



# CQUIN Differentiated MCH Workshop

May 25-27, 2021

## HIV TREATMENT IN PREGNANCY

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*Nothing to disclose*



HIV Learning Network

The CQUIN Project for Differentiated Service Delivery

# Outline

- 1 Pregnant women are of central importance to global HIV treatment**
- 2 Antiretrovirals in pregnancy and:**
  - Vertical transmission
  - Pregnancy outcomes
  - Congenital anomalies
  - Mother's health outcomes
  - Child outcomes
- 3 Current pregnancy antiretroviral treatment (ART) recommendations**
  - Evidence gaps

# Pregnant women are central to our global approach to HIV treatment

- **51% of persons living with HIV globally are women<sup>1</sup>**
- **~1.3 million women with HIV are pregnant each year<sup>1</sup>**
  - Most women with HIV will be pregnant at least once following diagnosis
- **Need to identify and provide the safest, most effective HIV treatment regimens for women and their children throughout their life course**
- **Pregnancy findings can affect HIV treatment of millions of individuals**

# HIV treatment in pregnancy and...

**Vertical transmission (VT)**

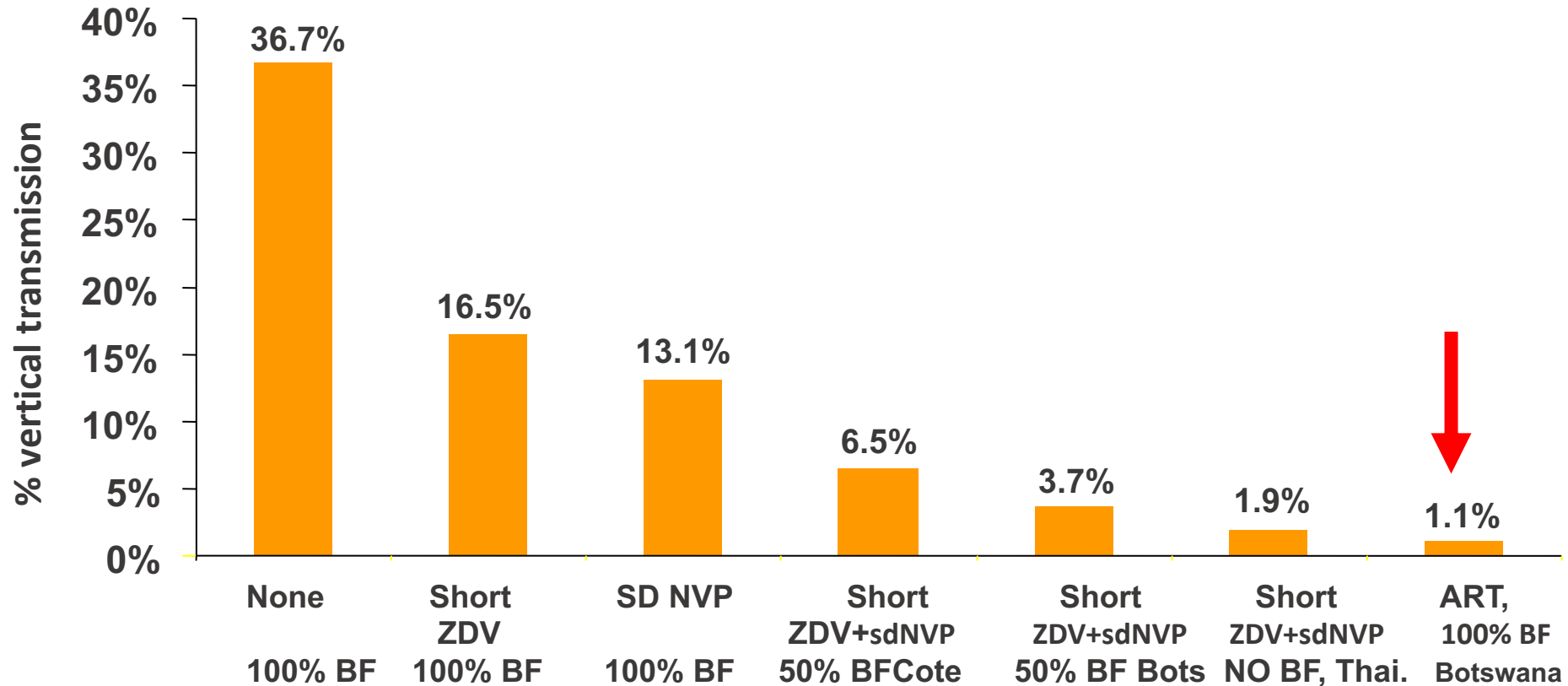
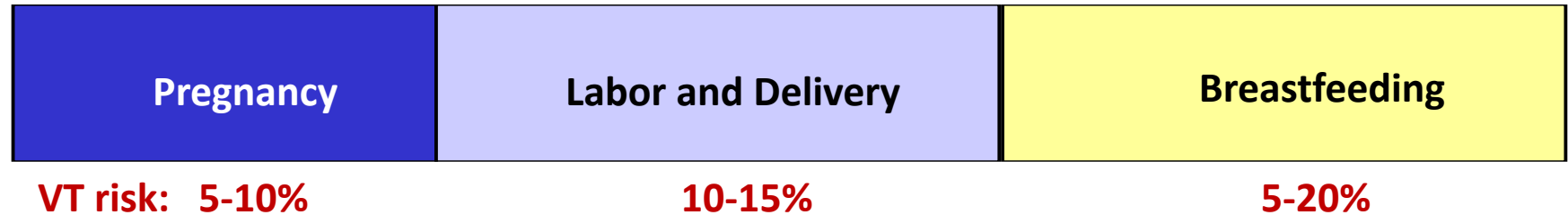
Pregnancy outcomes

Mother's health outcomes

Child outcomes

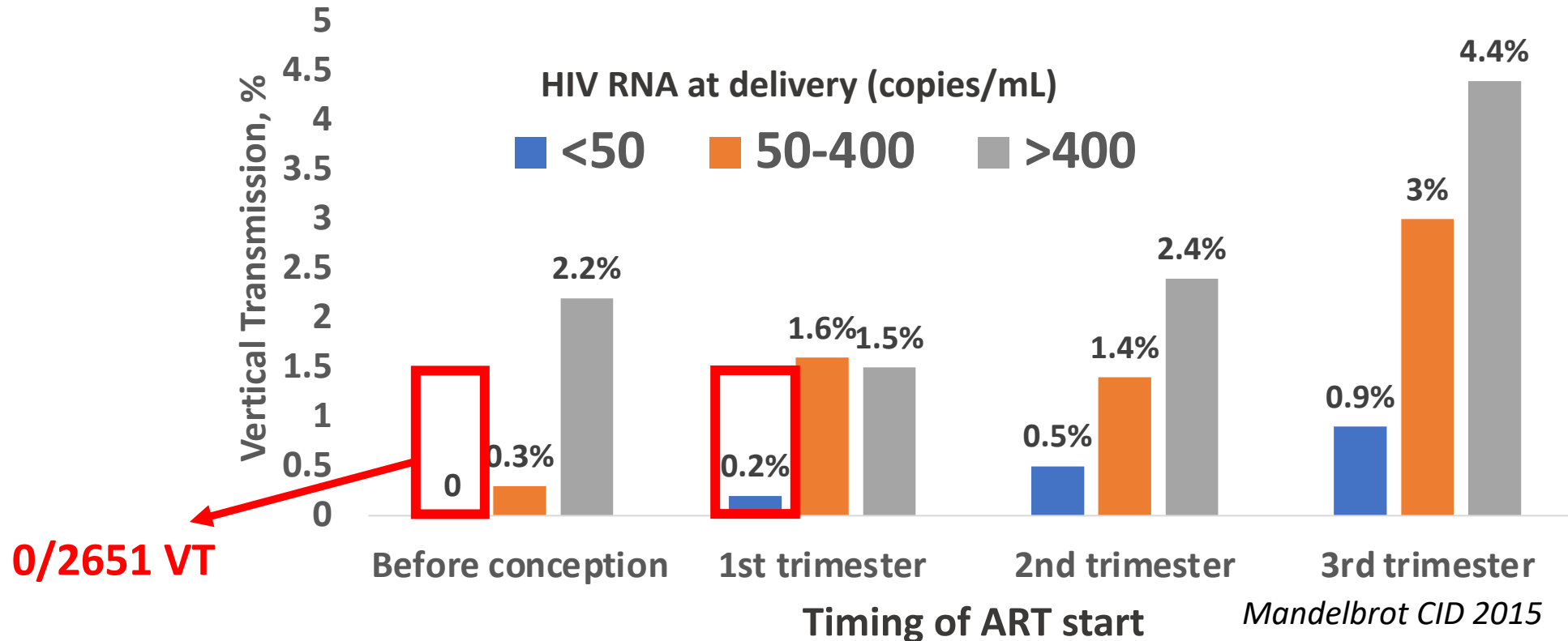
# Maternal combination ART dramatically reduces VT

**20%-45% risk of VT  
if no intervention**



# Transmission is very low with viral suppression on ART from early in pregnancy

8075 mothers on ART and their non-breastfed infants, 2000-2011, French Perinatal Cohort



- Earlier ART start = better (lowest transmission with pre-conception ART)
- Maternal HIV-1 RNA = independent predictor of vertical transmission
- U likely = U with ART from conception, viral suppression, no breastfeeding

# Does $U = U$ with breastfeeding while on ART?

## **Relatively little data in women with documented viral suppression during breastfeeding**

2 out of 677 BF babies in Mma Bana: both mothers on triple-NRTI

2 babies in PROMISE: mothers with detectable VL at delivery but VL suppression thereafter for both

## **Recommendations:**

Maternal ART during breastfeeding (in places where formula is not safe/feasible)

**$U$  is close to  $U$  during breastfeeding  
for women with sustained postnatal virologic suppression**

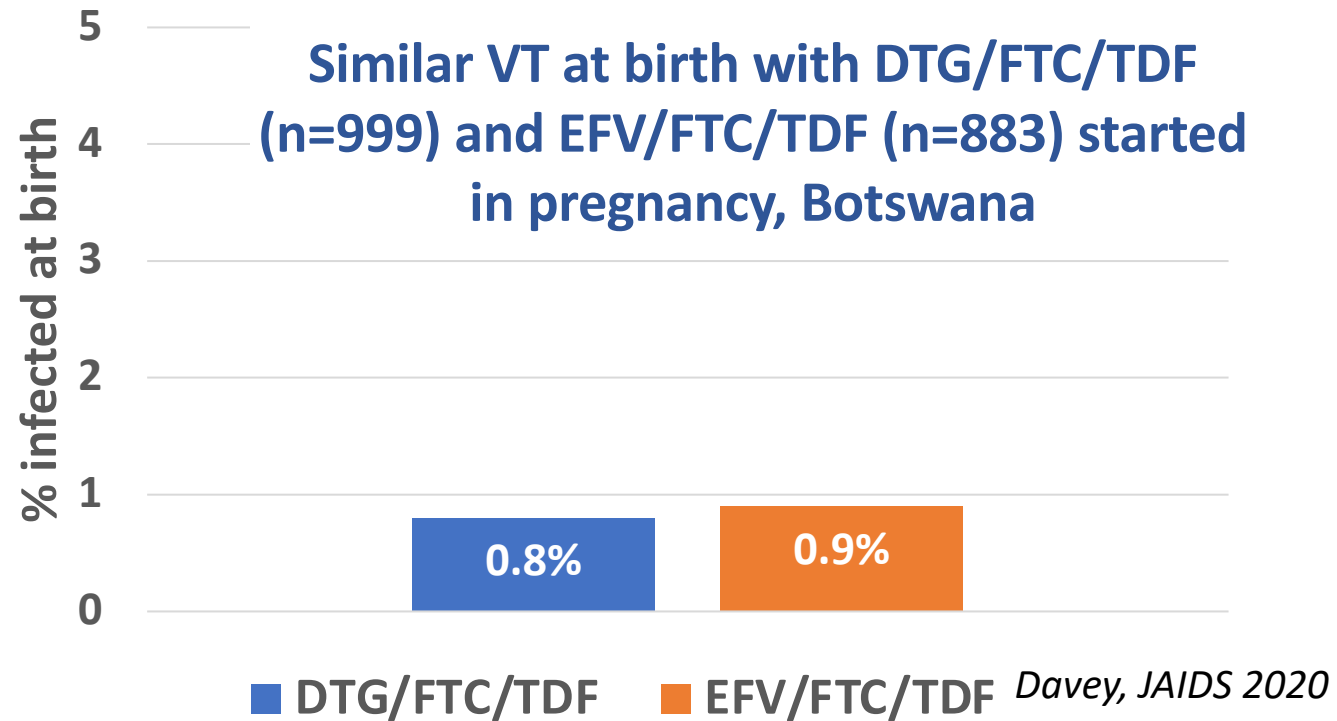
# Does ART regimen affect vertical transmission?

**DTG reduces viral load more rapidly in pregnancy than EFV** (*Kintu Lancet HIV 2020; Chinula AIDS 2020*)

**Meta-analysis: 5 trials of DTG/XTC/TDF (or TAF) vs. EFV/XTC/TDF (n=1,074)**

- Delivery VL suppression: DTG (90%) > EFV (72%),  $p=0.001$
- 5 cases VT: all in DTG arms (5/659, 1%)

*Asif AIDS 2020 Conference*

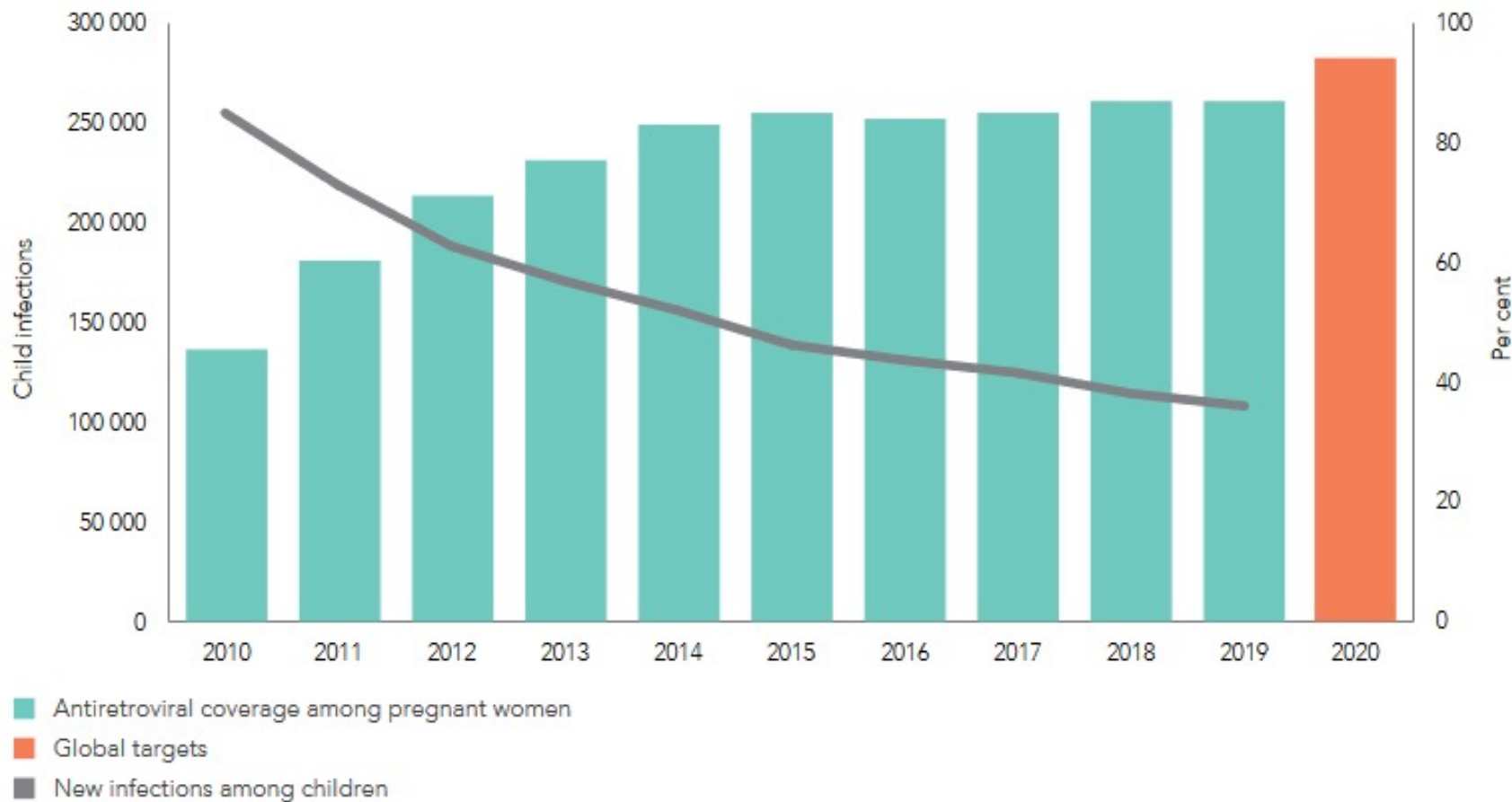


Although VL drops more quickly with DTG, both DTG- and EFV-ART are very effective at preventing vertical transmission



# How well are we doing with preventing VT globally?

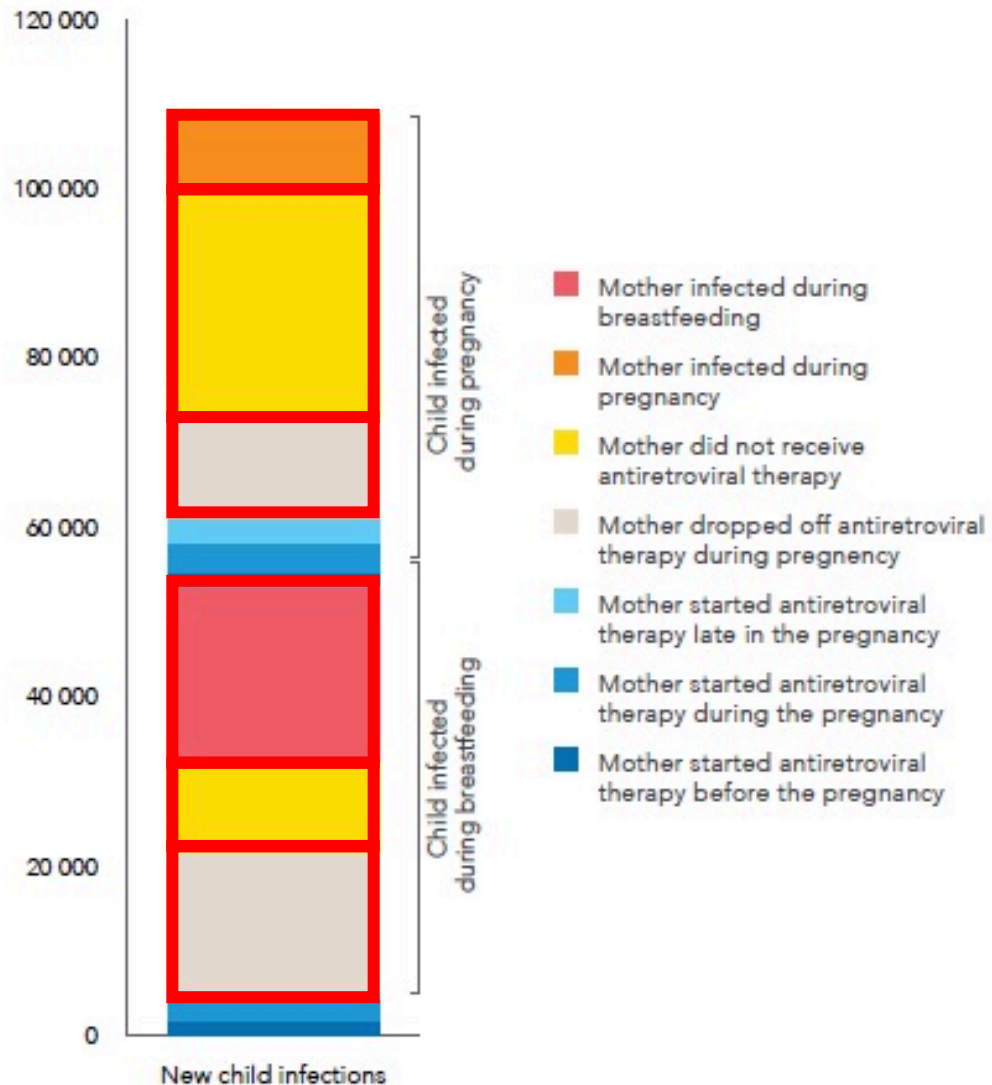
% of pregnant women on ART and new pediatric infections in focus countries, 2019



In 2019:

- 85% ART in pregnancy
- >50% conceived on ART
- **BUT, still ~150,000 new pediatric infections**

# Primary reasons for new HIV infections in children, 2019



## THE THREE PRIMARY MISSED OPPORTUNITIES FOR PREVENTING VERTICAL TRANSMISSION:

- 1 Mother did not receive ART (pregnancy > breastfeeding)
- 2 Incident HIV infection (breastfeeding > pregnancy)
- 3 Dropped off ART (breastfeeding > pregnancy)

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# Key points, vertical transmission

- 1 Viral suppression on maternal ART from early pregnancy can nearly eliminate VT through delivery, and rate as low as 1% possible even with breastfeeding**  
Lowest transmission with pre-conception ART
- 2 Work to do: increase ART coverage and maternal HIV re-testing (to diagnose incident HIV); reduce HIV incidence; and better support retention in care and ART adherence**

# Implications for care and service delivery

## **Identify and treat incident HIV infection during pregnancy/lactation:**

- Optimize HIV diagnosis & ART start in young women prior to / early in pregnancy
- High HIV burden settings (or women at high risk): re-test for HIV in 3<sup>rd</sup> trimester and potentially also during breastfeeding

## **Pregnant / lactating women taking ART:**

- Evaluate new interventions for providing ART in ways that are as accessible and acceptable as possible, and supporting adherence, particularly postpartum
- Refer to new WHO guidance on viral load monitoring March 2021

# HIV treatment in pregnancy and...

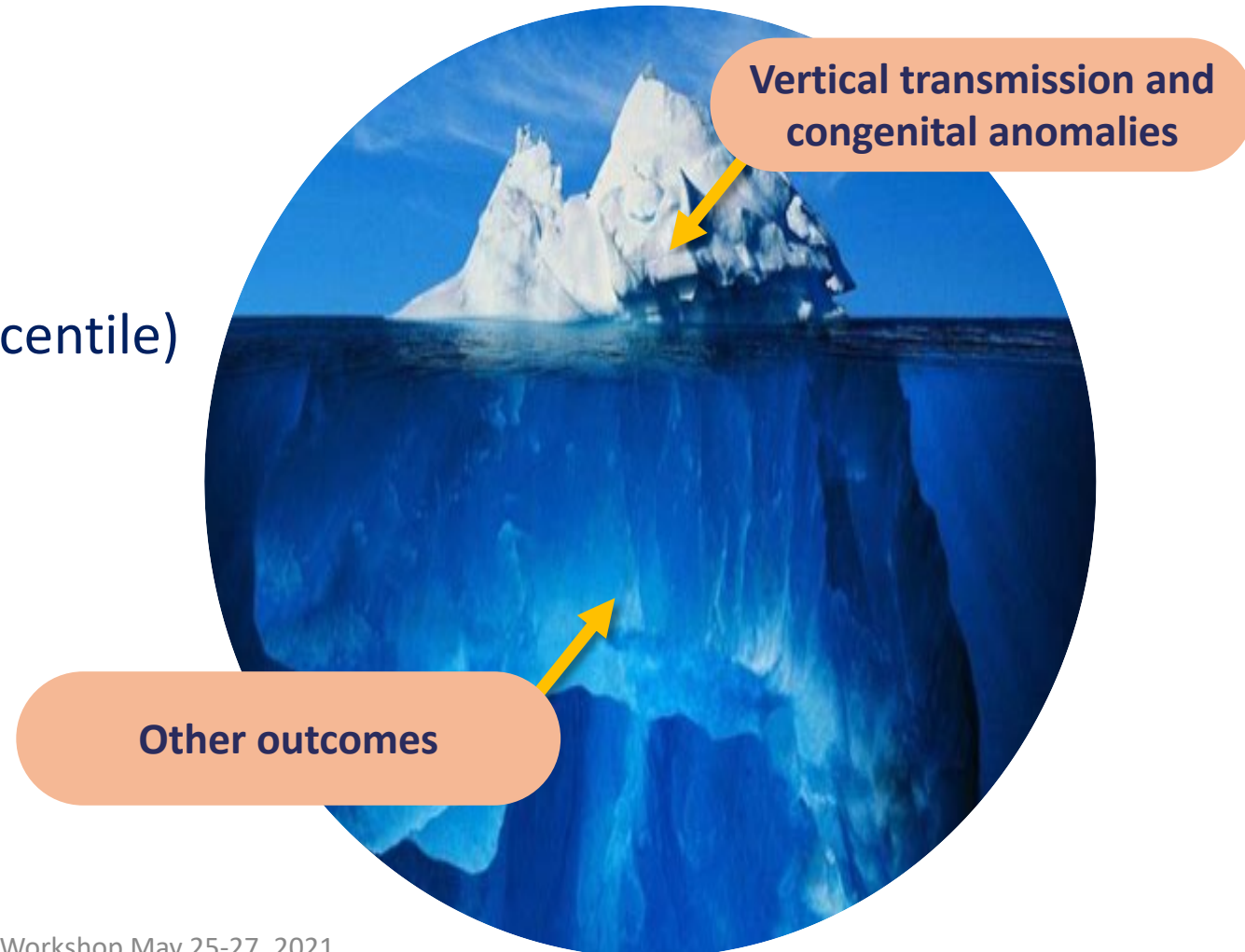
## Vertical transmission

### Pregnancy outcomes

- Preterm delivery (**PTD**, birth <37 weeks)
- Low birthweight (**LBW**, <2500g)
- Small for gestational age (**SGA**, <10<sup>th</sup> percentile)
- Stillbirth
- Neonatal Death

### Mother's health outcomes

### Child outcomes



# Why are preterm birth and low birthweight important?

- **Preterm birth = the leading cause of neonatal and under-5 mortality globally**
  - Poor long-term outcomes, especially in very preterm babies
- **Low birthweight (or small for gestational age) babies are at significantly higher risk of dying, particularly in low-income settings**

# Pre-ART era: women with HIV had much higher rates of adverse pregnancy outcomes than women without HIV

Perinatal outcome	Cohort	Number	HIV-positive	Total number	RR (95% CI)
Preterm b					4-1.82)
					1-2.34)
Very pret					0-1.65)
Low birth					1-1.86)
					3-2.52)
Very low					7-49.72)
Term low					3-1.72)
					5-5.93)
Preterm l					1-1.54)
					2-4.99)
Small for					4-1.51)
					5-3.46)
Very sma					5-1.71)
Miscarria					7-5.36)
Stillbirth					5-2.66)
Neonatal					5-6.29)
					1-6.54)

**Better outcomes with ART in pregnancy than without ART ...but not a free ride**

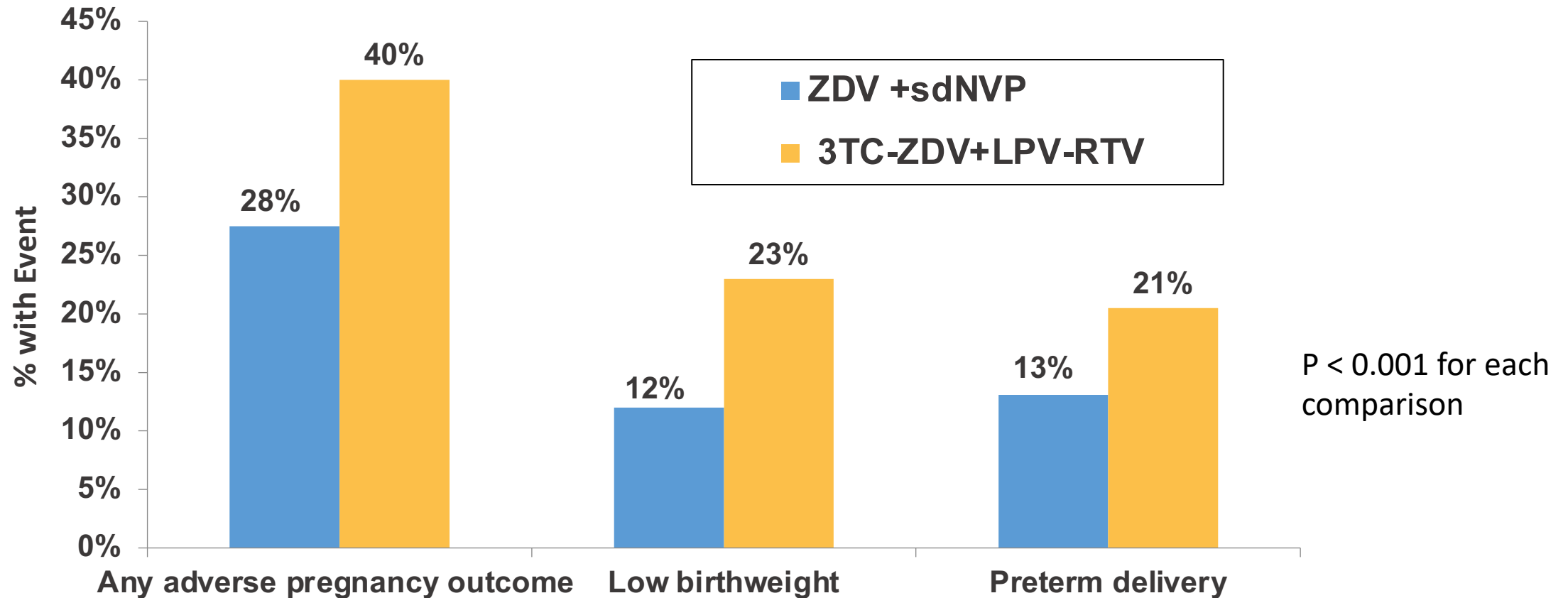
risk of perinatal outcomes risk of perinatal outcomes

Adverse Birth Outcomes, Antiretroviral Naïve Women 1980-2014

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Wedi et. al., Lancet Infect Dis, 2016

# Worse pregnancy outcomes with 3-drug ART than ZDV

PROMISE TRIAL (IMPAACT P1077)



**Women enrolled with CD4  $\geq 350$  cells/mm<sup>3</sup> and no AIDS illness**

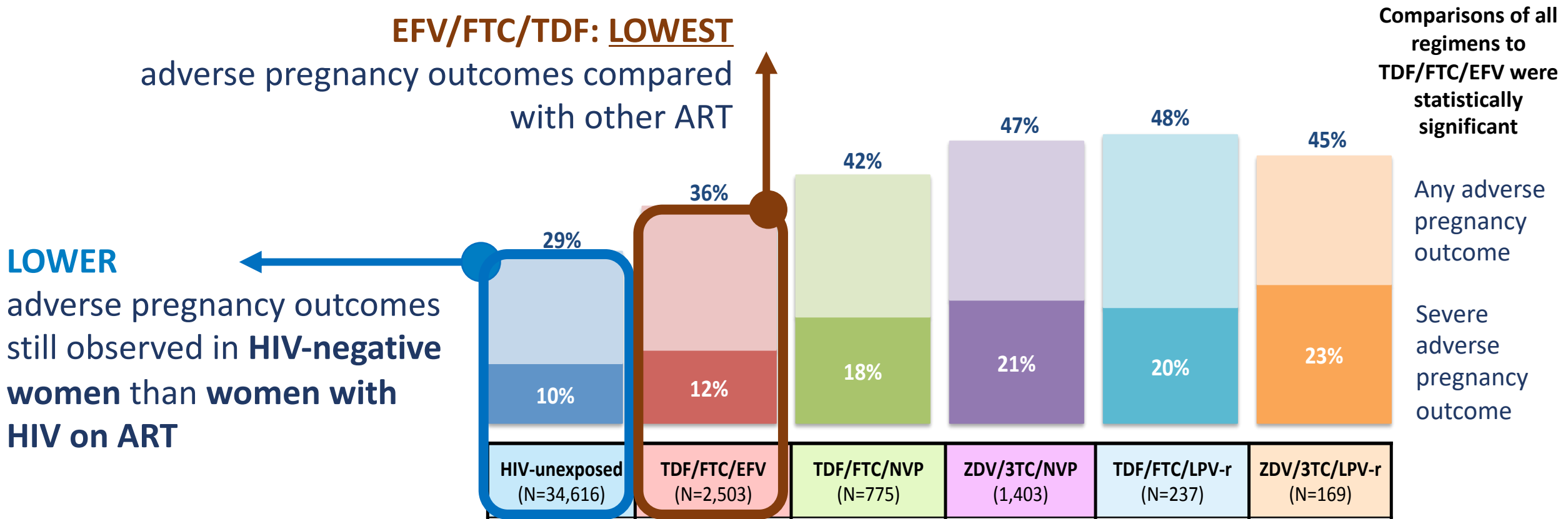
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Fowler NEJM 2016



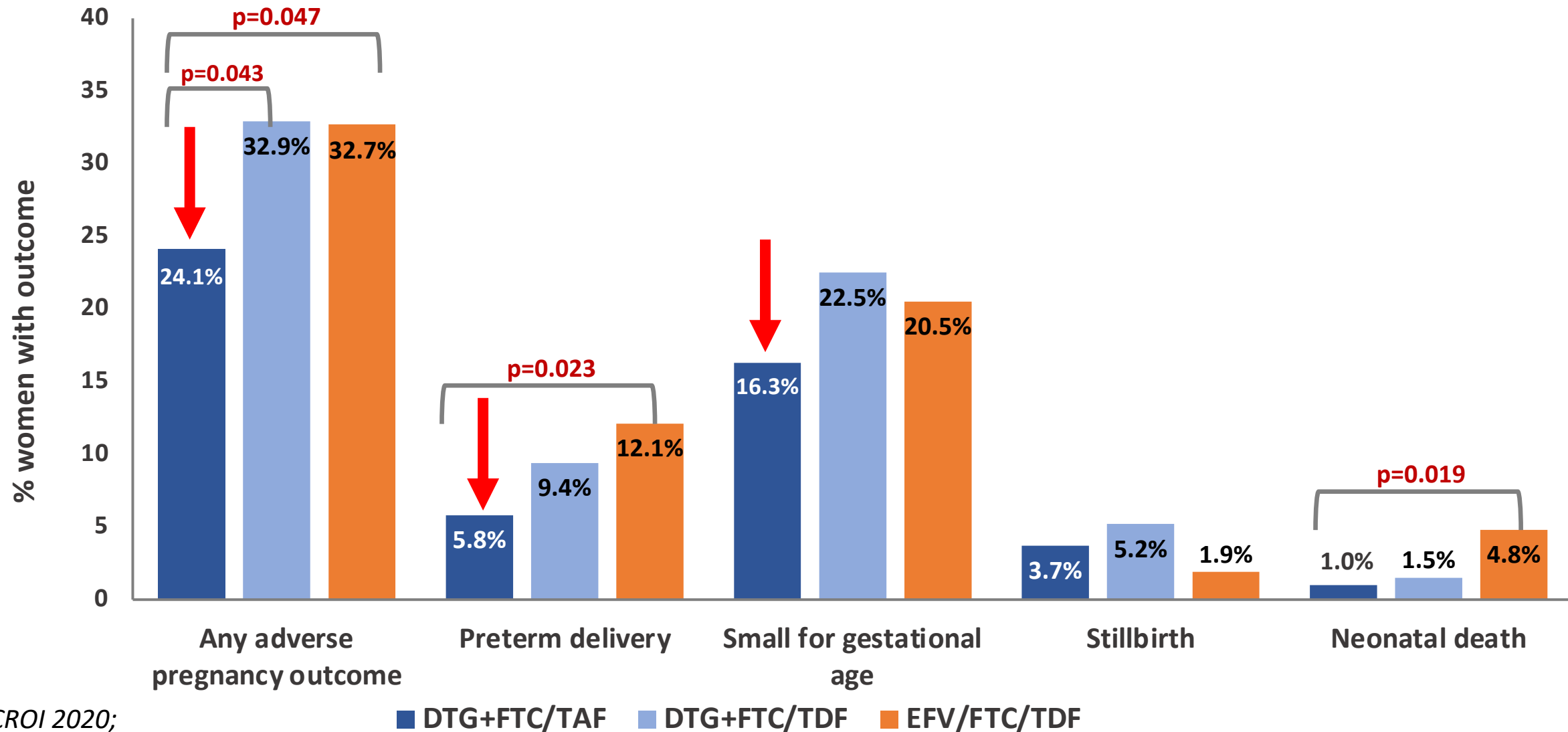
# Rates of adverse pregnancy outcomes differ by maternal ART regimen

## BOTSWANA TSEPAMO SURVEILLANCE STUDY



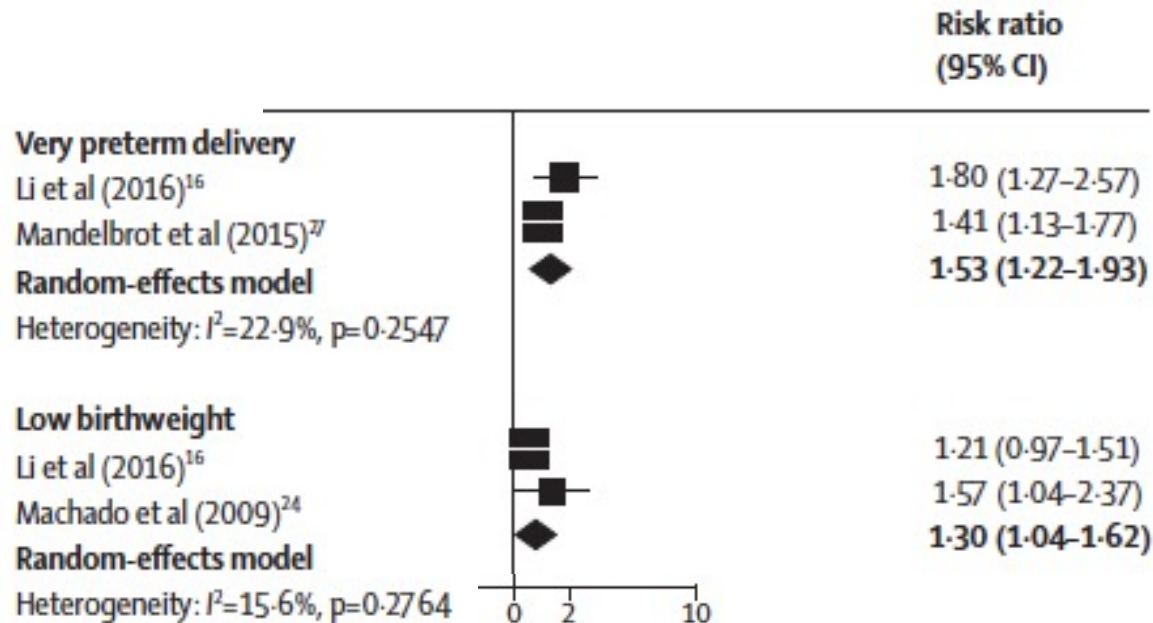
# Pregnancy outcomes also differ between more contemporary maternal ART regimens

VESTED TRIAL (IMPAACT 2010)



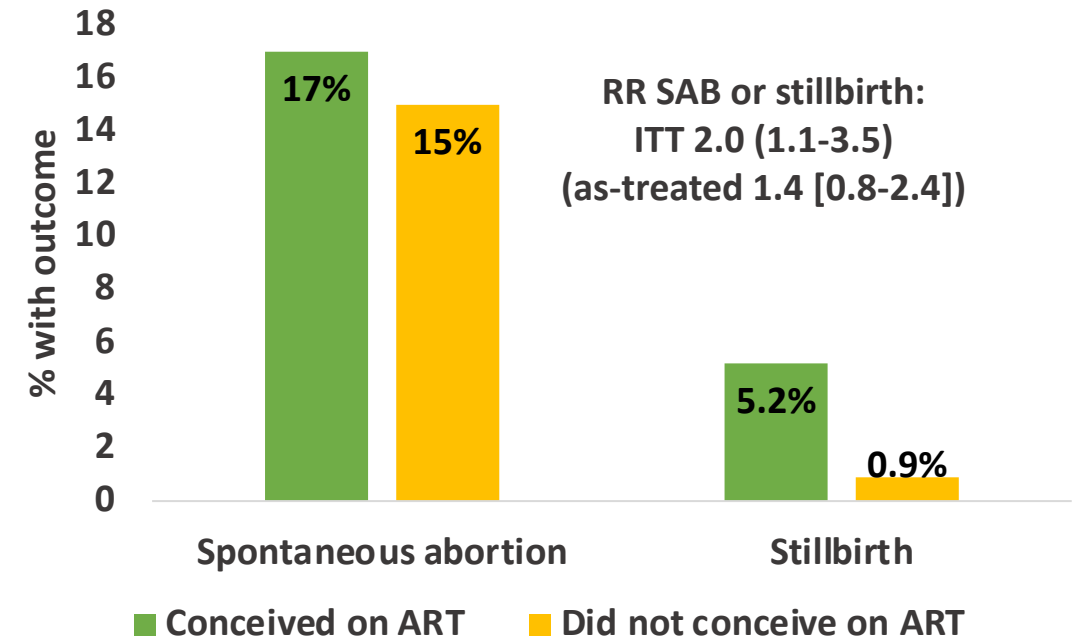
# Conception on ART and pregnancy outcomes

## Meta-analysis: ART start pre-conception vs. in pregnancy



Uthman Lancet HIV 2017

## PROMISE (IMPAACT P1077), 2<sup>nd</sup> Pregnancy



Hoffman CID 2019

- Conceiving on some regimens *may (?)* be associated with worse pregnancy outcomes
- Advantages of uninterrupted maternal ART outweigh possible risks**

# Key points, ART and pregnancy outcomes

## 1 **Pregnancy outcomes are worse in women with HIV, even on ART**

But better outcomes on ART than untreated HIV

## 2 **Pregnancy outcomes differ significantly by ART regimen**

## 3 **Common adverse pregnancy outcomes (preterm, small for gestational age) are major causes of child morbidity/mortality**

Gather and incorporate data for these outcomes in decisions

# Implications for care and service delivery

## **Need care services for:**

- Women with high-risk pregnancy and delivery
- Premature babies, SGA babies

# HIV treatment in pregnancy and...

Vertical transmission

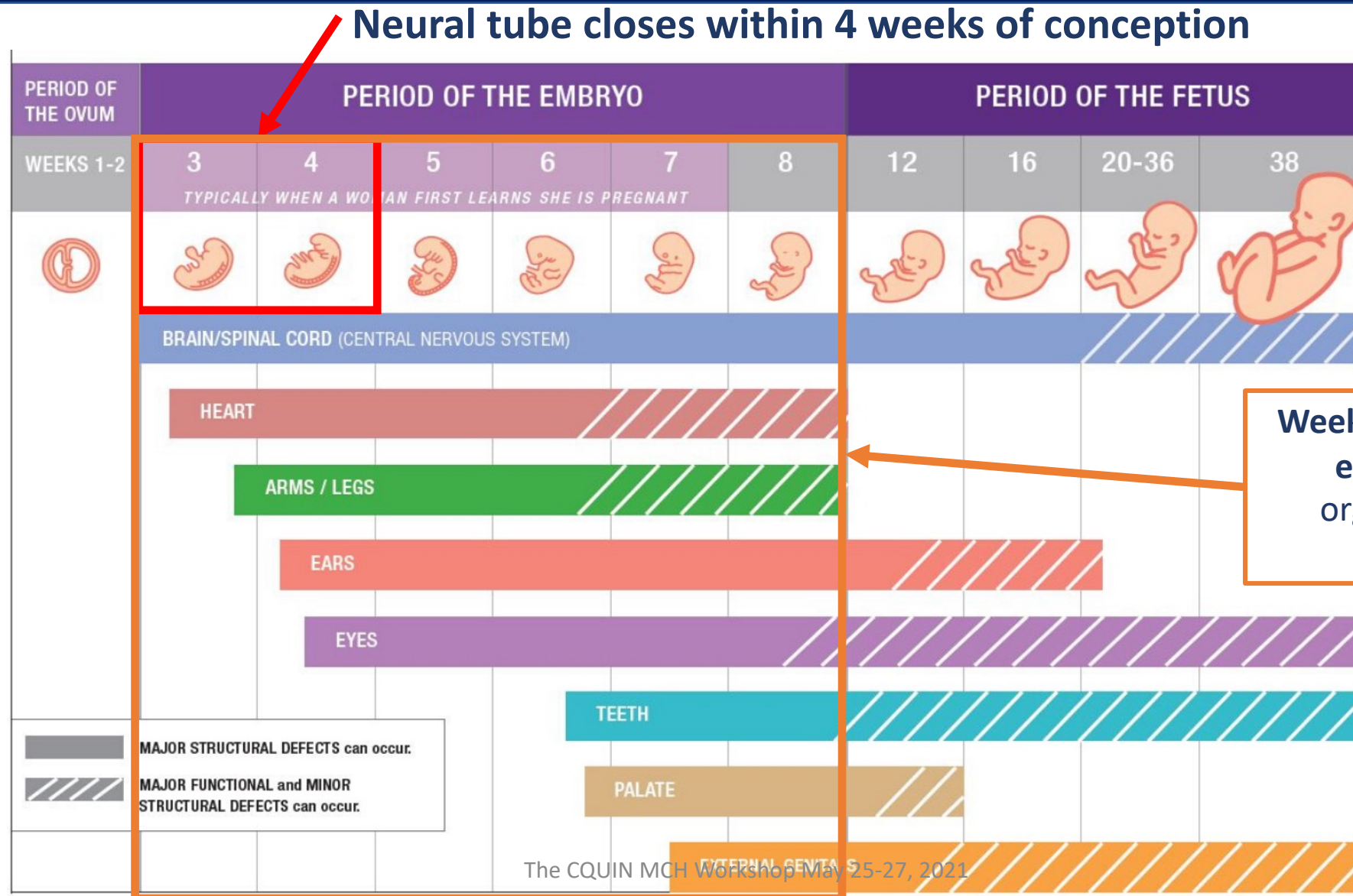
Pregnancy outcomes

**Congenital anomalies**

Mother's health outcomes

Child outcomes

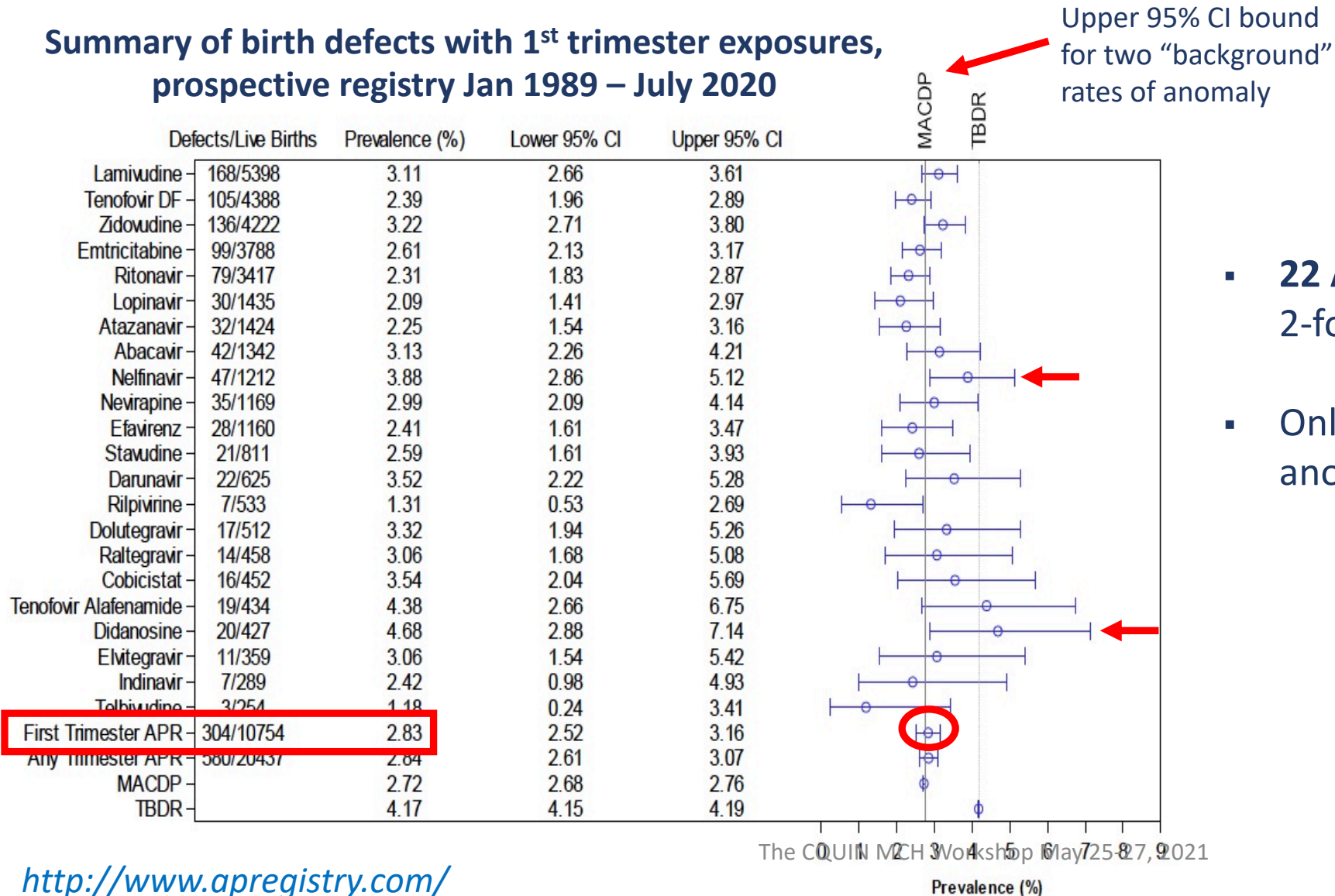
# Critical and sensitive periods in human development





# US antiretroviral pregnancy registry: congenital anomalies with 1<sup>st</sup> trimester exposure

## Summary of birth defects with 1<sup>st</sup> trimester exposures, prospective registry Jan 1989 – July 2020



- **22 ARVs** have enough data to detect a 2-fold increase in anomalies
- Only **ddI** and **nelfinavir** have elevated anomaly prevalence (no pattern)



# Preconception DTG and neural tube defects

Studies with greater than 50 pre-conception DTG exposures	# NTD / # Exposures, % prevalence
Tsepamo Botswana (AIDS 2020 Conf.)	7 / 3,591 ( <b>0.19%</b> )
Brazil retrospective cohort (Lancet HIV 2021)	2 / ~1,084 ( <b>0.18%</b> )
APR July 2020	1/479 ( <b>0.21%</b> )
CDC/MoH Botswana (NEJM 2019)	1 / 152 ( <b>0.66%</b> )
European DOLOMITE/EPPICC (Pre-CROI workshop 2020)	0 / 280* ( <b>0%</b> )
<b>At least 9 other studies, each with fewer than 100 women</b>	
<b>NTD prevalence in general population: 0.06% - 0.1%</b> (depending on folate fortification)	

*\*One pregnancy termination of fetus with neuronal migration disorder and severe microcephaly*

# Key points, congenital anomalies

- 1 True teratogens are very rare
- 2 Need prospective surveillance with large denominators to evaluate for rare events (particularly with preconception exposures)
- 3 Provide relevant pregnancy data to women to support their informed decisions

Kigali communique, July 2018:  
“... blanket exclusions that deny women equitable access to this optimal HIV treatment are not warranted or justified”



# HIV treatment in pregnancy and...

Vertical transmission

Pregnancy outcomes

**Mother's health**

Child outcomes



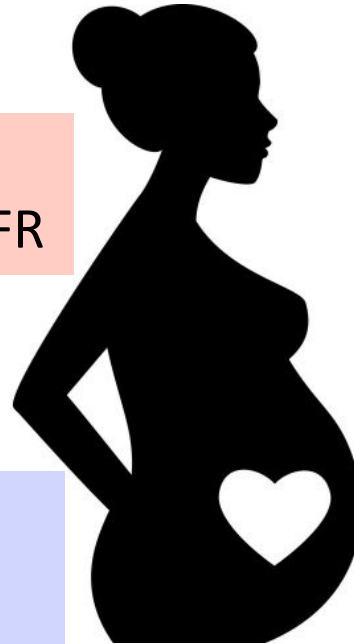
# Physiological changes in pregnancy can alter drug pharmacokinetics (PK)

## Elimination

- ✧ Higher cardiac output
- ✧ Increased renal blood flow/GFR

## Metabolism

Activity of drug-metabolizing enzymes (mostly increase)



## Absorption

- ✧ Nausea/vomiting
- ✧ Prolonged gastric transit time ↑
- ✧ Higher intestinal pH

## Distribution

- ✧ Higher blood volume (hemodilution)
- ✧ Decreased serum albumin ( free drug)
- ✧ More body fat
- ✧ Different transporter expression

- ✧ **Drug levels often (but not always) lower in late pregnancy (efficacy)**
- ✧ **Placental and breast milk transfer varies by drug**

# Summary: pregnancy pharmacokinetics for current ARVs

- **Good news!** despite lower pregnancy levels with most HIV drugs, usually sufficient to maintain efficacy
- **BUT** must evaluate pregnancy PK, because occasionally levels inadequate (e.g. cobicistat)

NRTIs		NNRTIs		INSTIs		Entry inhibitors	
Abacavir	↔	Doravirine	?	Bictegravir	?	Fostemsavir	?
Emtricitabine / lamivudine	↘	Efavirenz	→	Dolutegravir	↘	Ibalizumab	?
Tenofovir AF	↔	Etravirine	→	Elviteg./cobi	↓↓	Maraviroc	↓
Tenofovir DF	↘	Nevirapine	→	Raltegravir	↓	Long-acting agents	
Zidovudine	↔	PIs		Boosters		CAB LA	?
		Atazanavir/r	↓	Cobicistat	↓↓	Rilpivirine LA	?
		Darunavir/r	↓	Ritonavir	↓	Islatravir	?
		Lopinavir/r	↓				

# ART in pregnancy and maternal health outcomes

**Previously: maternal HIV drug resistance** with short-course (1-2-drug) ARV

**Rarely: virologic failure** on ART due to lower plasma drug levels in pregnancy (e.g. cobicistat-boosted regimens)

**Infrequently: adverse effects** may differ in pregnancy/postpartum

- **Weight gain** (DTG, TAF)
- **Hypertensive disorders of pregnancy** (NVP, *Zash 2018*; DTG at conception, *Zash CROI 2021 Abstract 1302*; ART initiation in pregnancy, *Chadwick CROI 2021 Abstract 575*; PIs and pre-eclampsia *Conner CROI 2021 Abstract 578*)
- **Gestational diabetes** (*lower* with DTG- vs. EFV-ART) (*Mmasa, HIV Medicine 2021*)
- **Gastrointestinal intolerance** (LPV/r) *Cohan 2015*
- **Hepatitis** (NVP) *Renet J Ob/Gyn Canada 2013*
- **? Postpartum suicidal ideation** (EFV) *Jones AIDS Behav 2020*

# HIV treatment in pregnancy and...

Vertical transmission

Pregnancy outcomes

**Mother's health outcomes**

**Weight**



```
graph LR; Weight --> LowWeight[Low maternal weight → low birthweight, small for gestational age, preterm]; Weight --> HighWeight[High maternal weight → macrosomia, Cesarean delivery, hypertension, diabetes];
```

**Low maternal weight →**  
low birthweight, small for  
gestational age, preterm

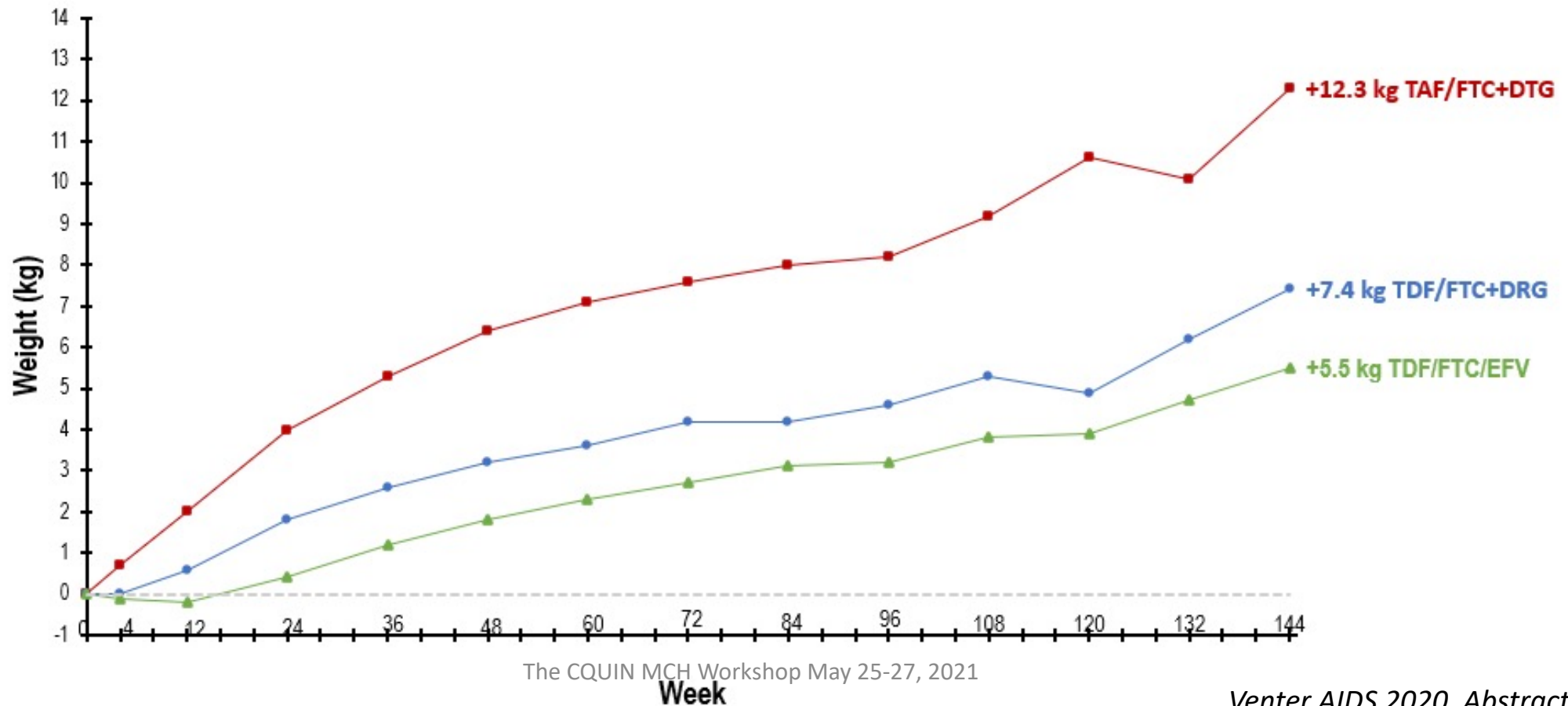
Child outcomes

**High maternal weight →**  
macrosomia, Cesarean delivery,  
hypertension, diabetes

# ART and weight gain in non-pregnant adults

Integrase inhibitors (including DTG), and TAF → excess weight gain, particularly in women

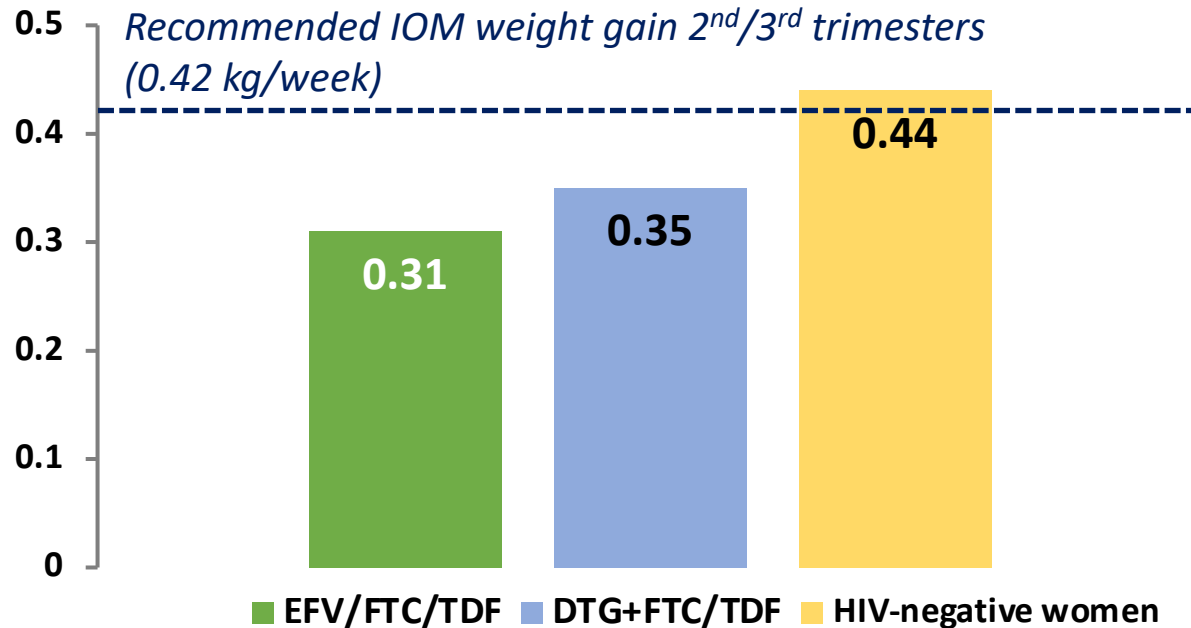
ADVANCE trial weight: women





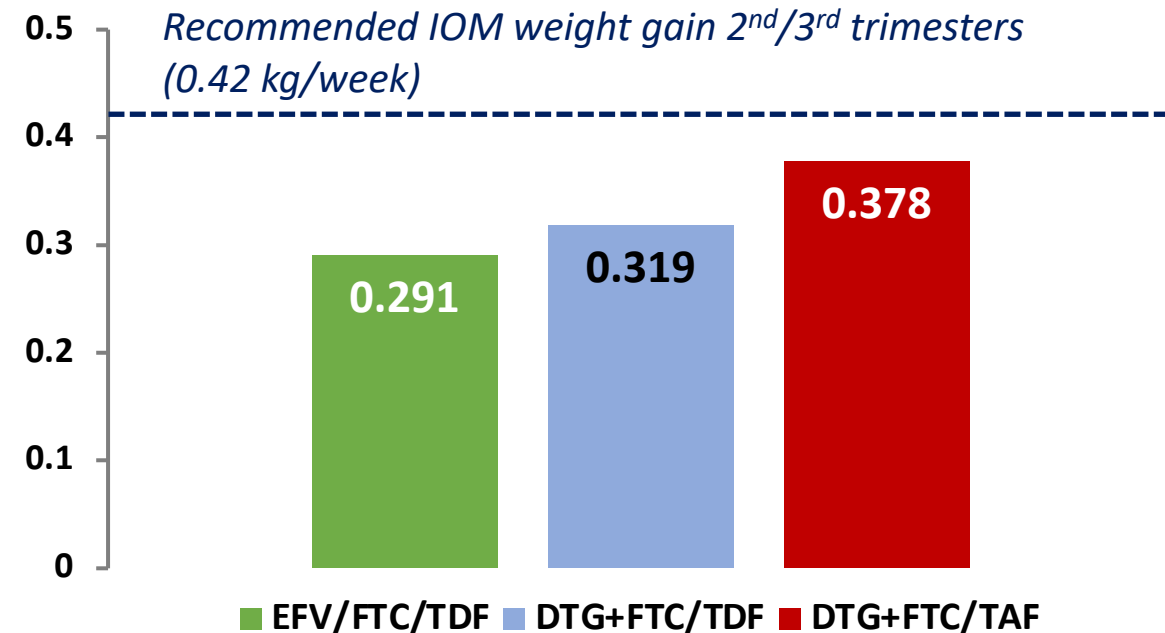
# Antepartum weight gain differs by ART regimen started in pregnancy

**Botswana Tsepamo, Observational:**  
*ART initiated 1-17 weeks gestation*



Caniglia, eClin Med, 2020

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



Chinula CROI 2020 130LB

All between-group comparisons statistically significant  
except EFV vs DTG+FTC/TDF arms, IMPAACT 2010

**In both studies: lower-than-recommended weight gain occurred more frequently in women starting EFV/FTC/TDF**

# Weight in pregnancy and adverse outcomes, CROI 2021

## VESTED (IMPAACT 2010)

*CROI Hoffman #176*

DTG vs EFV, TAF vs TDF  
started in pregnancy (RCT)

- Low weight gain pregnancy: **higher** risk adverse pregnancy outcomes
- Weight gain → lower risk

## TSEPAMO

*CROI Zash #571*

DTG- and EFV-ART pre-conception (observational)

- Low (<50kg) baseline pregnancy weight : **severe adverse** pregnancy outcomes
- High (>90kg) baseline pregnancy weight: macrosomia, maternal hypertension

## ADVANCE

*CROI Baxevanidi #572*

DTG vs EFV, TAF vs TDF  
preconception (projected)

- **Pre-pregnancy obesity** in women on DTG+F/TAF ≥144 weeks **predicted** to lead to **more pregnancy complications** seen with obesity

# Key points for ART in pregnancy and weight change

- 1 Pregnancy weight gain differs by ART regimen**
- 2 Lower-than-recommended and higher-than-recommended pre-pregnancy weight (and pregnancy weight gain) can adversely affect different pregnancy outcomes**

Greater pregnancy weight gain may be protective in some women
- 3 Unknown: implications over longer term, with subsequent pregnancies, and in different populations**

# HIV treatment in pregnancy and...

Vertical transmission

Pregnancy outcomes and neonatal death

Mother's health outcomes

**Child outcomes**

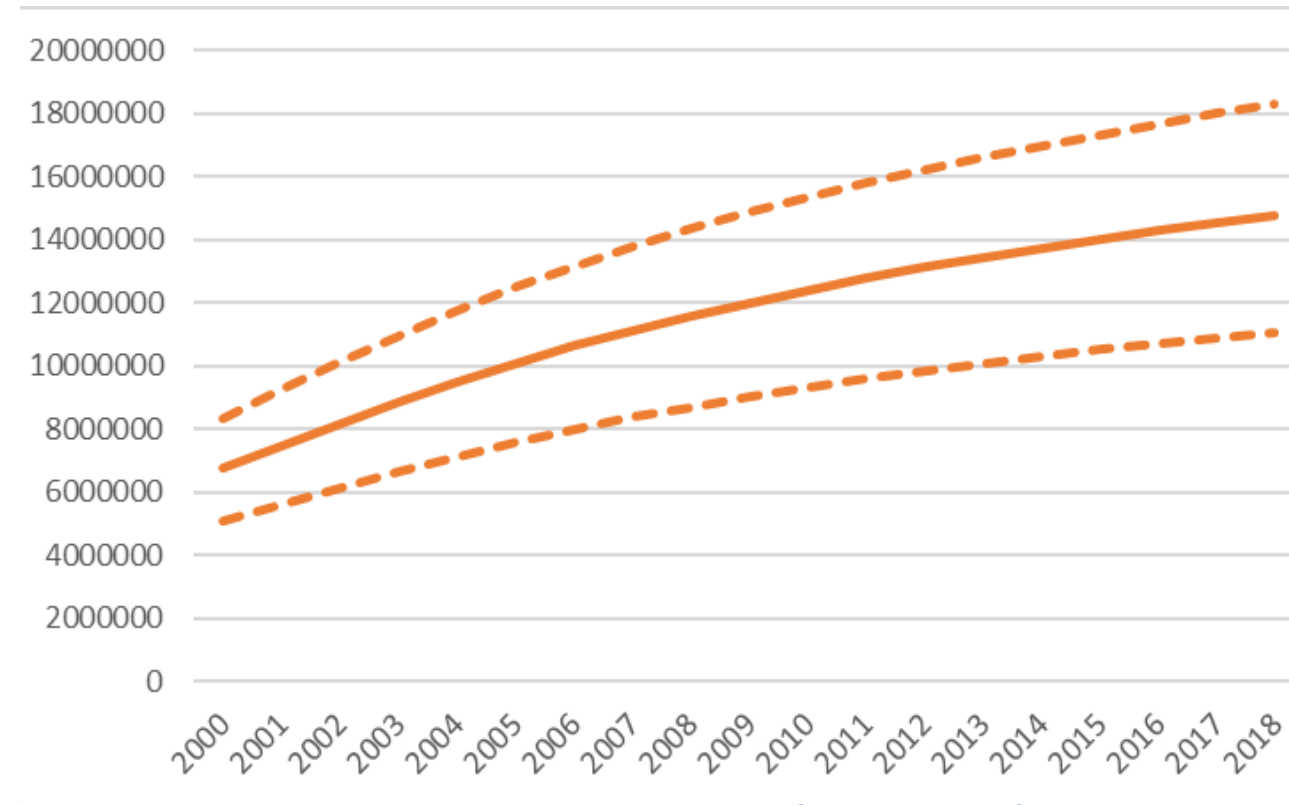


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# HIV-exposed, uninfected (HEU) children

- 15 million HEU children
- HEU children have higher morbidity & mortality in LMIC
- Outcomes improved by breastfeeding (where recommended) and by ART in pregnancy *Arikawa CID 2018*
- Important to understand long-term impacts of HIV- and ARV-exposure

Number of children HIV exposed and uninfected globally, 2000-2018



Source: UNAIDS 2019 estimates

# ART in pregnancy and child growth and neurodevelopment



**Service delivery implications: early intervention identification and treatment of developmental delay**



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# Outline

Why are pregnant women a critical group of persons with HIV and not a niche population?

What we know about antiretroviral regimens in pregnancy and

- Vertical transmission

- Pregnancy outcomes

- Mother's health outcomes

- Child outcomes

**Current pregnancy antiretroviral recommendations and evidence gaps**



# WHO guidelines: antiretrovirals during pregnancy

	First-line	Second-line
Preferred	DTG + FTC/TDF	AZT/3TC + ATV/r (or LPV/r)
Alternative	EFV 400 + FTC/TDF	AZT/3TC + DRV/r

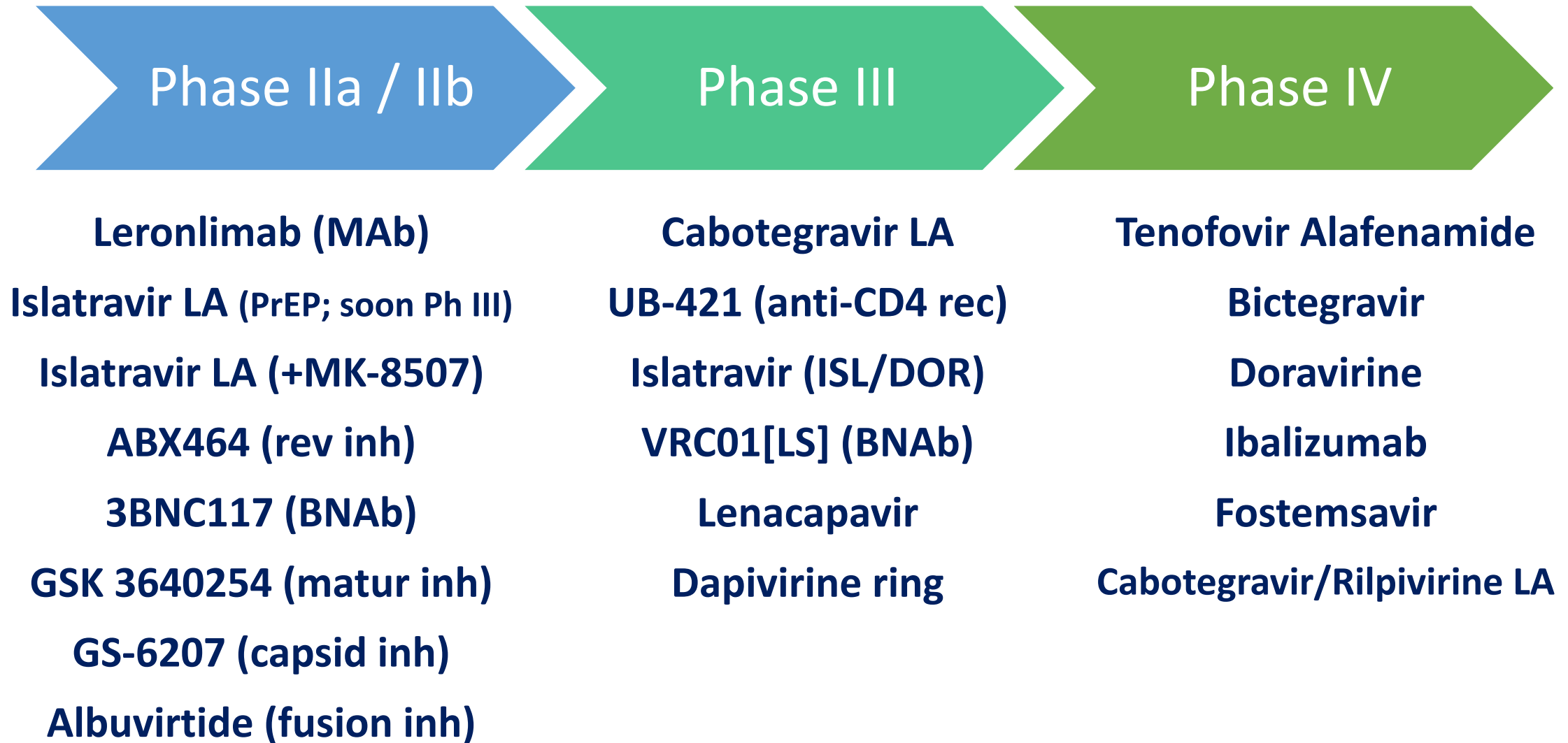
Including DTG in 1<sup>st</sup> trimester, with information-sharing



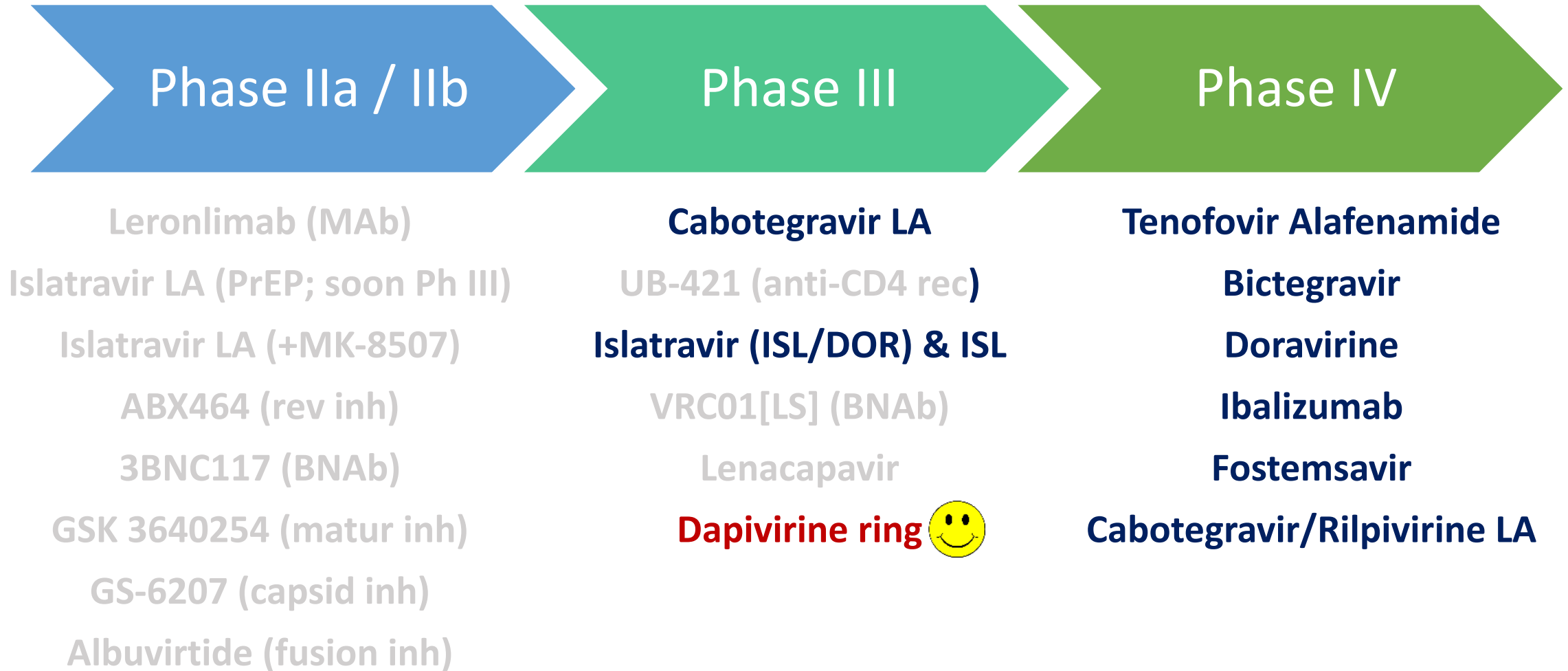
A woman-centered approach in which the woman  
“...receives full information about risks and benefits...and  
is **supported in making voluntary choices** around  
medical therapy ...”



# Newer HIV treatment/prevention agents, and current phase of study



# Newer HIV agents : plans for study in pregnancy?



- **Long-acting CAB, RIL, ISL:** if become pregnant in clinical trial can consent to stay on drug (PK, safety data)
- **DOR, BIC, TAF, LA CAB:** “opportunistic” studies in routine care (IMPAACT 2026, PANNA networks, others)
- **Dapivirine ring:** DELIVER randomized trials in pregnant (NCT03965923) and breastfeeding (NCT04140266) women

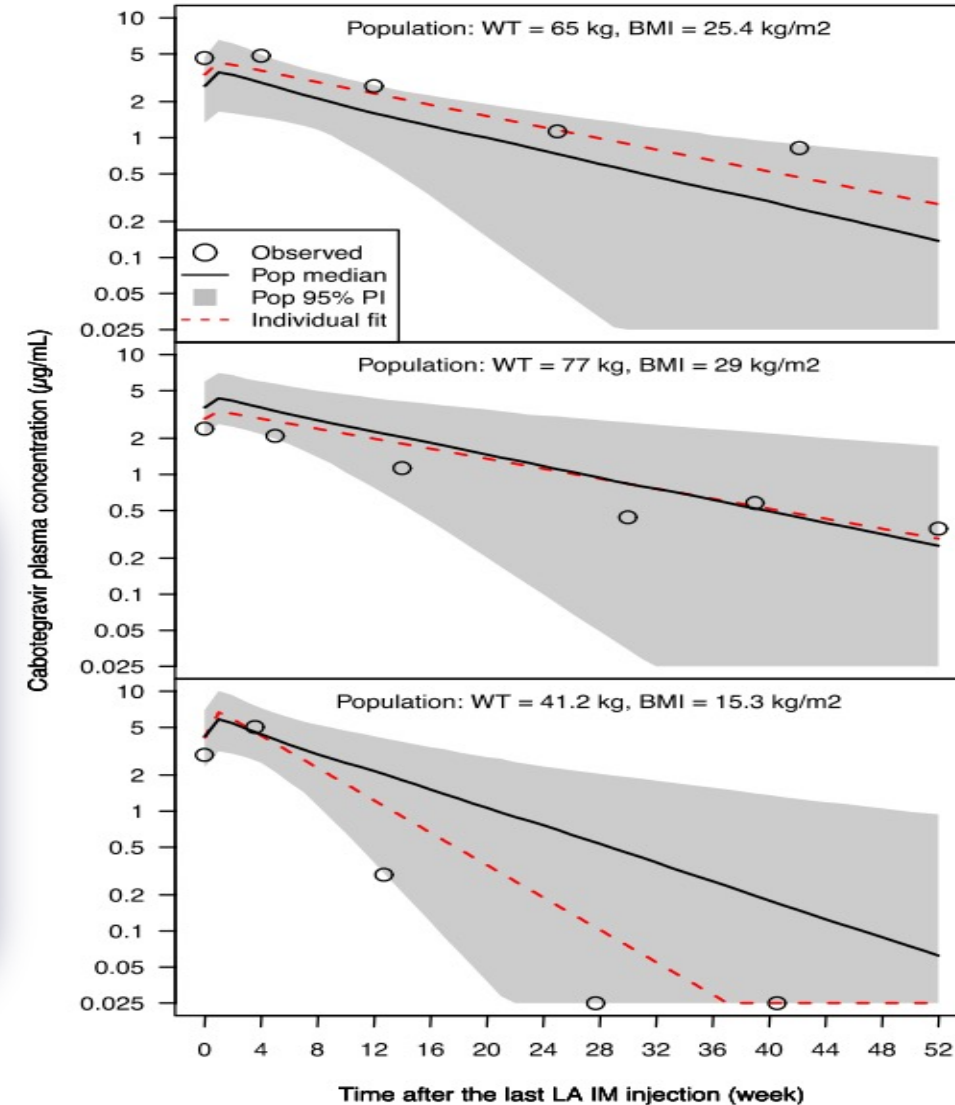
# Long-acting agents for HIV prevention and treatment

- Important drugs!
- Even if stop 1<sup>st</sup> TM, drug present through delivery
- Almost no human pregnancy/lactation data

## Cabotegravir in pregnancy :

- PK 3 women conceiving on CAB LA (stopped drug): rate of decline in expected range for non-pregnant (*Patel CROI 2020*)
- Low placental transfer of CAB *ex vivo* (*Pencole AIDS 2020*)

## CAB concentration after last injection in 3 women becoming pregnant on CAB LA



*Patel, CROI 2020 abstract 775*

# [Eventual] implications for care and service delivery

**Long-acting agents (for HIV prevention and treatment) may be particularly useful during periods of particular risk or adherence challenge**

- Need pharmacokinetic, safety data in pregnancy and lactation
- Consider and evaluate models of care for offering these drugs postpartum, during pregnancy





In conclusion



# Key points

**Optimizing care of pregnant women is central to our global approach to HIV treatment**

**We know how to prevent vertical transmission, BUT implementation gaps remain AND antiretroviral regimen can affect multiple pregnancy, maternal and child health outcomes**

Need to holistically consider all of these outcomes in our care

**Women deserve high-quality evidence for medications that they will use throughout their lifecourse, including during pregnancy and lactation**



## **Acknowledgements:**

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