✓		
Cote d'Ivoire	✓			✓		
DRC		✓			✓	
Eswatini	✓			✓		
Ethiopia	✓			✓		
Haiti		✓		✓		
Kenya		✓			✓	
Malawi	✓			✓		
Mozambique	✓			✓		
Nigeria		✓			✓	
Rwanda	✓			✓		
South Africa		✓			✓	
Tanzania			✓	✓		✓
Uganda			✓	✓		
Ukraine		✓		✓		
Venezuela		✓		✓		
Zambia	✓			✓		
Zimbabwe			✓		✓	

World Health Organization

Illustrative prescribing algorithm for TLD use in females



¹ A **woman of childbearing potential is defined** is a pre-menopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women who are single; women whose husbands have been vasectomized or whose husbands have received or are utilizing mechanical contraceptive devices. (US FDA definition)

² TLD with post-partum contraception

Major factors that can influence the transition to DTG in first-line ART

Clinical/epidemiological

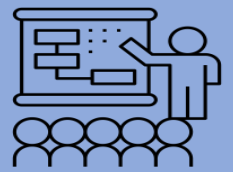
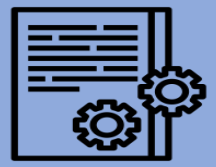

- % of HIV+ women of childbearing potential
- % of patients using suboptimal 1st line regimens (eg: NVP, PI/r)
- Availability of 2nd and 3rd line options
- % PDR to NNRTIs

Commodities



- EFV and DTG stocks
- Access to contraceptive options
- Access to viral load
- Availability of FDCs and standalone formulations
- Availability of generic formulations

Programme/policy


- Inclusion in national guidelines
- Supply chain capacity
- Capacity building & training of health care providers
- Policy translation to community
- Toxicity monitoring & pregnancy safety monitoring systems

Considerations for transition to TLD

Is DTG safe for women of reproductive potential?

- Balance a possible increase in risk of NTD with potential benefits of TLD
  - Better tolerance, more rapid viral suppression (VS), higher rates of VS, projected lower transmission to partners and infants, similar birth outcomes

What is rate of pretreatment HIV drug resistance?

- If population-level pretreatment resistance to EFV or NVP is ≥10% WHO guidance suggests a rapid transition to non-NNRTI-based 1st line regimen
- Alternative options include DTG- and protease inhibitor-based regimens

- Is it necessary to measure viral load (VL) prior to switching patients from current 1st-line regimens to TLD?
  - No strong evidence on which to base policy
  - Recognizing VL availability is rapidly increasing but still not widely available- options include:
    1. Measure VL; transition those with VS to TLD; those with unsuppressed VL transition to DTG+2 NRTIs
    2. Transition all to TLD, measure VL at 3-6 months to confirm VS

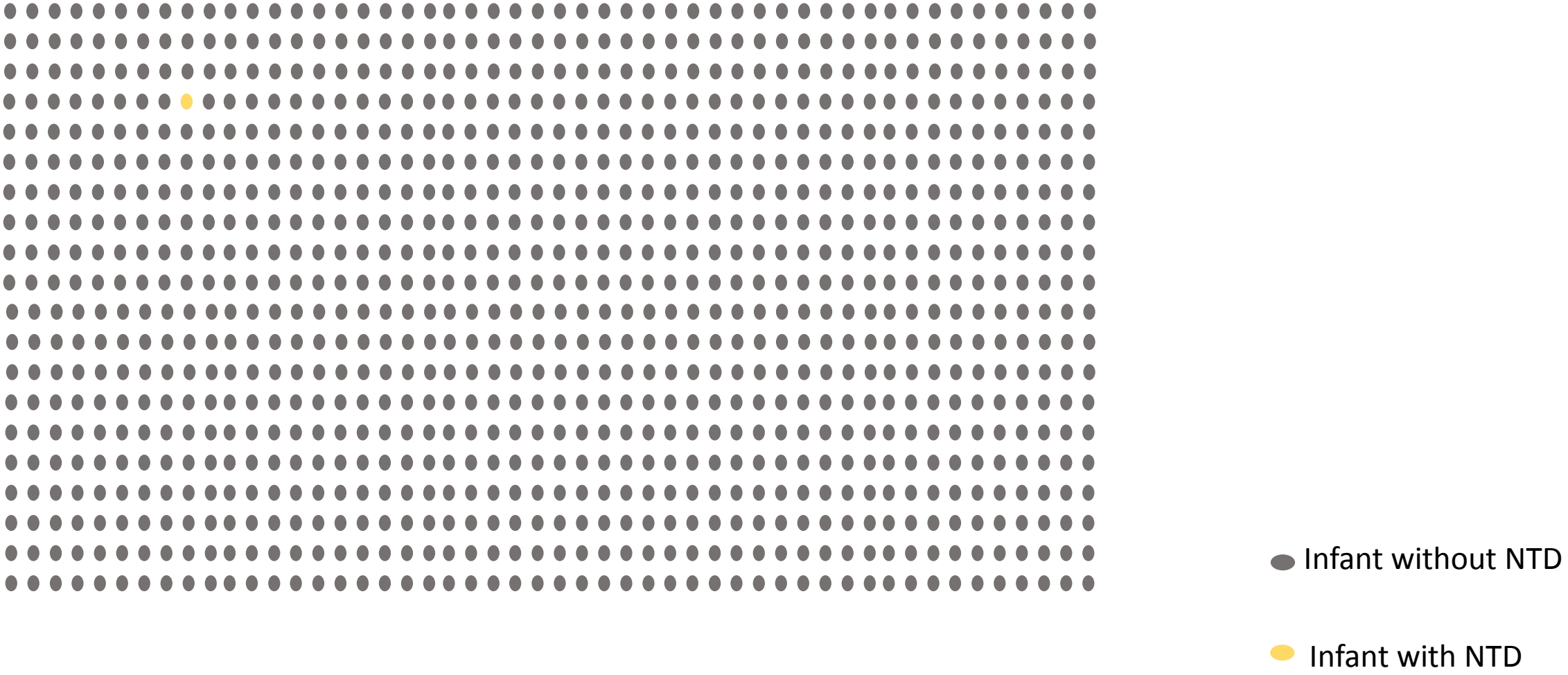
Ensuring access to consistent and reliable contraception

- Access to contraception varies across and within country programs
  - Potential for new threats to FP access with the expanded Mexico city policy
  - User fees may further impede FP access in some settings; Options may also be more limited in faith-based settings
  - The current issues also provide an opportunity to enhance FP access and services for women living with HIV
- FP and contraception traditionally provided within the MCH
  - Importance of integration within ART programs where women will be accessing ART
    - Special considerations within DSD models of care
- Substantial numbers of women living with HIV want to more children and women are often not the only decision makers around and contraceptive use

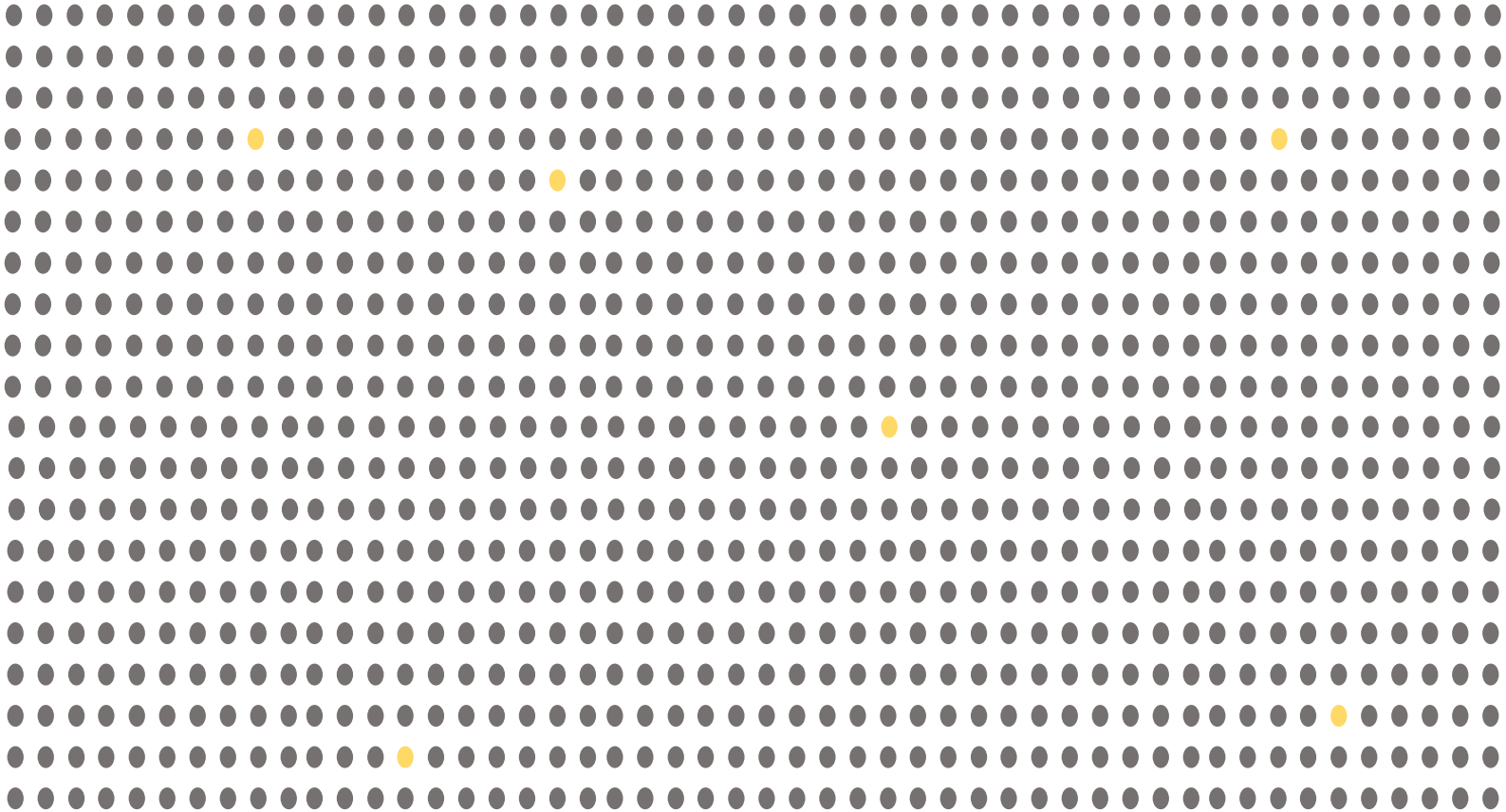
Enabling women to make an informed choice

- How to effectively communicate concepts of risk to the individual and the community; and to link risk with ART choice?
- The burden around education and communication will likely to fall to facility health care workers
  - Already shouldering heavy burden of the HIV response
  - Traditionally guided by algorithms
  - Experience communicating risk and supporting patient choice are limited
    - AFASS to determine infant feeding approach was not successful
  - Effective training, mentoring, tools and ongoing support for health care workers will be essential

Ordinarily, of every 1000 thousand babies born we expect to see one NTD



For women taking DTG we may see 6 or 7 babies out of every 1000 may have an NTD



Infant without NTD

Infant with NTD

What should countries be doing to monitor for NTDs and other outcomes?

- Surveillance for birth defects and other rare outcomes is difficult and costly
  - There is a global need to implement birth outcomes surveillance systems
  - However, it must be rigorously done to provide meaningful data
  - The DTG-NTD issue should make countries consider the importance of birth outcome surveillance and what might be appropriate for a particular setting
  - Technical assistance is available to inform and support implementation
- Monitoring systems are generally already in place to measure uptake, efficacy and impact of the transition
  - Systems to monitor drug-related adverse events are weak and need to be strengthened
  - Other critical life events (i.e. pregnancy, breastfeeding) are also not routinely recorded and warrant attention

Resources

- Several cost benefit analyses have been completed and presented
- WHO is developing implementation guidance
- ICAP will be posting and disseminating a health care worker training (in English, French and Portuguese) in the next weeks
- A variety of tools and materials are under development to support decision making, training and implementation
- Tsepamo team is working diligently to continue to obtain high quality data to further inform the NTD question. Several external groups have been convened to evaluate and analyze all available data on an ongoing basis

In conclusion

- The findings of a possible association between DTG and NTD has derailed plans for the rapid roll-out of TLD as the preferred ART regimen
- Country programs are facing a number of complex issues around DTG use and implementation
  - Limited experience to help address these issues
- While we may feel we are between a rock and a hard place, there are enormous opportunities to address these issues and continue to improve health outcomes for people living with HIV
  - We must continue to learn from each other
  - The collective experience will inform future work