HIV Treatment in Pregnancy

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IMPAACT Annual Meeting 2021

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Outline

1. **Pregnant women are of central importance in 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

→ Paradigm shift: consider *all* of these outcomes, and protect pregnant women *through* research

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Pregnant women are central to our global approach to HIV treatment

- **51% of persons living with HIV globally are women[1]**
- **~1.3 million women with HIV are pregnant each year[1]**
  - Most women with HIV will be pregnant at least once following diagnosis
- **Need pregnancy data to identify 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**

[1]*UNAIDS 2020*

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HIV treatment in pregnancy and…

Vertical transmission (VT)

Pregnancy outcomes

Mother's health outcomes

Child outcomes

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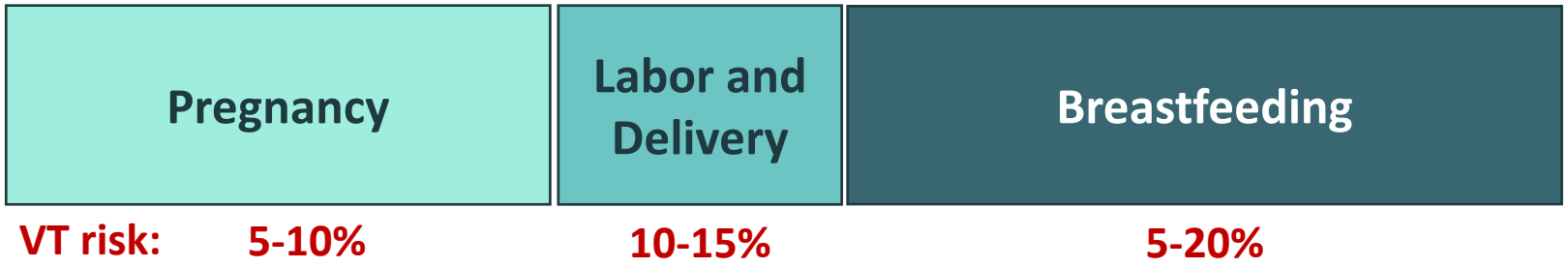
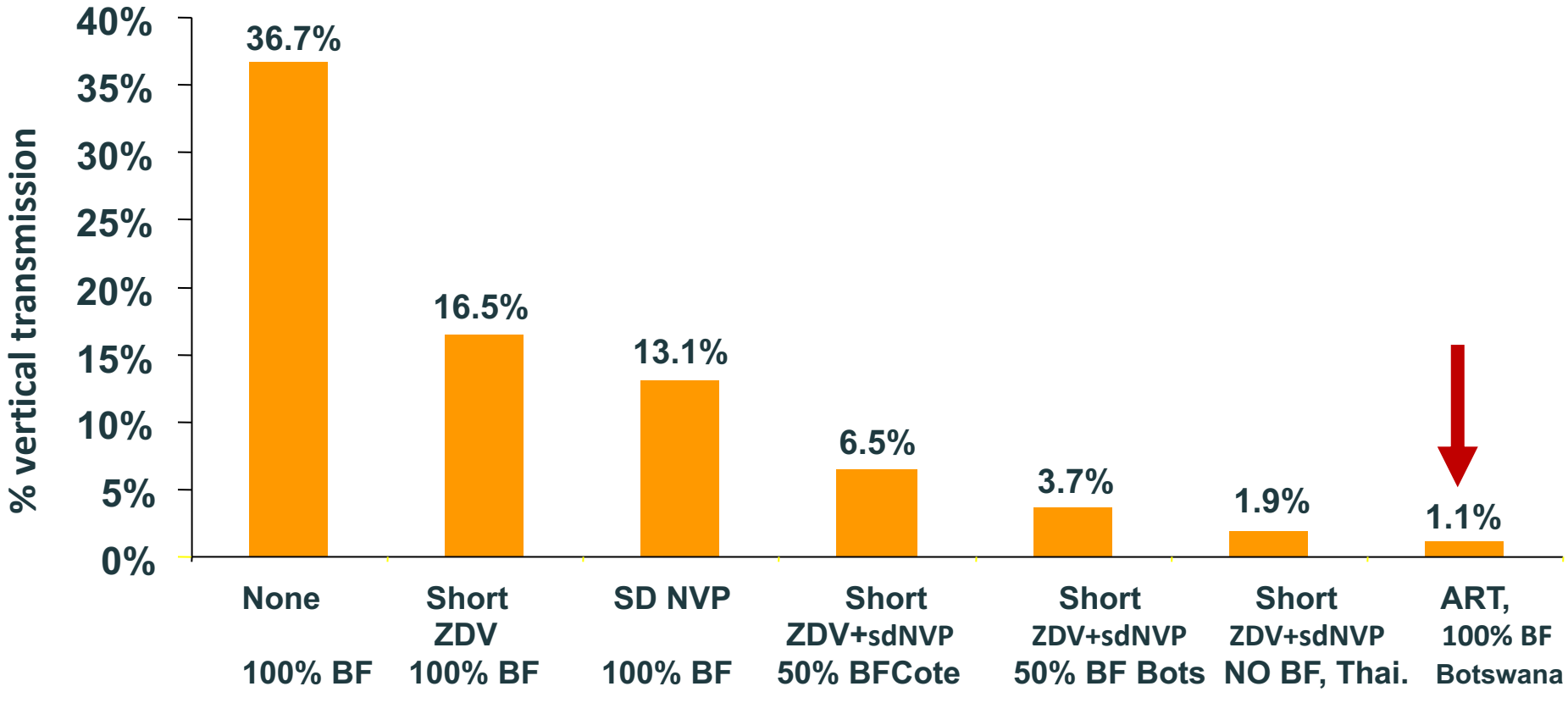
Maternal combination ART dramatically reduces VT

20%-45% risk of VT if no intervention





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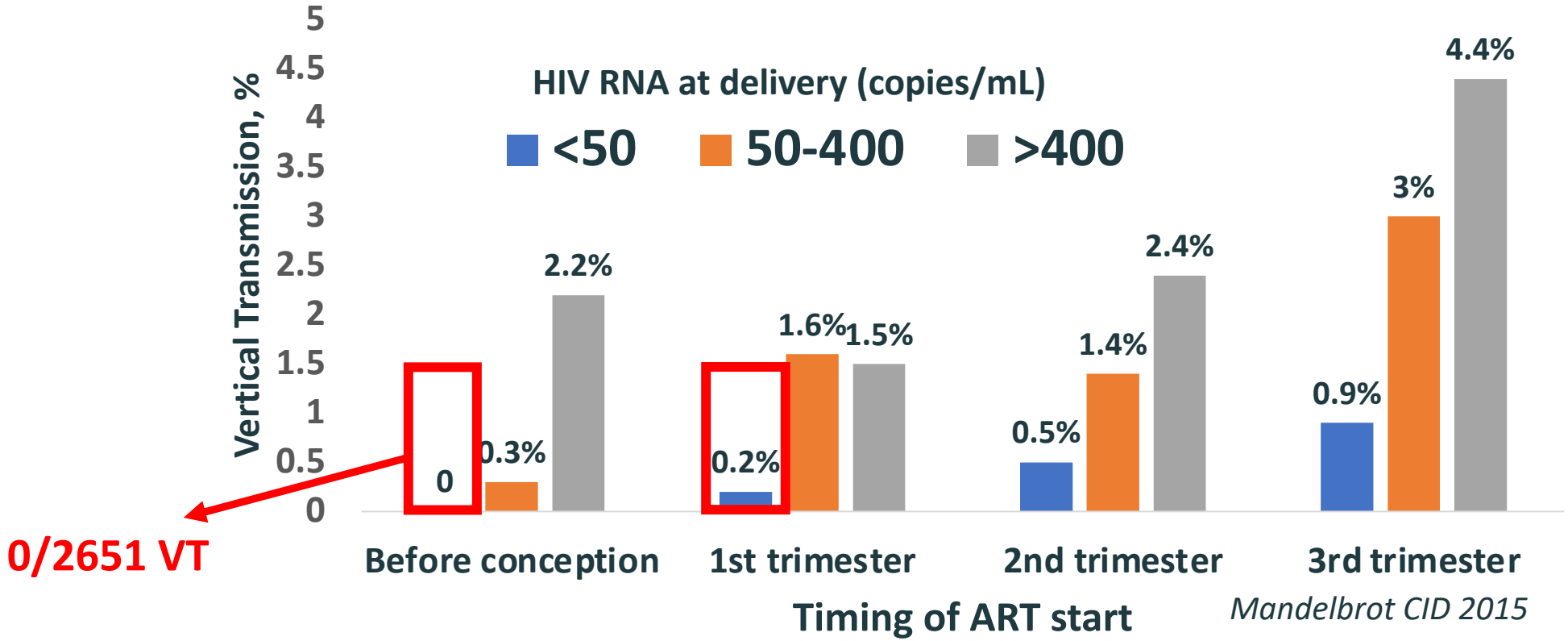
Transmission is very low with viral suppression on ART from early in pregnancy

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



Mandelbrot CID 2015

- 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

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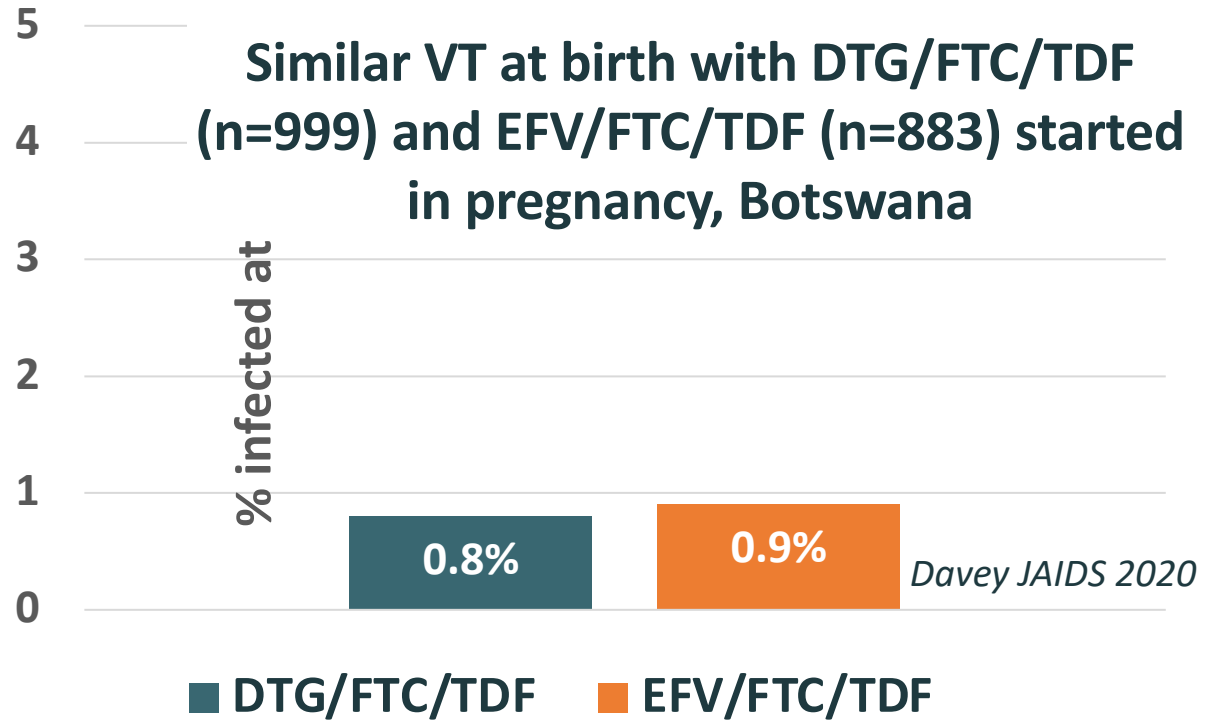
Does ART regimen affect vertical transmission?

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%)

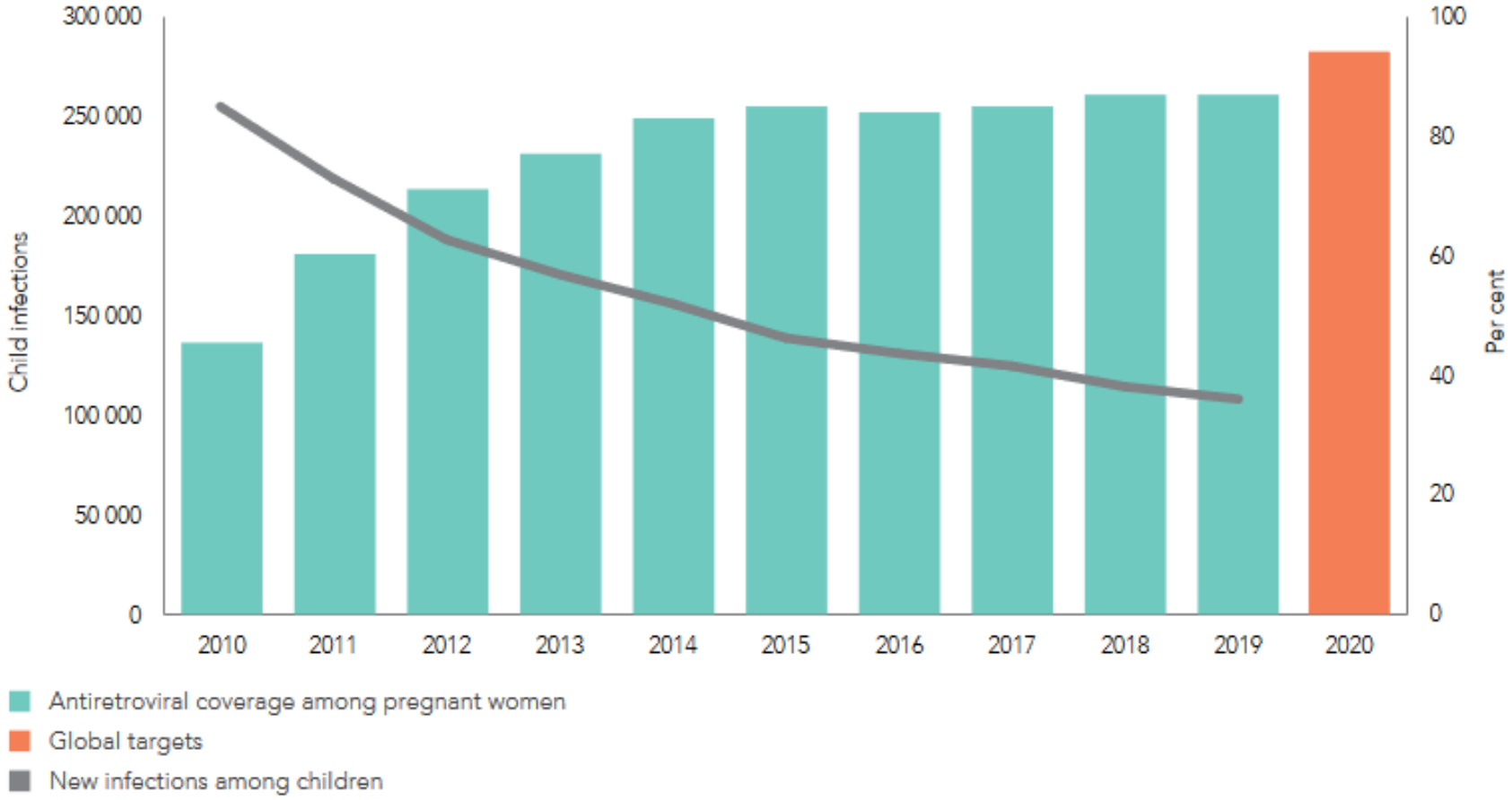
Asif AIDS 2020 Conference



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

UN Start Free, Stay Free UNAIDS 2020

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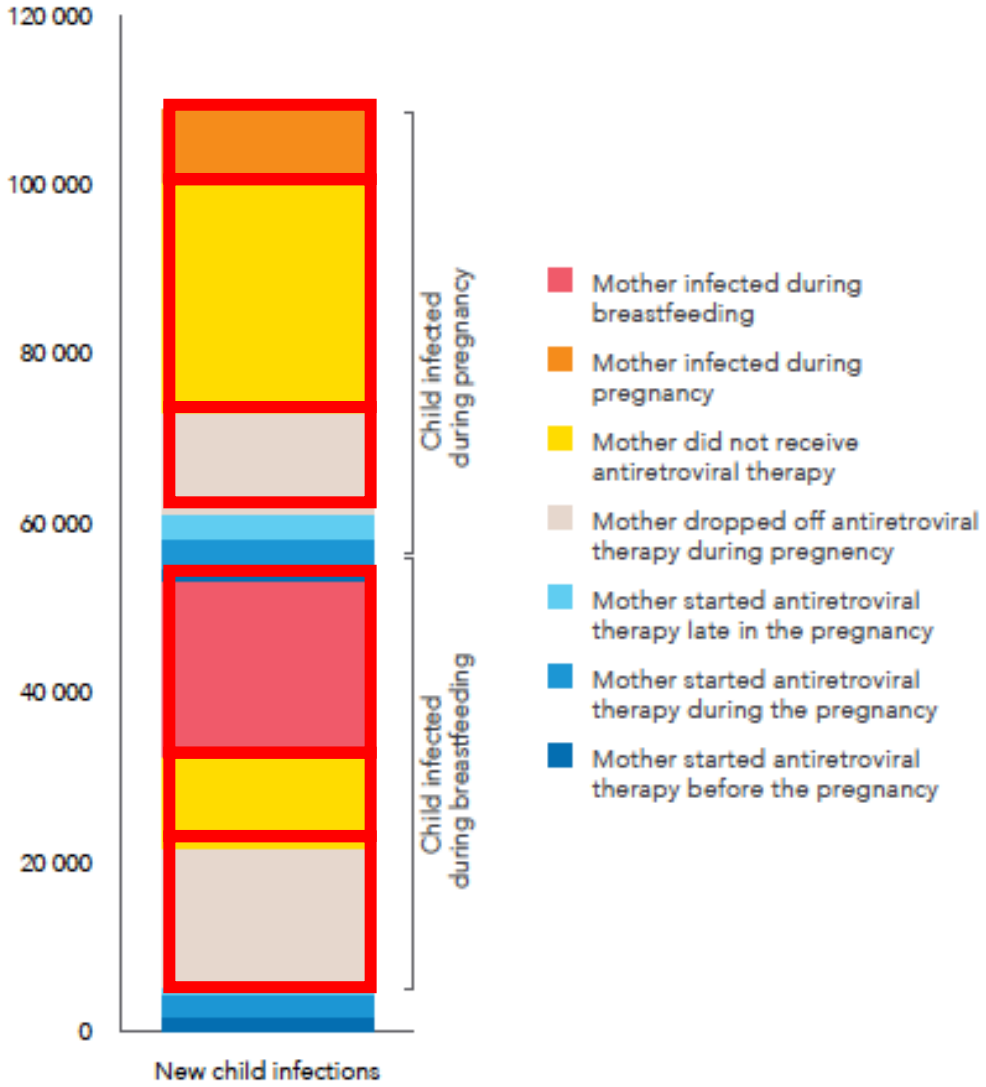
Primary reasons for new HIV infections in children, 2019



Focus countries 2019, UNAIDS 2020

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**

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HIV treatment in pregnancy and…

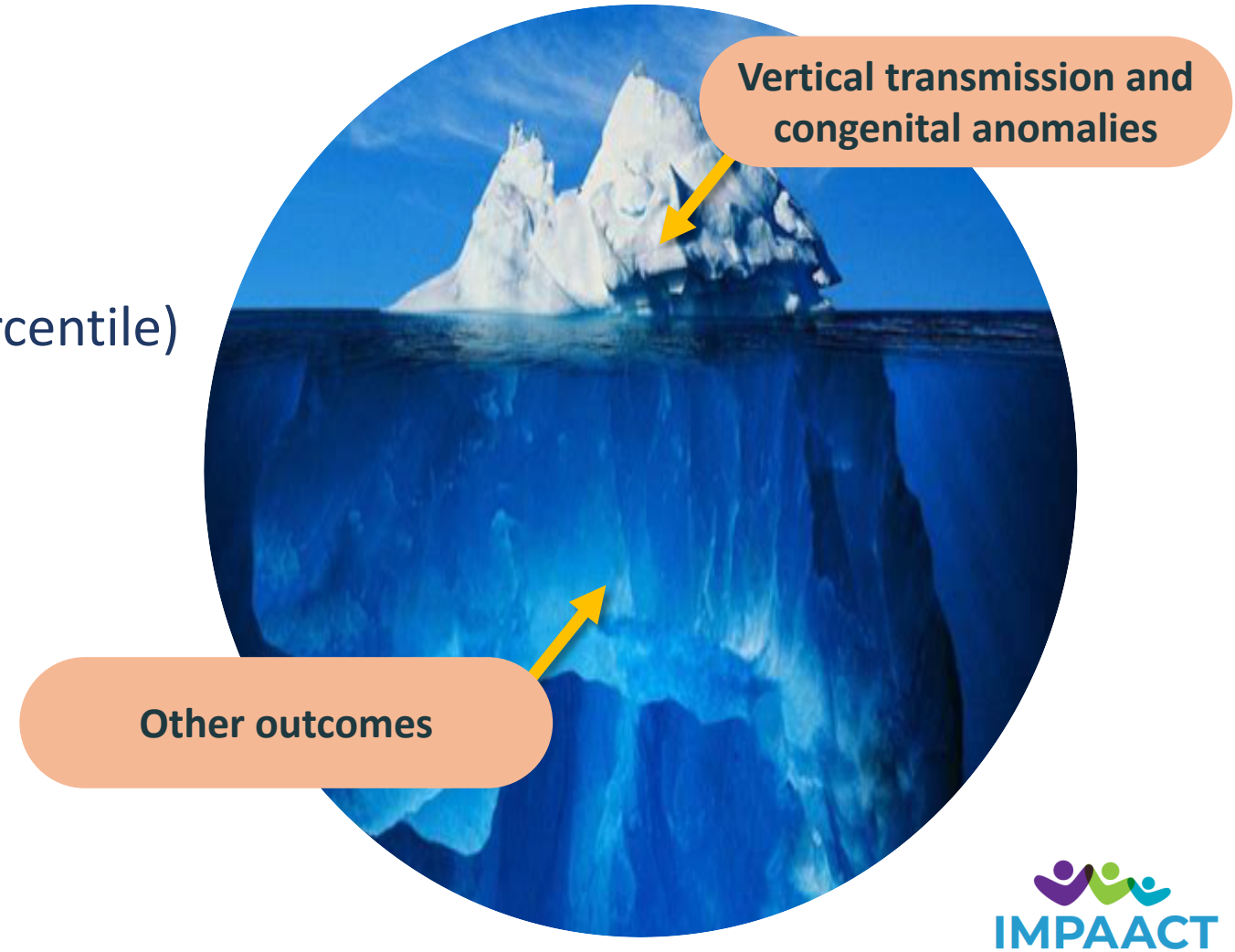
Vertical transmission

Pregnancy outcomes

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

Mother's health outcomes

Child outcomes



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Why are preterm birth and low birthweight so 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**

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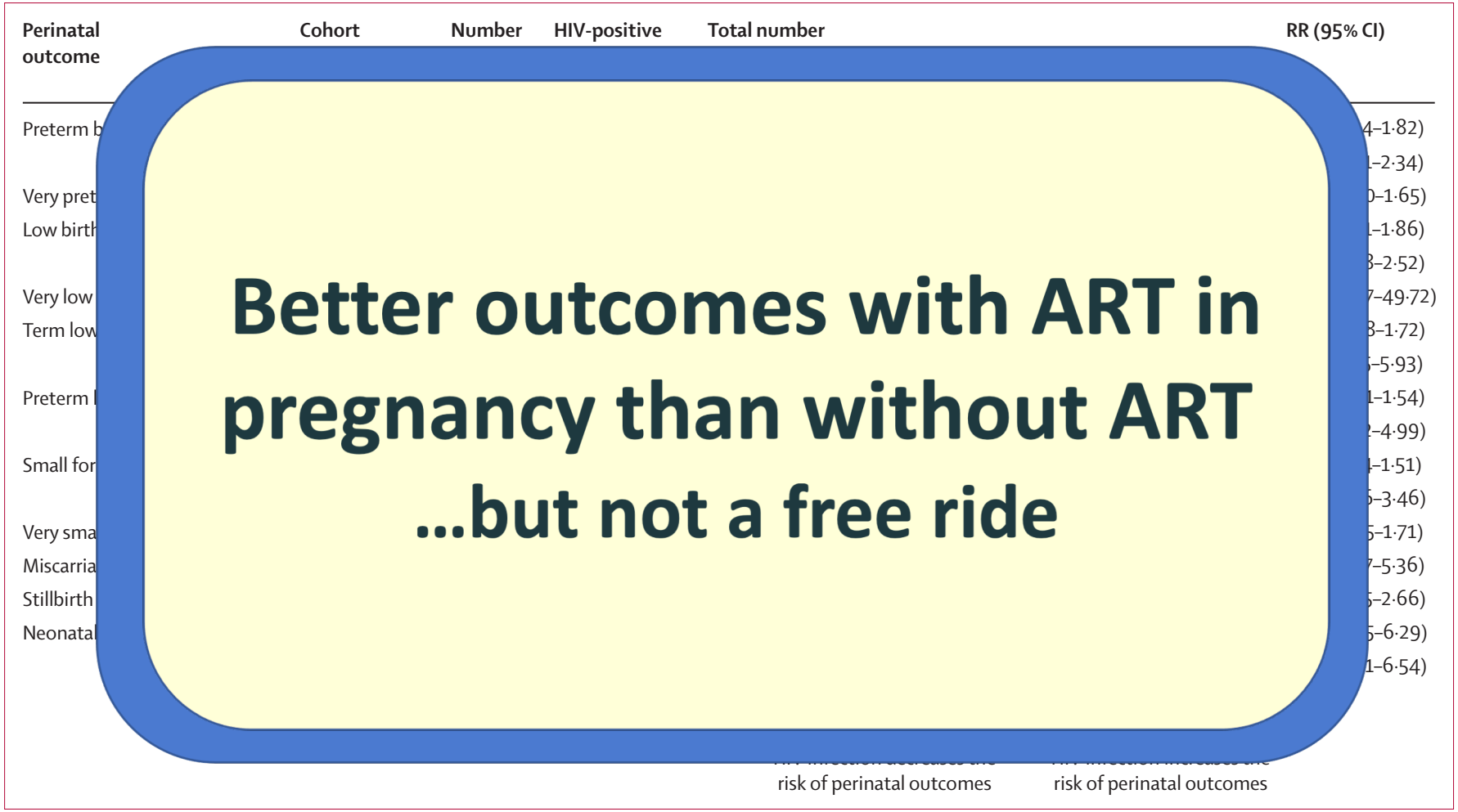
Pre-ART era: women with HIV had much higher rates of adverse pregnancy outcomes than women without HIV



Adverse Birth Outcomes, Antiretroviral Naïve Women 1980-2014

Wedi et. al., Lancet Infect Dis, 2016

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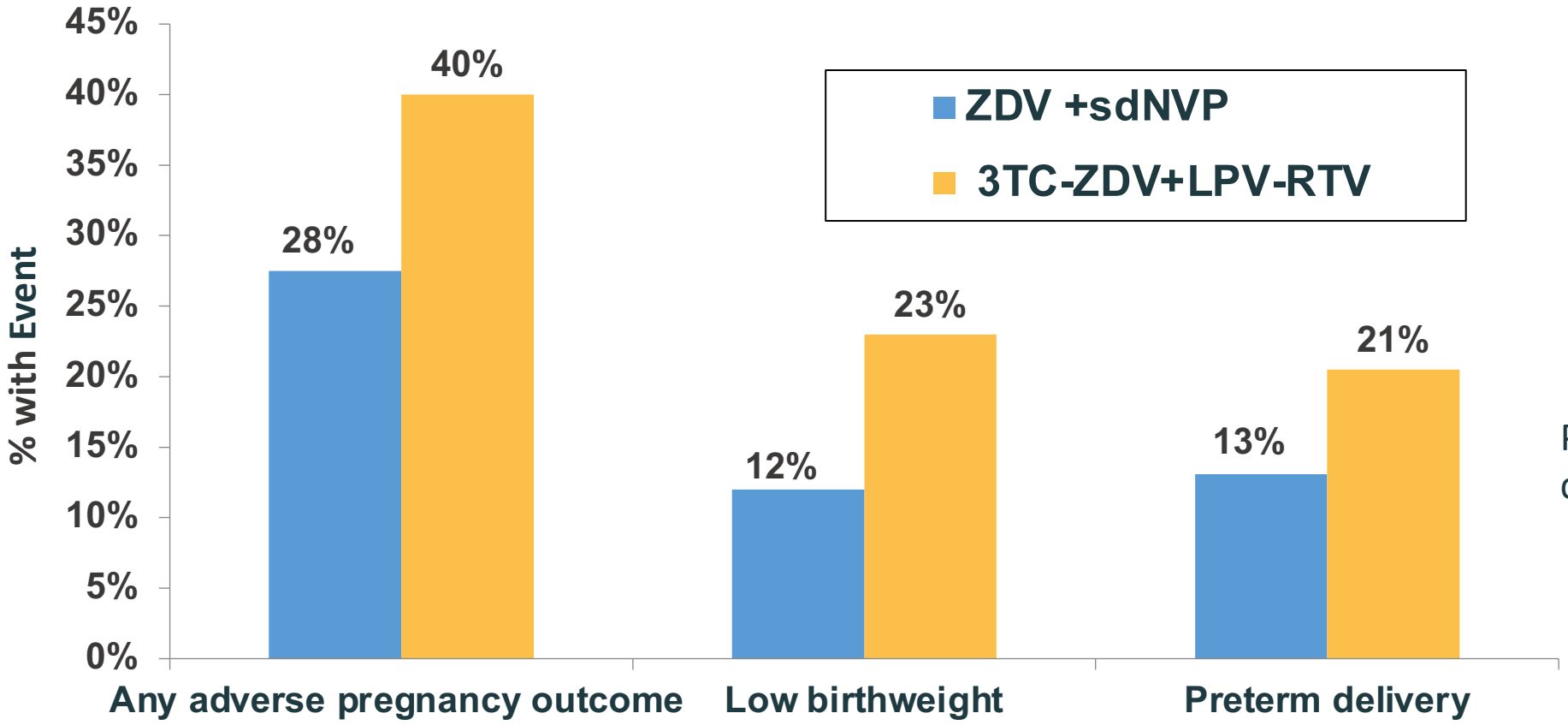
Worse pregnancy outcomes with 3-drug ART than with ZDV

PROMISE TRIAL (IMPAACT P1077)



P < 0.001 for each comparison

Women enrolled with CD4 ≥350 cells/mm^3 and no AIDS illness

Fowler NEJM 2016

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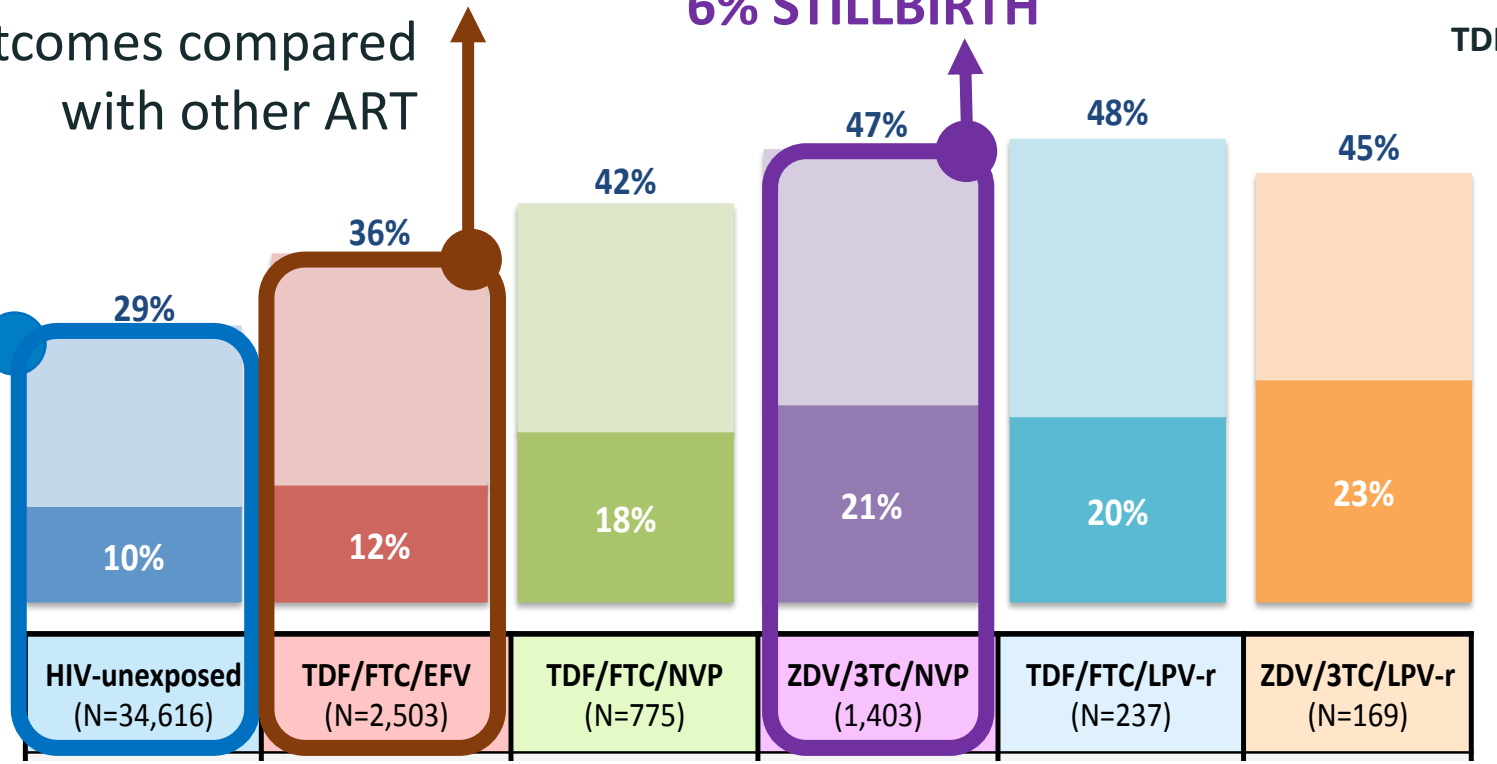
Rates of adverse pregnancy outcomes differ by maternal ART regimen

BOTSWANA TSEPAMO SURVEILLANCE STUDY

EFV/FTC/TDF: LOWEST
adverse pregnancy outcomes compared with other ART

LOWER
adverse pregnancy outcomes still observed in **HIV-negative women** than **women with HIV on ART**



Comparisons of all regimens to TDF/FTC/EFV were statistically significant

Any adverse pregnancy outcome

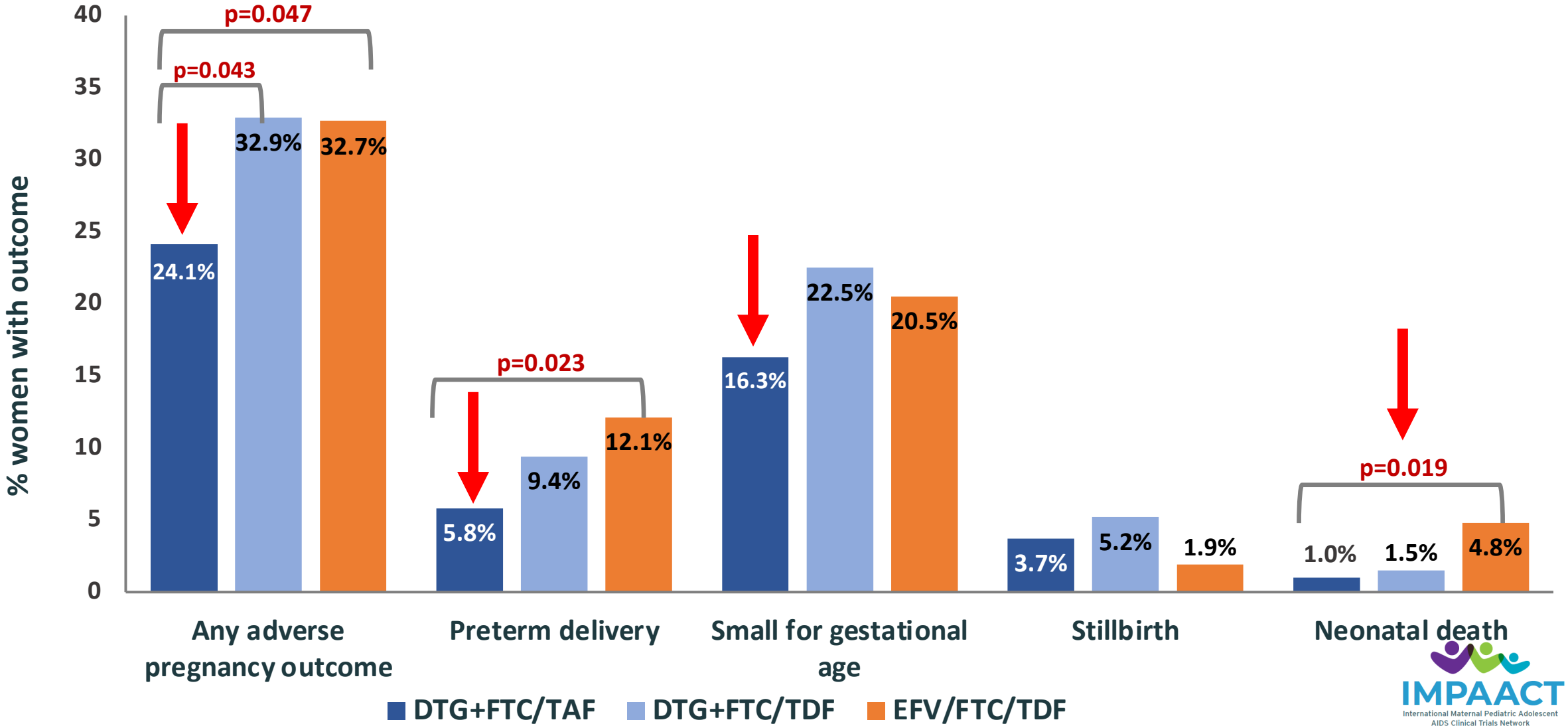
Severe adverse pregnancy outcome

Zash JAMA Pediatrics 2017; slide adapted from Zash

Adjusted for age, education, and gravida

What about pregnancy outcomes with more contemporary maternal ART regimens?

VESTED TRIAL (IMPAACT 2010)



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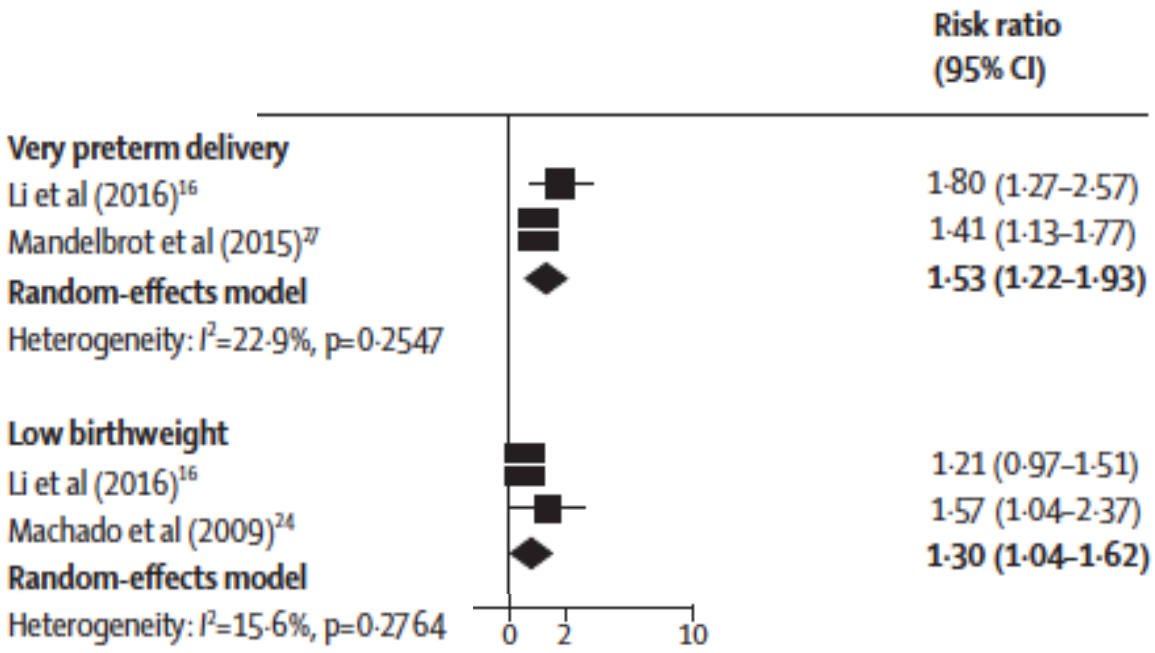
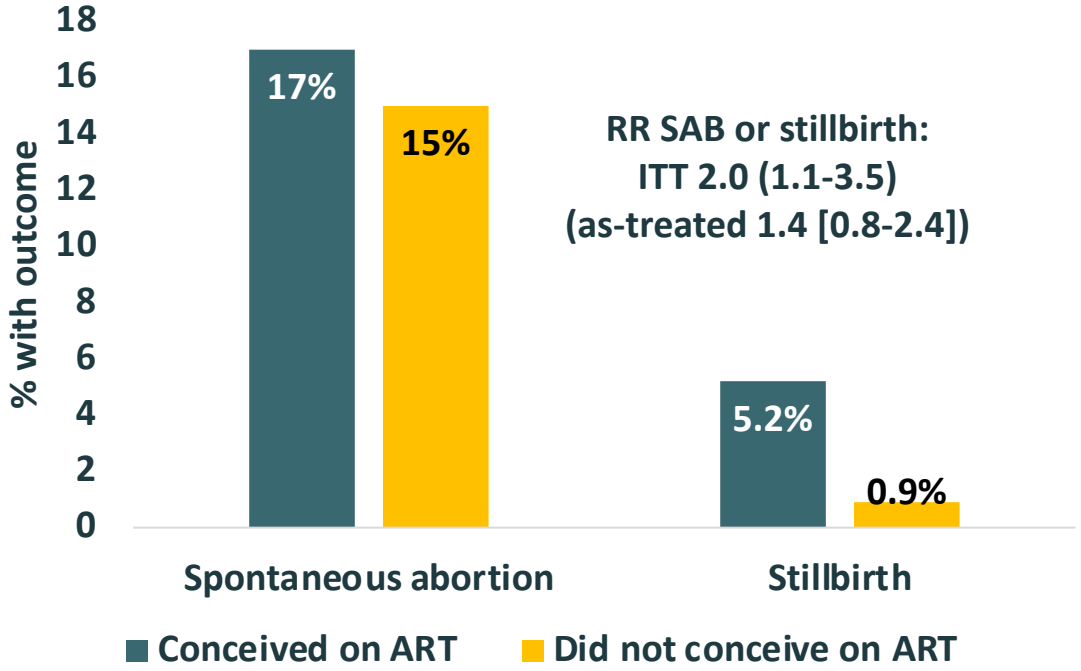
Conception on ART and pregnancy outcomes

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



Uthman Lancet HIV 2017

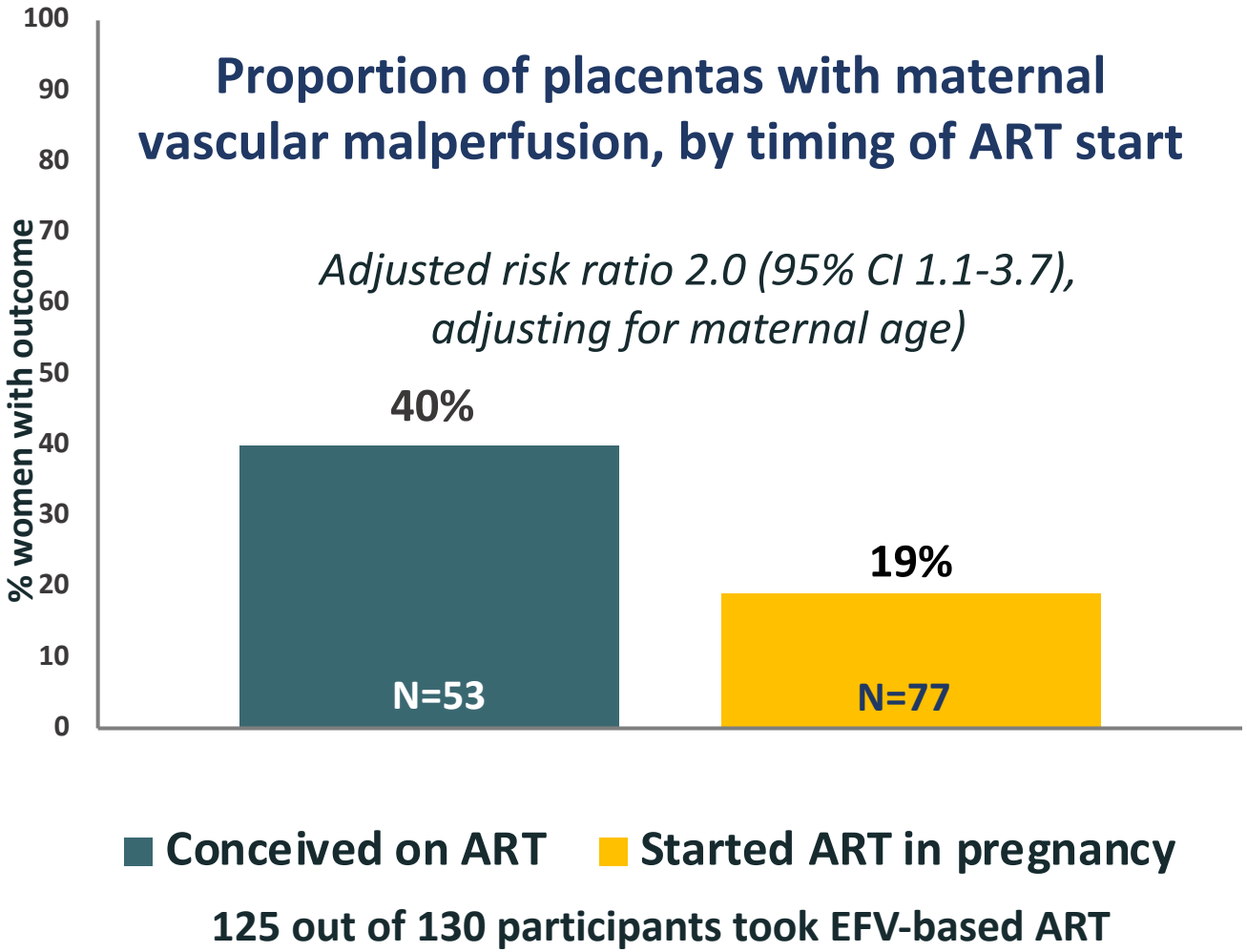
PROMISE (IMPAACT P1077), 2nd Pregnancy



Hoffman CID 2019

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

Higher prevalence of placental maternal vascular malperfusion with ART from conception



- ART before conception → 2-fold higher placental MVM
- MVM was significantly associated with preterm delivery and LBW

Ikumi, AIDS 2021

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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

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HIV treatment in pregnancy and…

Vertical transmission

Pregnancy outcomes

Congenital anomalies

Mother's health outcomes

Child outcomes

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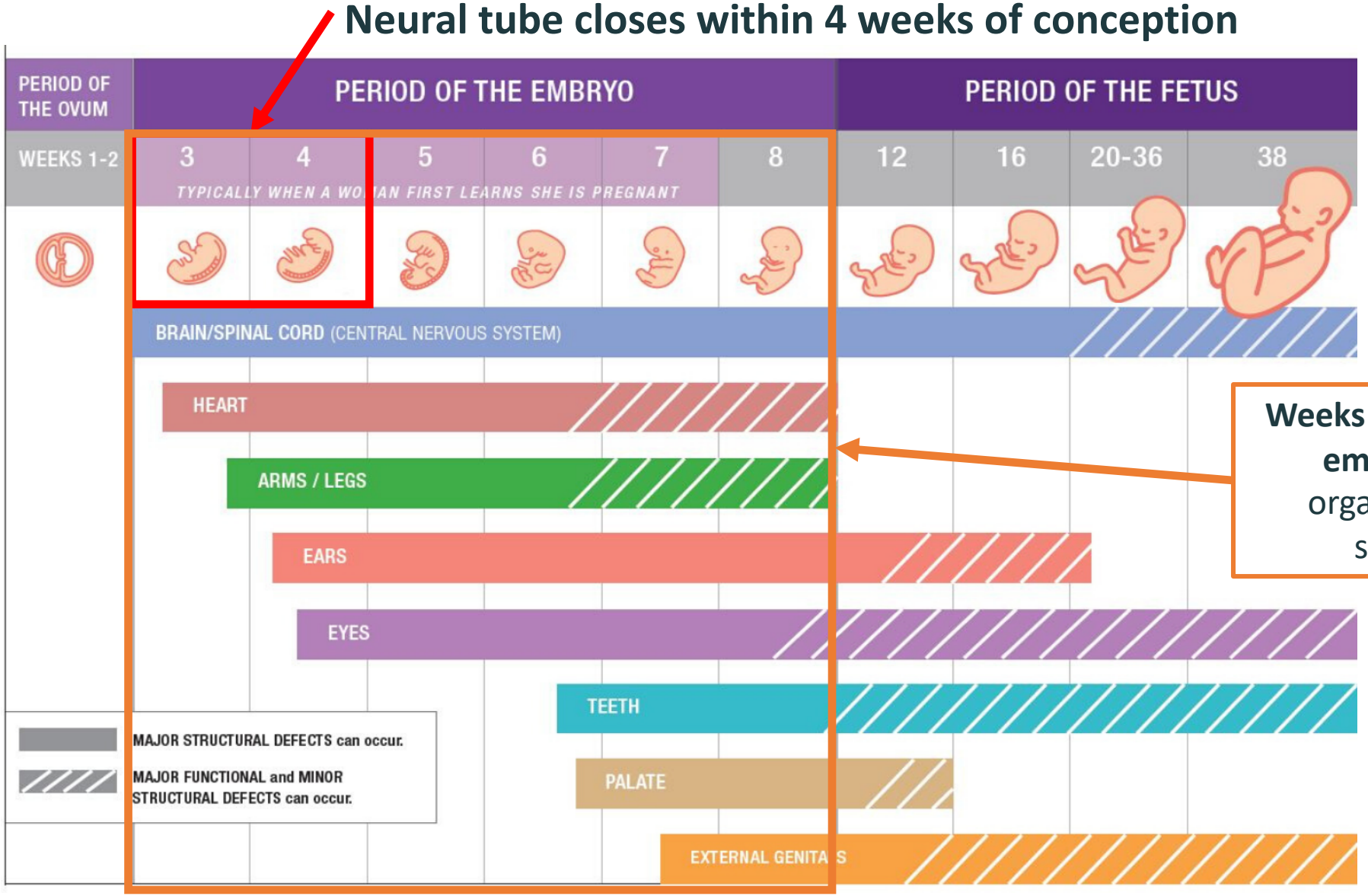
Critical and sensitive periods in human development



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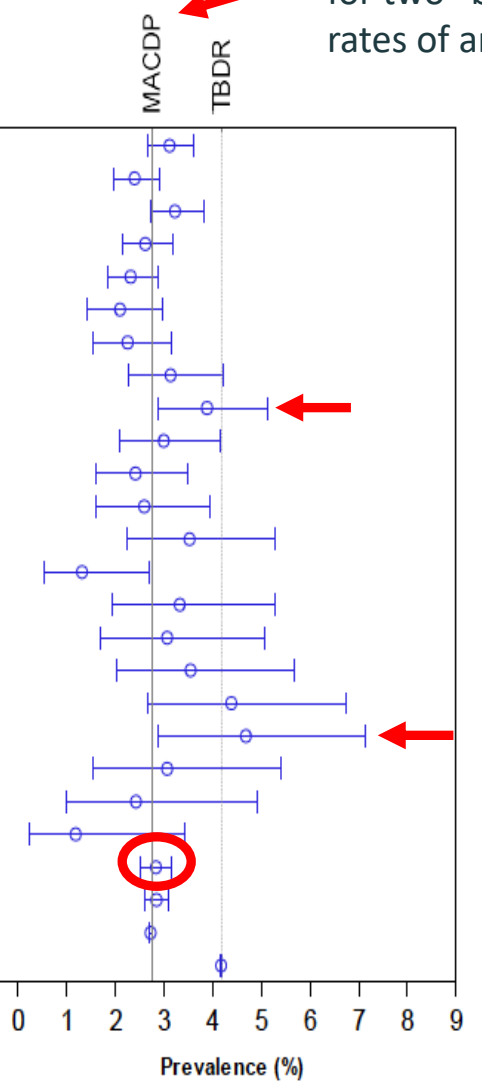
Antiretroviral pregnancy registry (APR): congenital anomalies with 1st trimester exposure

Summary of birth defects with 1st trimester exposures, prospective registry Jan 1989 – July 2020

Upper 95% CI bound for two "background" rates of anomaly

	Defects/Live Births	Prevalence (%)	Lower 95% CI	Upper 95% CI
Lamivudine	168/5398	3.11	2.66	3.61
Tenofovir DF	105/4388	2.39	1.96	2.89
Zidovudine	136/4222	3.22	2.71	3.80
Emtricitabine	99/3788	2.61	2.13	3.17
Ritonavir	79/3417	2.31	1.83	2.87
Lopinavir	30/1435	2.09	1.41	2.97
Atazanavir	32/1424	2.25	1.54	3.16
Abacavir	42/1342	3.13	2.26	4.21
Nelfinavir	47/1212	3.88	2.86	5.12
Nevirapine	35/1169	2.99	2.09	4.14
Efavirenz	28/1160	2.41	1.61	3.47
Stavudine	21/811	2.59	1.61	3.93
Darunavir	22/625	3.52	2.22	5.28
Rilpivirine	7/533	1.31	0.53	2.69
Dolutegravir	17/512	3.32	1.94	5.26
Raltegravir	14/458	3.06	1.68	5.08
Cobicistat	16/452	3.54	2.04	5.69
Tenofovir Alafenamide	19/434	4.38	2.66	6.75
Didanosine	20/427	4.68	2.88	7.14
Elvitegravir	11/359	3.06	1.54	5.42
Indinavir	7/289	2.42	0.98	4.93
Telbivudine	3/254	1.18	0.24	3.41
First Trimester APR	304/10754	2.83	2.52	3.16
Any Trimester APR	580/20437	2.84	2.61	3.07
MACDP		2.72	2.68	2.76
TBDR		4.17	4.15	4.19



- **~200** 1st TM exposures to detect **2-fold** increase in **any** anomaly (~3%)
- **~2,000** to detect **3-fold** increase in **rare** anomaly like NTD (0.1%)
- **22 ARVs** have enough data to detect a 2-fold increase in anomalies
- Only **ddI and nelfinavir** have elevated anomaly prevalence (no pattern)

http://www.apregistry.com/

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Preconception DTG and neural tube defects

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

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

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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

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HIV treatment in pregnancy and…

Vertical transmission

Pregnancy outcomes

Mother's health

Child outcomes

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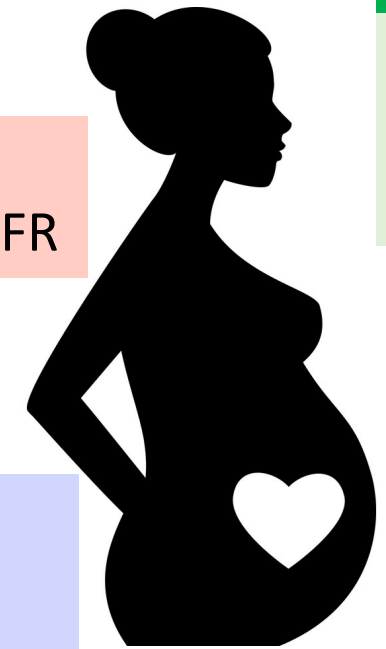
Physiological changes in pregnancy can alter drug pharmacokinetics (PK)

Absorption

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

Elimination

- Higher cardiac output
- Increased renal blood flow/GFR



Distribution

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

Metabolism

Activity of drug-metabolizing enzymes (mostly increase)

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

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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	
Abacavir	↔
Emtricitabine / lamivudine	↘
Tenofovir AF	↔
Tenofovir DF	↘
Zidovudine	↔

NNRTIs	
Doravirine	?
Efavirenz	→
Etravirine	→
Nevirapine	→
Rilpivirine	↓

PIs	
Atazanavir/r	↓
Darunavir/r	↓
Lopinavir/r	↓

INSTIs	
Bictegravir	?
Dolutegravir	↘
Elviteg./cobi	↓↓
Raltegravir	↓

Boosters	
Cobicistat	↓↓
Ritonavir	↓

Entry inhibitors	
Fostemsavir	?
Ibalizumab	?
Maraviroc	↓

Long-acting agents	
CAB LA	?
Rilpivirine LA	?
Islatravir	?

Clinicalinfo.hiv.gov

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ART in pregnancy and maternal health outcomes

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

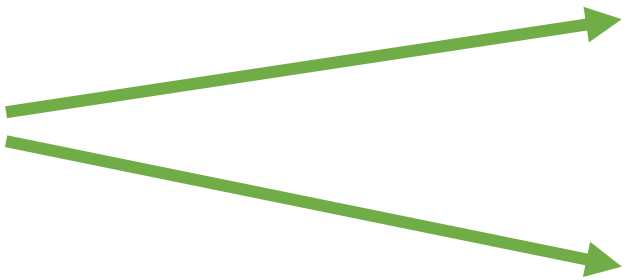
Rarely: virologic failure on ART due to lower plasma drug levels in pregnancy (e.g. cobicistat-boosted regimens)

Infrequently: adverse effects may differ in pregnancy/postpartum

- **Weight gain** (DTG, TAF)
- **Gestational diabetes** (unexpectedly: *lower* with DTG- vs EFV-ART in 1 study) *(Mmasa, HIV Medicine 2021)*
- **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)*
- **Gastrointestinal intolerance** (LPV/r) *Cohan 2015*
- **Hepatitis** (NVP) *Renet J Ob/Gyn Canada 2013*
- **? Postpartum suicidal ideation** (EFV) *Jones AIDS Behav 2020*

ART in pregnancy and maternal health outcomes

Maternal pre-pregnancy BMI and pregnancy weight gain



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

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

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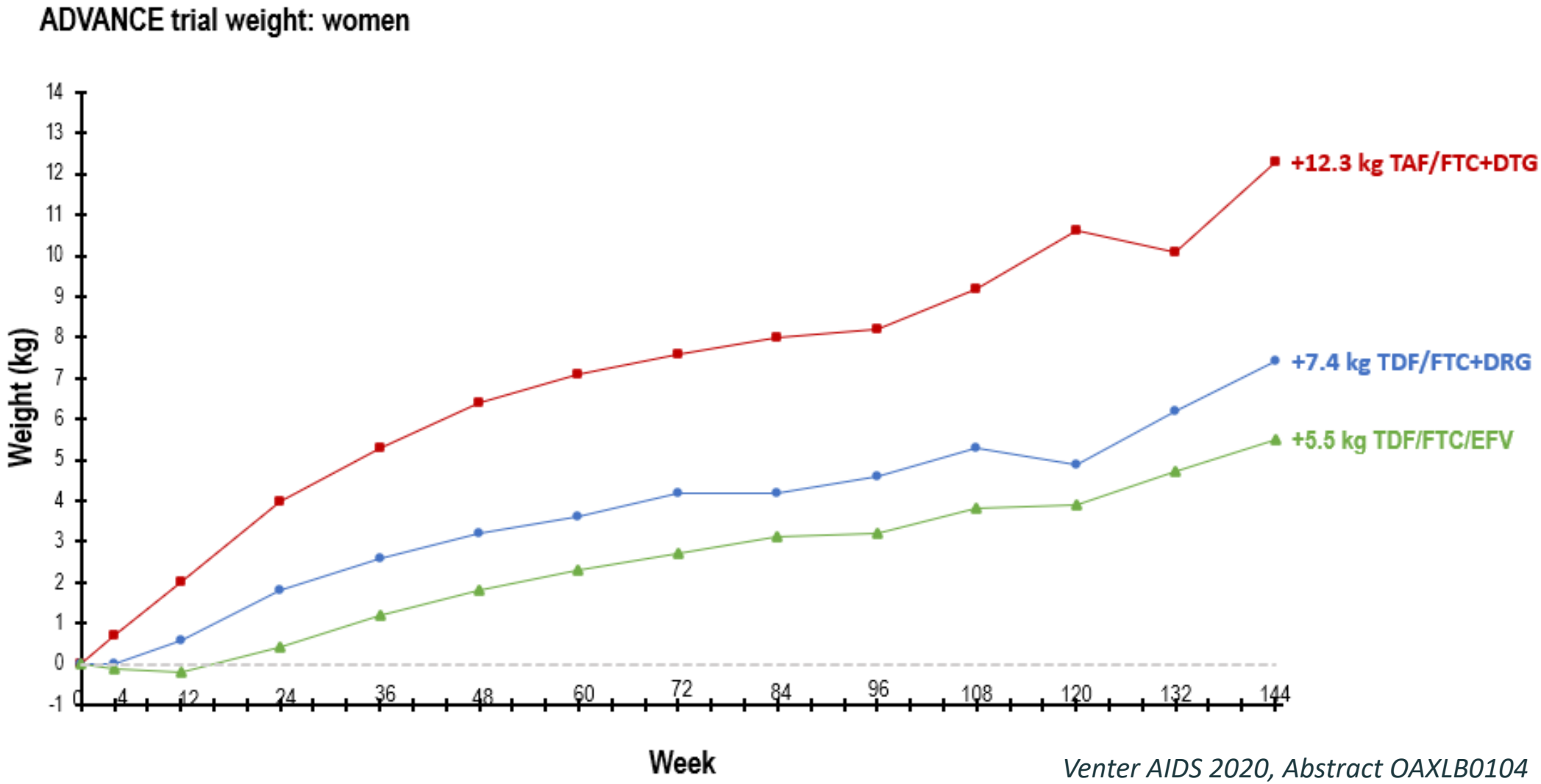
ART and weight gain in non-pregnant women

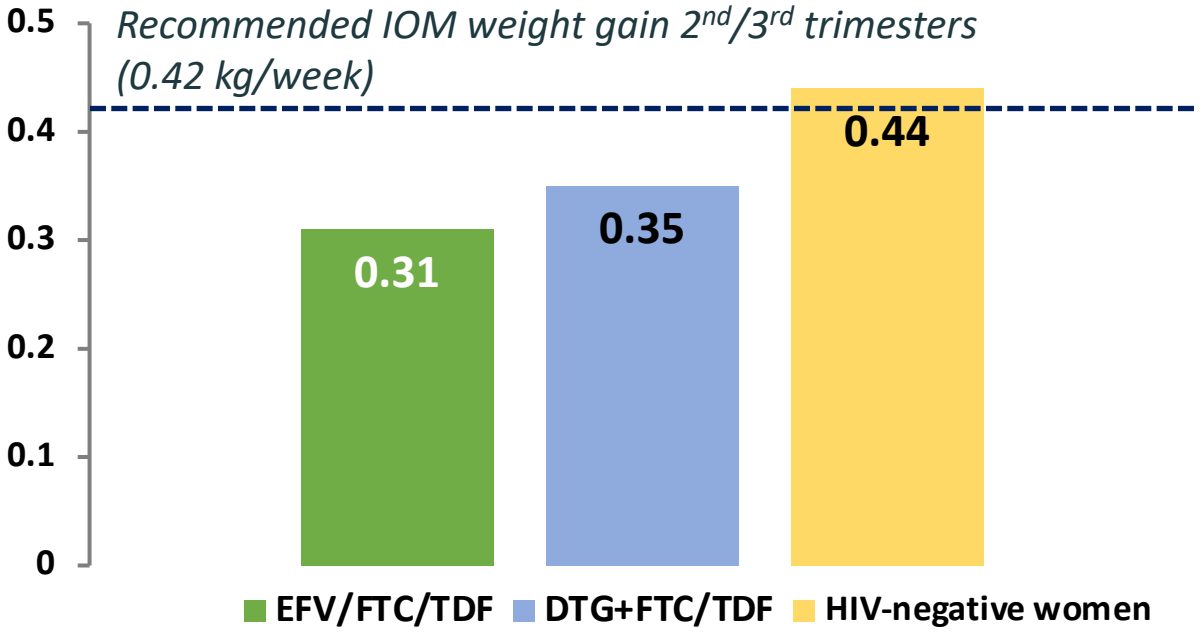
Integrase inhibitors and TAF → excess weight gain (particularly in women w/ INSTIs)



Venter AIDS 2020, Abstract OAXLB0104

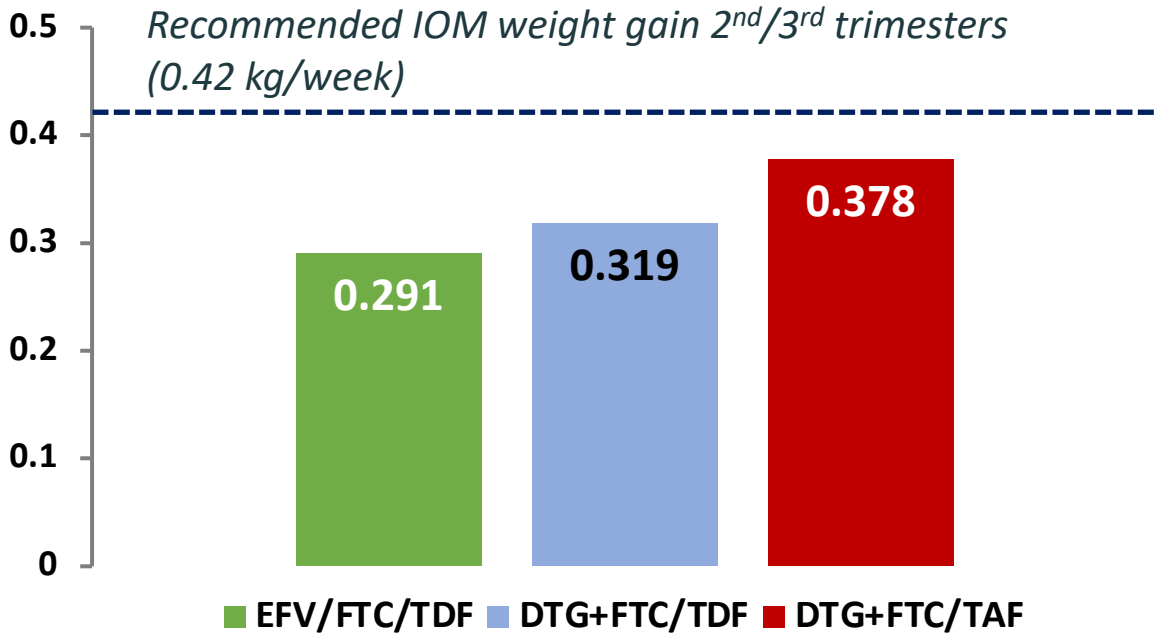
Antepartum weight gain differs by ART regimen started in pregnancy

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

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Weight in pregnancy & 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

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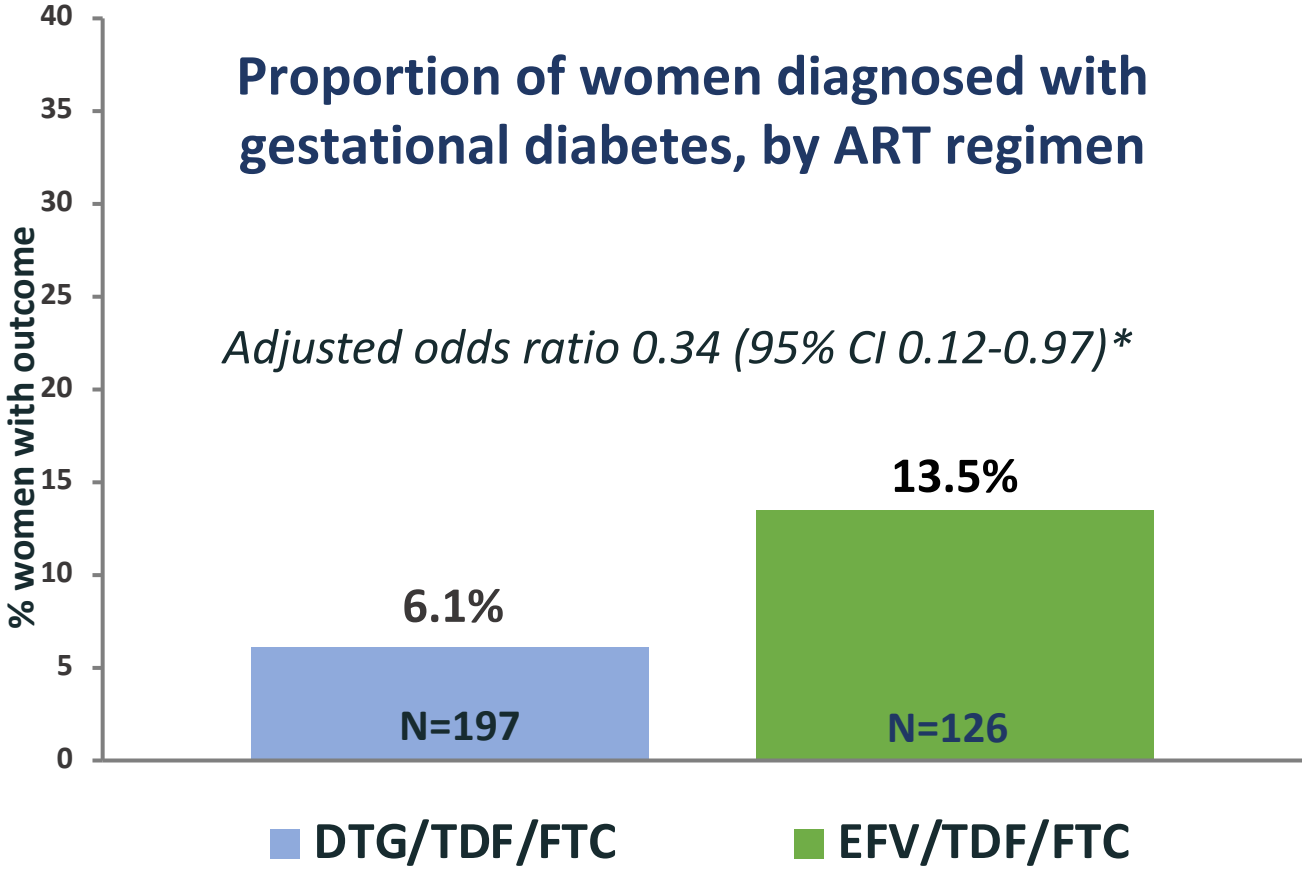
Gestational diabetes with DTG- vs. EFV-based ART in pregnancy



*Adjusted for age, BMI, gravidity, CD4, and whether ART started prior to or during pregnancy

Women taking DTG-based ART were significantly less likely to have gestational diabetes (by OGTT) than women taking EFV-based ART

Mmasa, HIV Med 2021

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Key points, ART and maternal health

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
   - Unknown: implications over longer term, with subsequent pregnancies, and in different populations

3. **Important to gather high-quality data on clinical endpoints with different ART regimens**

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HIV treatment in pregnancy and…

Vertical transmission

Pregnancy outcomes and neonatal death

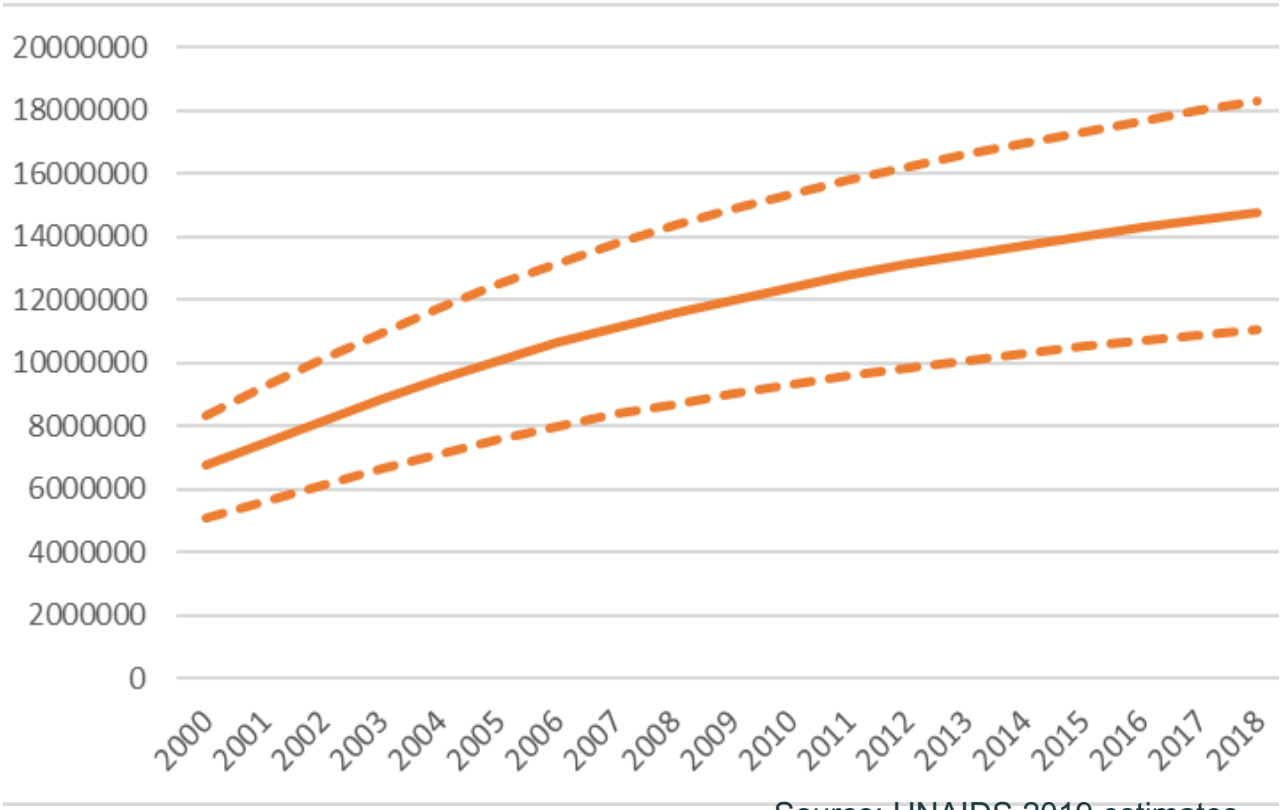
Mother's health outcomes

Child outcomes

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

See CROI 2021 Van Lettow Abstract 585

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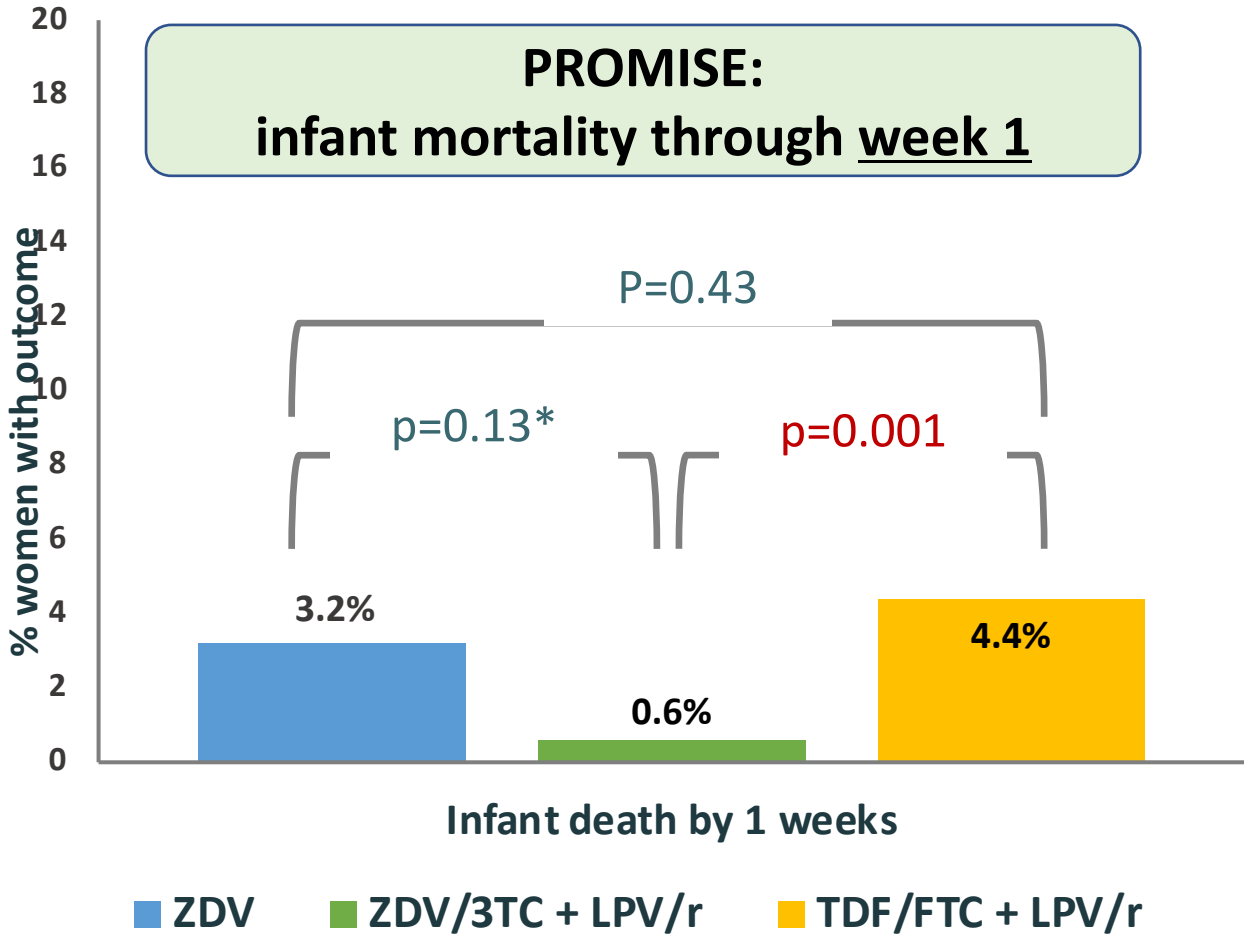
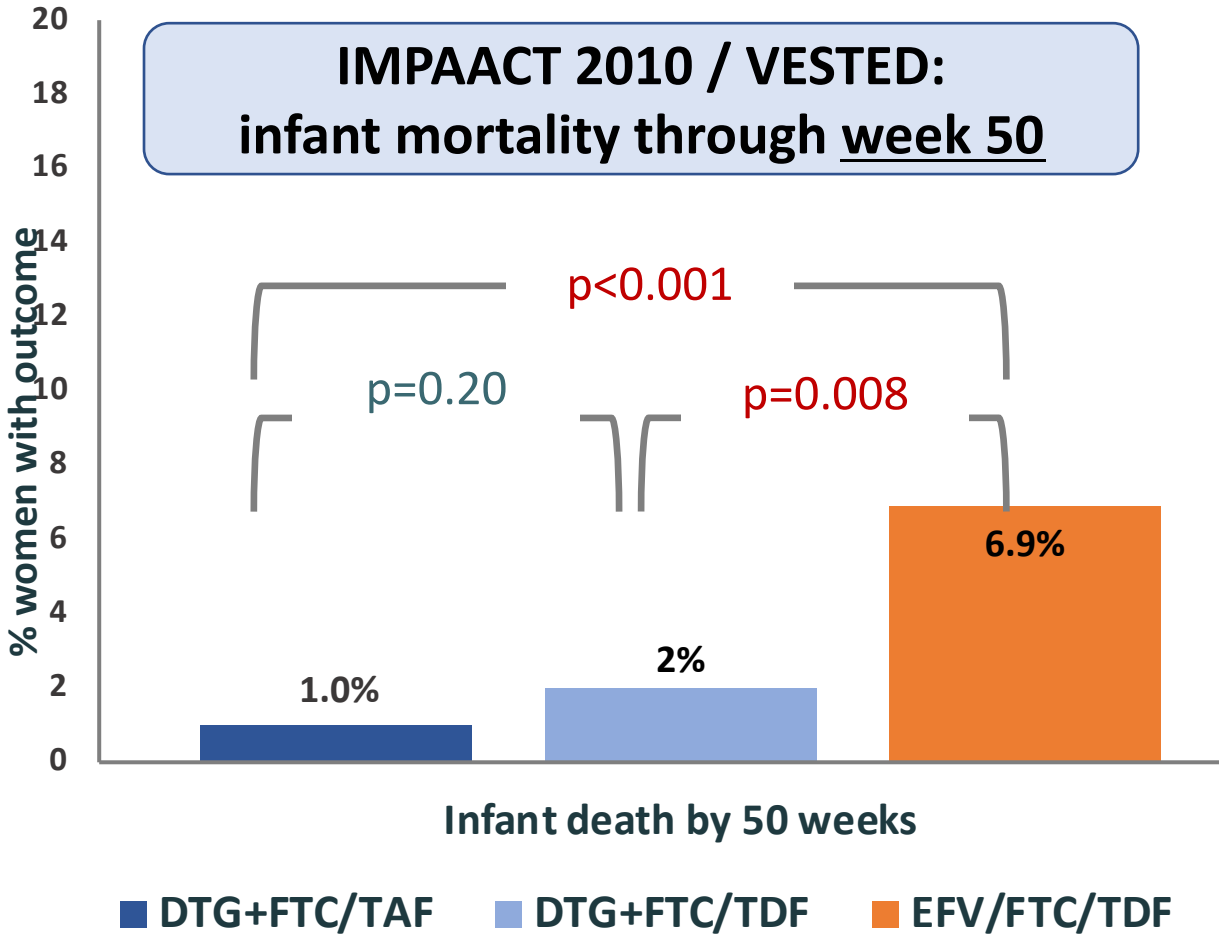
Neonatal/infant mortality *may* vary by maternal ARV regimen



** Period 1 of study*



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ART in pregnancy and child growth and neurodevelopment

Research gaps: outcomes in older children and with newer antiretrovirals

See Jao #590 and Sirajee #592

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

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Antiretrovirals used in treating adults, 2020

NRTIs
TAF (tenofovir alafenamide fumarate)
FTC (emtricitibine), 3TC lamivudine)
ABC (abacavir)
TDF (tenofovir disoproxil fumarate)
ZDV (zidovudine)

INTEGRASE INHIBITORS
BIC (bictegravir)
DTG (dolutegravir)
RAL (raltegravir)
ELV/c (elvitegravir/cobicistat)

PROTEASE INHIBITORS
DRV/r (darunavir/ritonavir)
ATV/r (atazanavir/ritonavir)
ATV/cobi, DRV/cobi (cobicistat boost)
LPV/r (lopinavir/ritonavir)

NNRTIs
DOR (doravirine)
EFV (efavirenz)
RPV (rilpivirine)
ETR (etravirine)
NVP (nevirapine)

ENTRY INHIBITORS
Ibalizumab
Fostemsavir
CCR5 BLOCKER
MVC (maraviroc)
LONG-ACTING AGENTS
CAB LA (cabotegravir)
RIL LA (rilpivirine)

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ARVs for pregnant women, US DHHS 2020

NRTIs	
TAF (alternative)	
FTC , 3TC	
ABC	
TDF	
ZDV (alternative)	
INTEGRASE INHIBITORS	
BIC	Insufficient data
DTG	
RAL	
ELV/c	Not recommended
PROTEASE INHIBITORS	
DRV/r	
ATV/r	
ATV/cobi, DRV/cobi	Not recommended
LPV/r	Not recommended

NNRTIs	
DOR	Insufficient data
EFV (alternative)	
RPV (alternative)	
ETR	Not recommended
NVP	Not recommended
ENTRY INHIB	
Ibalizumab	Insufficient data
Fostemsavir	Insufficient data
CCR5 BLOCKER	
MVC	Not rec in ART-naive
LONG-ACTING	
CAB LA	Insufficient data
RIL LA	Insufficient data

Also: insufficient data for 2-drug treatment in pregnancy (e.g. DTG/3TC, CAB/RIL)
See CROI 2021 Abstract Mandelbrot 570

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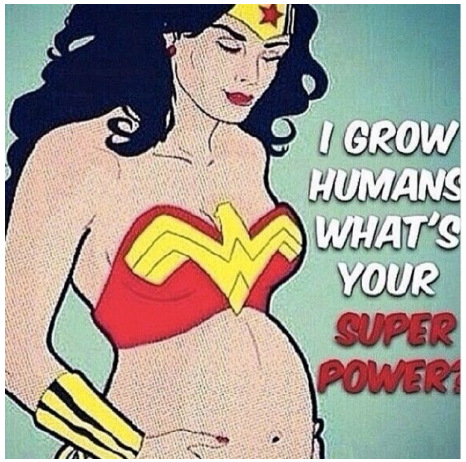
Guidelines: preferred antiretrovirals during pregnancy

	NRTIs		INSTIs		PIs	NNRTIs
DHHS and EACS	TDF/XTC or ABC/3TC	+	DTG or RAL BID	**OR**	DRV/r or ATV/r *(DHHS)*	
WHO	TDF/3TC	+	DTG		**OR**	EFV 400

If conceive on ART with HIV-1 RNA suppression: generally continue regimen

(consider switch if on cobicistat-boosted regimen; recommend switch if on d4T, ddI, FPV, IDV, NFV, SQV, TPV, two-drug ART, triple-NRTI)



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 …"*

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

Phase IIa / IIb	Phase III	Phase IV
Leronlimab (MAb)	Cabotegravir LA	Tenofovir Alafenamide
Islatravir LA (PrEP; soon Ph III)	UB-421 (anti-CD4 rec)	Bictegravir
Islatravir LA (+MK-8507)	Islatravir (ISL/DOR)	Doravirine
ABX464 (rev inh)	VRC01[LS] (BNAb)	Ibalizumab
3BNC117 (BNAb)	Lenacapavir	Fostemsavir
GSK 3640254 (matur inh)	Dapivirine ring	Cabotegravir/Rilpivirine LA
GS-6207 (capsid inh)		
Albuvirtide (fusion inh)		

Adapted with permission from slide prepared by C Thorne/A Pozniak

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Newer HIV agents : plans for study in pregnancy?

Phase IIa / IIb	Phase III	Phase IV
Leronlimab (MAb)	**Cabotegravir LA**	**Tenofovir Alafenamide**
Islatravir LA (PrEP; soon Ph III)	UB-421 (anti-CD4 rec)	**Bictegravir**
Islatravir LA (+MK-8507)	**Islatravir (ISL/DOR) & ISL**	**Doravirine**
ABX464 (rev inh)	VRC01[LS] (BNAb)	**Ibalizumab**
3BNC117 (BNAb)	**Lenacapavir**	**Fostemsavir**
GSK 3640254 (matur inh)	**Dapivirine ring** 	**Cabotegravir/Rilpivirine LA**
GS-6207 (capsid inh)		
Albuvirtide (fusion inh)		

- **Long-acting CAB, RIL, ISL, LEN:** 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

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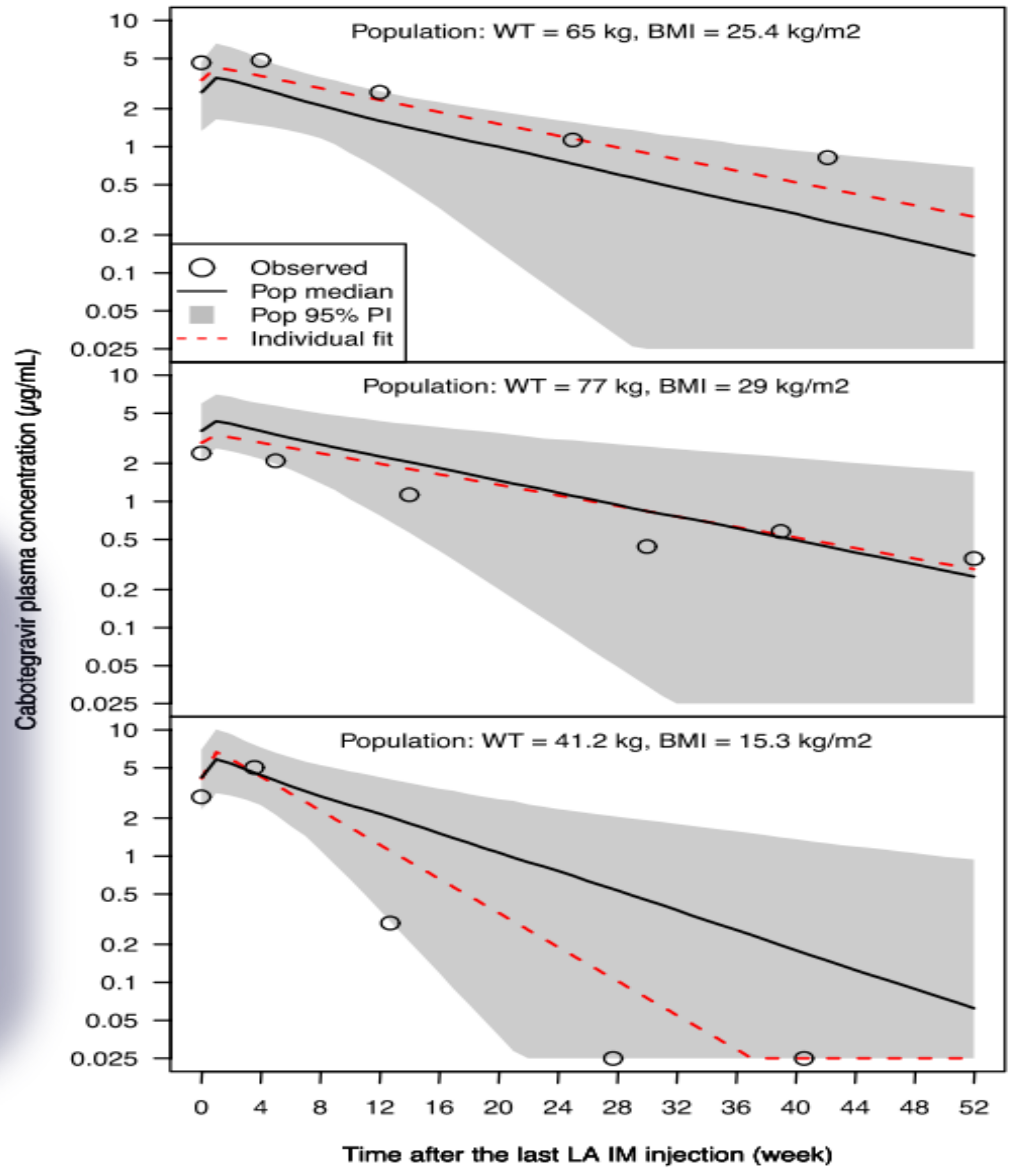
Long-acting agents for HIV prevention and treatment

- Important drugs! Potentially useful postpartum
- Even if stop 1st 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

Outline

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

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Generally poor track record for studying drugs in pregnancy

"During trials, participants have close monitoring…why leave pregnant women to experiment with drugs but without adequate follow-up?"

d

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How do we improve upon the status quo?

Conceptual shifts that will facilitate inclusion of pregnant women in research

Vulnerable **population**	***Complex*** **population**
Protection *from* research	**Protection *through* research**
Presumptive *exclusion*	**Fair *inclusion***

The PHASES Working Group, call to action, 2020

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A call to include pregnant women in research

Gathering momentum for change: numerous initiatives, e.g.

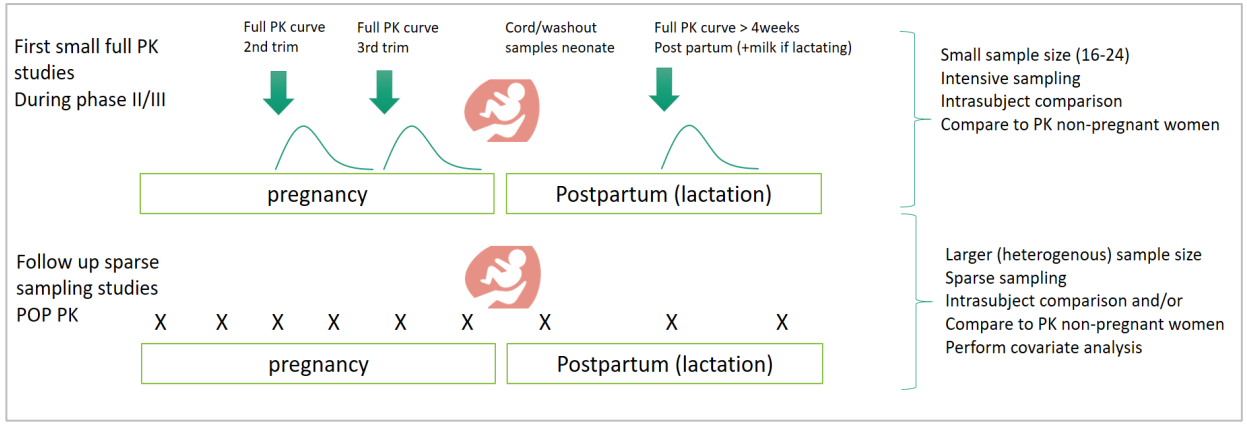
U.S. Task Force on Research Specific to Pregnant & Lactating Women (PRGLAC)

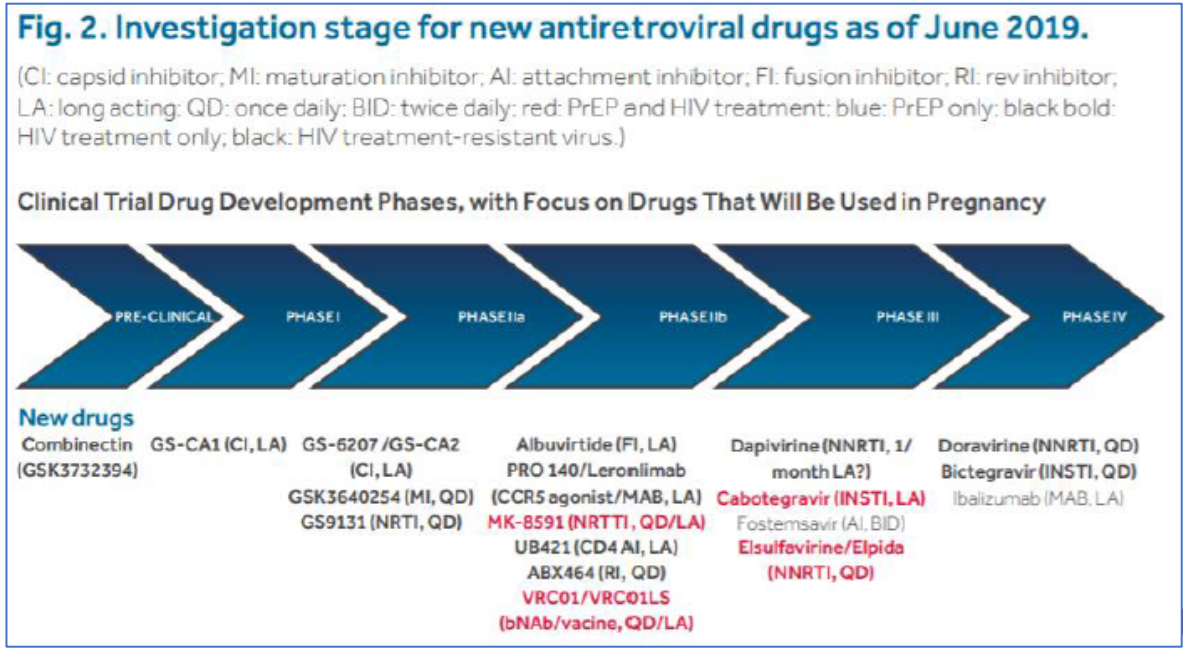
FDA draft guidance, Second Wave Initiative, PHASES Project, and many others globally

IMPAACT and WHO: advancing research on HIV drugs during pregnancy/lactation

WHO & IMPAACT Dec 2019: advancing pharmacology studies in pregnant and lactating women

Figure 1 Proposed approach to pharmacokinetic studies of ARVs during pregnancy and the postpartum period





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WHO & IMPAACT 2020 - now

Workshop Part 1

World Health Organization IMPAACT

Welcome to the Virtual Workshop on Approaches to Enhance and Accelerate Study of New Drugs for HIV and Associated Infections in Pregnant Women

DECEMBER 8-10, 2020

Workgroups

- Non-clinical
- Trials in pregnant women
- Study design
- Surveillance
- Advocacy

Workshop Part 2

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

World Health Organization

SAVE THE DATES!!!

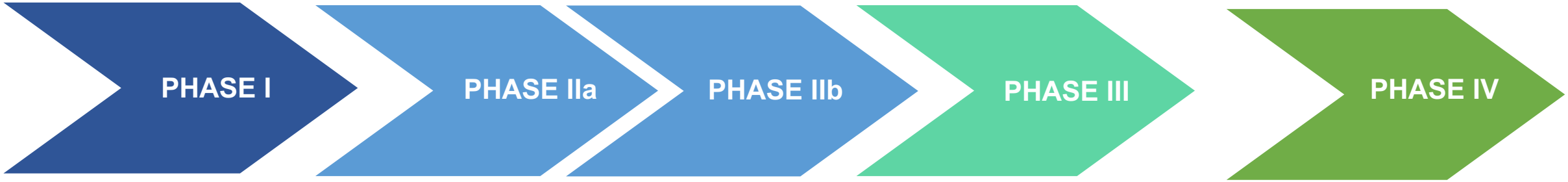
Virtual Workshop on

"Approaches to Enhance and Accelerate Study of New Drugs for HIV and Associated Infections in Pregnant Women"

(Part 2)

6 & 7 July 2021

Potential ways to increase the inclusion of pregnant women in research



Steps under consideration for accelerating ethical inclusion of pregnant women in research:

Earlier completion of non-clinical studies ←

Women becoming pregnant in trial can consent to stay on drug → PK/safety data (unless reason not to)

For high-priority drugs: dedicated pregnancy PK +/- larger safety study during Phase III or early post-approval

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 understand and incorporate 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

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Thank you!

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& to the many women who take part in this research

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