CROI Updates: Women and Pregnancy

Smitha Gudipati, MD

Division of Infectious Disease

Henry Ford Hospital

Background: Pregnancy and HIV

51% of PLWH globally are women

~1.3 million women with HIV are pregnant each year and most women with HIV will be pregnant at least once following their diagnosis

Need pregnancy data to identify 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

UNAIDS 2020

Highlights For Today

- Are Dolutegravir and TAF regimens safe in women of childbearing age or pregnant with HIV?
- What are our concerns about congenital abnormalities in children of mothers with HIV on ART?
- How do we prevent maternal to child transmission?

Are Dolutegravir and TAF regimens safe in women of childbearing age or pregnant with HIV?

Dolutegravir vs Efavirenz in Late Pregnancy to 72 Weeks Postpartum

- DolPHIN-2 Final Results
  - Primary endpoint analysis: DTG superior response at delivery (VL<50 copies)
  - Secondary outcome analysis: maintaining VL<50 copies and <1000 copies and occurrence of MTCT
  - Current analysis: Follow up of women and infants to 72 weeks postpartum

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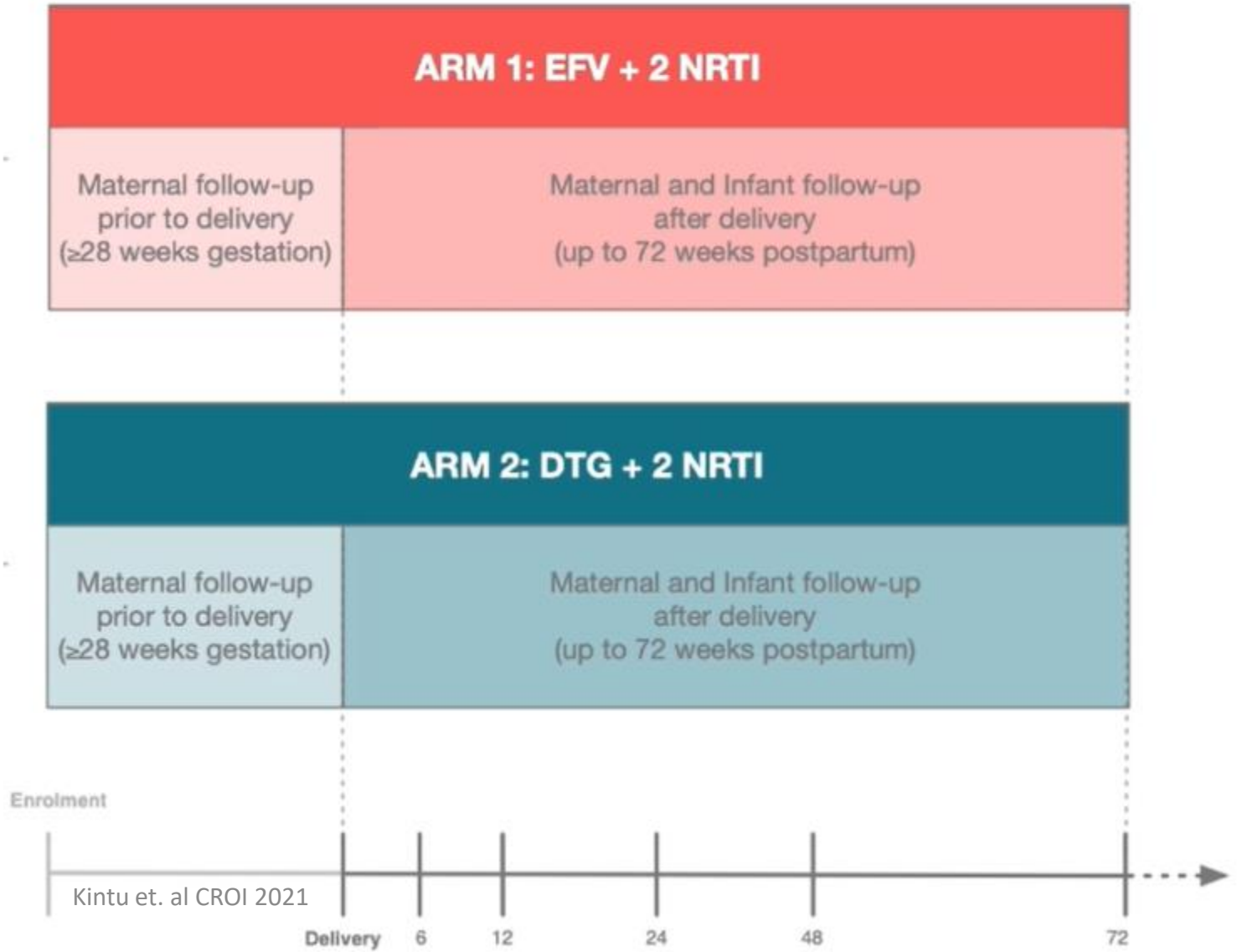
Study Design

- Key Eligibility Criteria
  - Aged ≥18yrs
  - Untreated HIV
  - ≥28 weeks gestation



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Results	DTG arm	EFV arm
Median time to suppression (VL<50 copies)	4.14 weeks	12.14 weeks

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Virological failure	3 persons	8 persons
MTCT	3 in utero transmissions	1 postpartum transmission (breastfeeding)

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Conclusions

- The results support the WHO treatment recommendations for use of DTG in pregnancy
- Both regimens were safe and well tolerated
- The DTG-based regimen had superior virologic efficacy which was maintained through the breastfeeding period
- The infant HIV infection in EFV arm highlights potential for transmission during breastfeeding in women despite evidence of virologic suppression

Safety/Efficacy of DTG vs EFV, TDF vs TAF In Pregnancy/Postpartum

- IMPAACT 2010 trial
- Phase III, 3 arm, randomized, open-label trial
  - DTG + FTC/TAF
  - DTG + FTC/TDF
  - EFV/FTC/TDF
- Previously reported that DTG therapy had superior virologic efficacy to EFV/FTC/TDF and DTG/FTC/TAF had lowest rate of adverse pregnancy outcomes
- Presenting virologic efficacy and safety data from enrollment through 50 weeks postpartum

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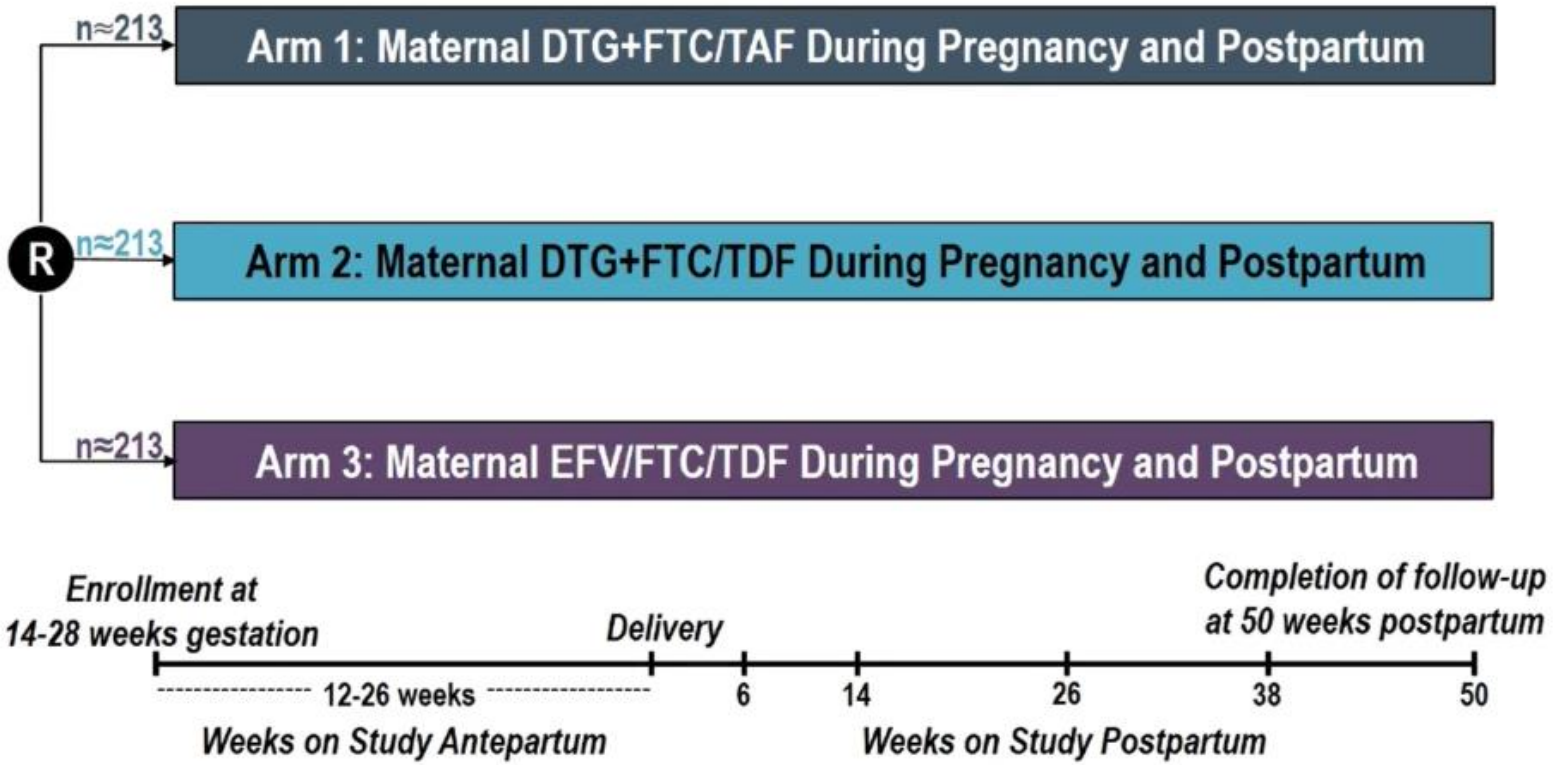
IMPAACT 2010 Study Design



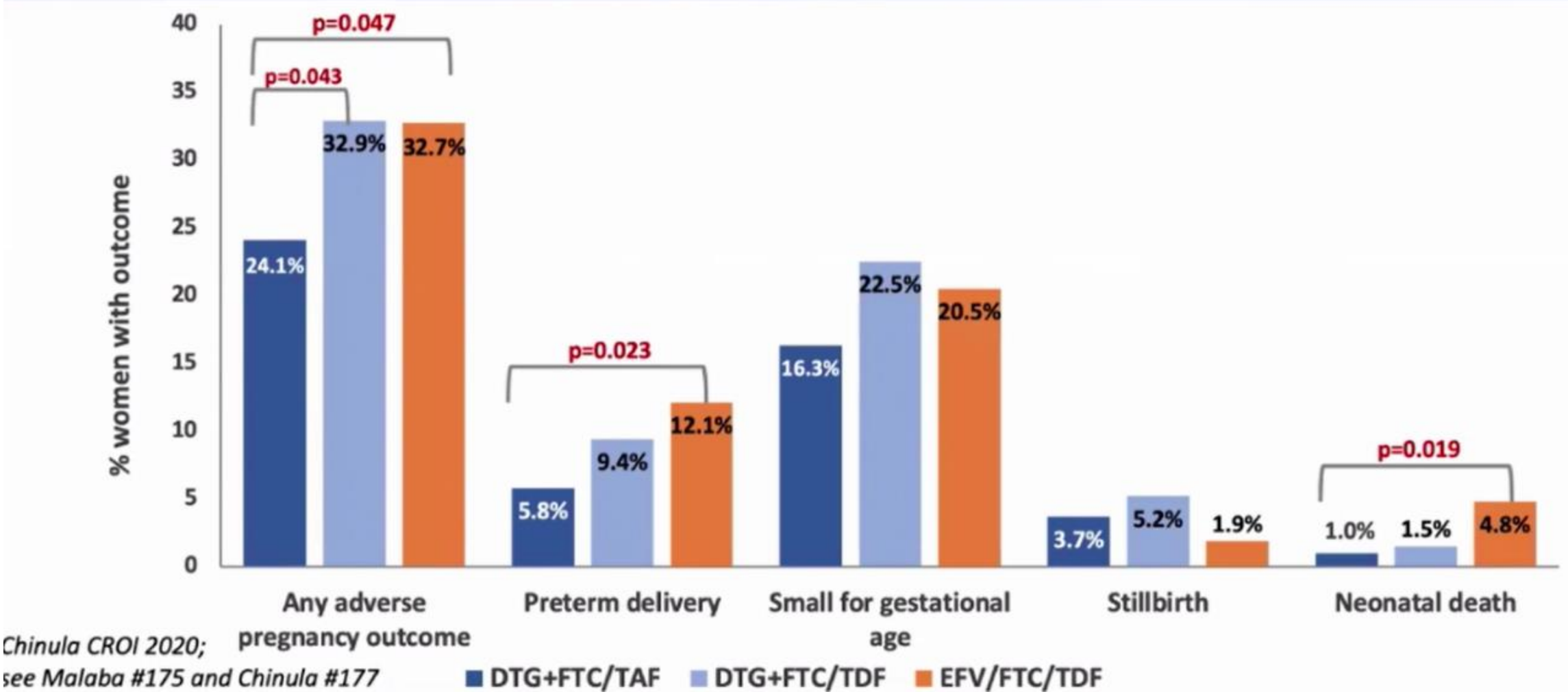
Key Eligibility Criteria

- Pregnant WLHIV 14-28 weeks gestation
- ART-naïve (up to 14 days ART in current pregnancy allowed)

Participants were enrolled at 22 sites in 9 countries

IMPAACT

VESTED TRIAL (IMPAACT 2010)



Chinula CROI 2020;
see Malaba #175 and Chinula #177

Chinula et al. CROI 2021

Conclusions

- Rates of maternal and infant grade >3 AEs were similar across arms from enrollment to Week 50 postpartum
  - Infant mortality was higher (though stillbirths somewhat less frequent) in the EFV arm
- The proportion of women with virologic suppression at week 50 postpartum was similarly high in the combined DTG 3-drug ART arms vs the EFV arm
  - Most women experienced virologic failure (and switched ART due to virologic failure) in the EFV arm
- The rate of weight loss was significantly higher in the EFV arm and lowest in the DTG+FTC/TAF arm, which had the highest prevalence of obesity at week 50 postpartum
- Results from this study provide additional reassuring data for use of DTG and TAF during pregnancy and postpartum

Recommendations for the Use of Antiretroviral Drugs During Pregnancy

Are

- The Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends dolutegravir (DTG) as a *Preferred* antiretroviral (ARV) drug throughout pregnancy and now also recommends DTG as a *Preferred* ARV for women who are trying to conceive. This decision was based on updated data showing that that the increased risk of neural tube defects (NTDs) associated with the use of DTG is very small and the advantages of DTG which include once-daily dosing, being generally well tolerated, and producing rapid, durable viral load suppression, which is important for maternal health and the prevention of perinatal HIV transmission.
- With this change, the Panel has removed DTG-specific recommendations, but added content about balancing the risks and benefits of specific ARV drugs in the face of limited data. The Panel continues to emphasize the importance of counseling and informed decision making regarding the use of DTG and all ARV drugs during pregnancy and for people who are trying to conceive and has revised the Counseling Guide in Appendix C, accordingly.
- Lopinavir/ritonavir, formerly classified as an *Alternative* ARV is now *Not Recommended Except in Special Circumstances* based on data about increased risks of preterm delivery and small for gestational age infants (see Antiretroviral Drug Regimens and Maternal and Neonatal Outcome) as well as requirements for twice daily dosing and potential nausea and vomiting.

- The Panel recommends tenofovir alafenamide (TAF) as an *Alternative* nucleoside reverse transcriptase inhibitor for ARV therapy regimens now that additional data about the use and safety of TAF in pregnancy has become available.
- The Panel has revised language about its recommendations about cobicistat containing ARV regimens that pose a risk for low drug levels and viral rebound in the second and third trimesters to point out that some health care providers and their patients may choose to continue with frequent viral load monitoring, rather than switching to a new regimen.

What are our concerns about congenital abnormalities in children of mothers with HIV on ART?

The Antiretroviral Pregnancy Registry

- Voluntary, international, prospective exposure-registration cohort study
  - Started as Zidovudine in a Pregnancy Registry in 1989, became the APR in 1993
  - As of July 31, 2020, includes >20,437 live births with ART exposure
- Designed to assist clinicians and patients in weighing potential risk and benefits of HIV treatment used during pregnancy
  - Provides early warning signals of major teratogenicity
  - Estimates prevalence of major birth defects and compares to the general population
  - Analyzes prospective, retrospective and clinical studies

Conclusions

- The APR found no significant difference in congenital abnormality prevalence overall or by trimester of exposure compared to population-based surveillance systems
- A detailed review of cases for DDI, NFV and TAF did not identify a pattern of congenital abnormalities
- The APR finds no apparent increases in the frequency of defects with first trimester exposures compared to exposures starting later in pregnancy and no pattern to suggest a common cause

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 **(0.19%)**
Brazil retrospective cohort (Lancet HIV 2021)	2 / ~1,084 **(0.18%)**
APR July 2020	1/479 **(0.21%)**
CDC/MoH Botswana (NEJM 2019)	1 / 152 **(0.66%)**
European DOLOMITE/EPPICC (Pre-CROI workshop 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*

Modified from table prepared by L Mofenson

What are our concerns about congenital abnormalities in children of mothers with HIV on ART?

Key Points:

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

How do we prevent maternal to child transmission?

Background

- In 2019 globally
  - 85% of pregnant women were on ART
  - >50% conceived on ART
  - BUT, still ~150,000 new pediatric infections
- The three primary missed opportunities for preventing vertical transmission
  - Mother did not receive ART (pregnancy > breastfeeding)
  - Incidental HIV infection (breastfeeding > pregnancy)
  - Dropped off ART (breastfeeding > pregnancy)

Focus countries 2019, UNAIDS 2020

Maternal to Child Transmission

MTCT remains a key global health priority

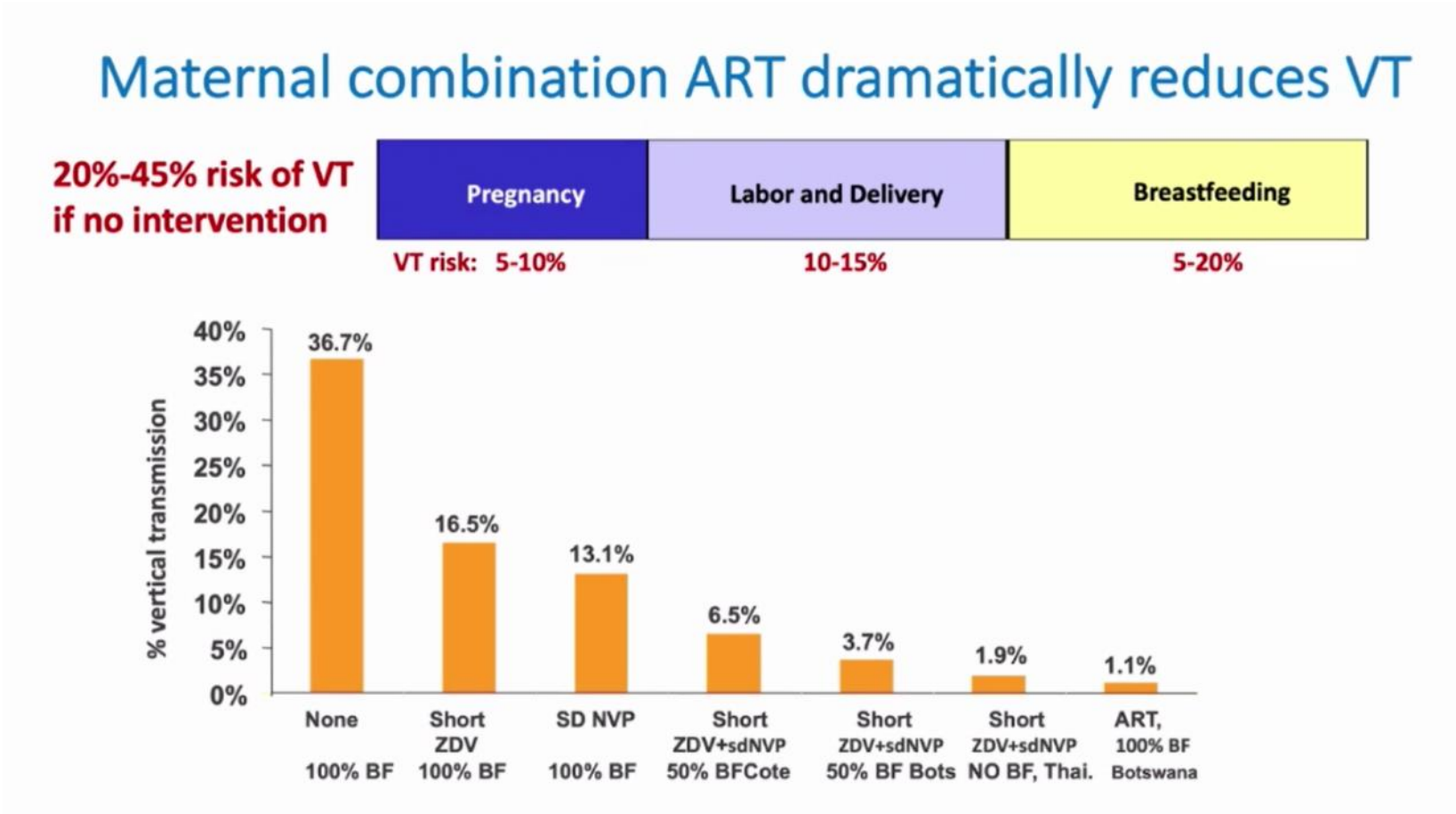
Late initiation is associated with a 7-fold increased risk of MTCT and doubling of infant mortality

Maternal VL is directly related to MTCT and DTG results in rapid VL decline

Currently, WHO recommends DTG-based regimens for pregnant and childbearing potential women

Plenary session; HIV treatment in pregnancy: beyond prevention of vertical transmission; CROI 2021

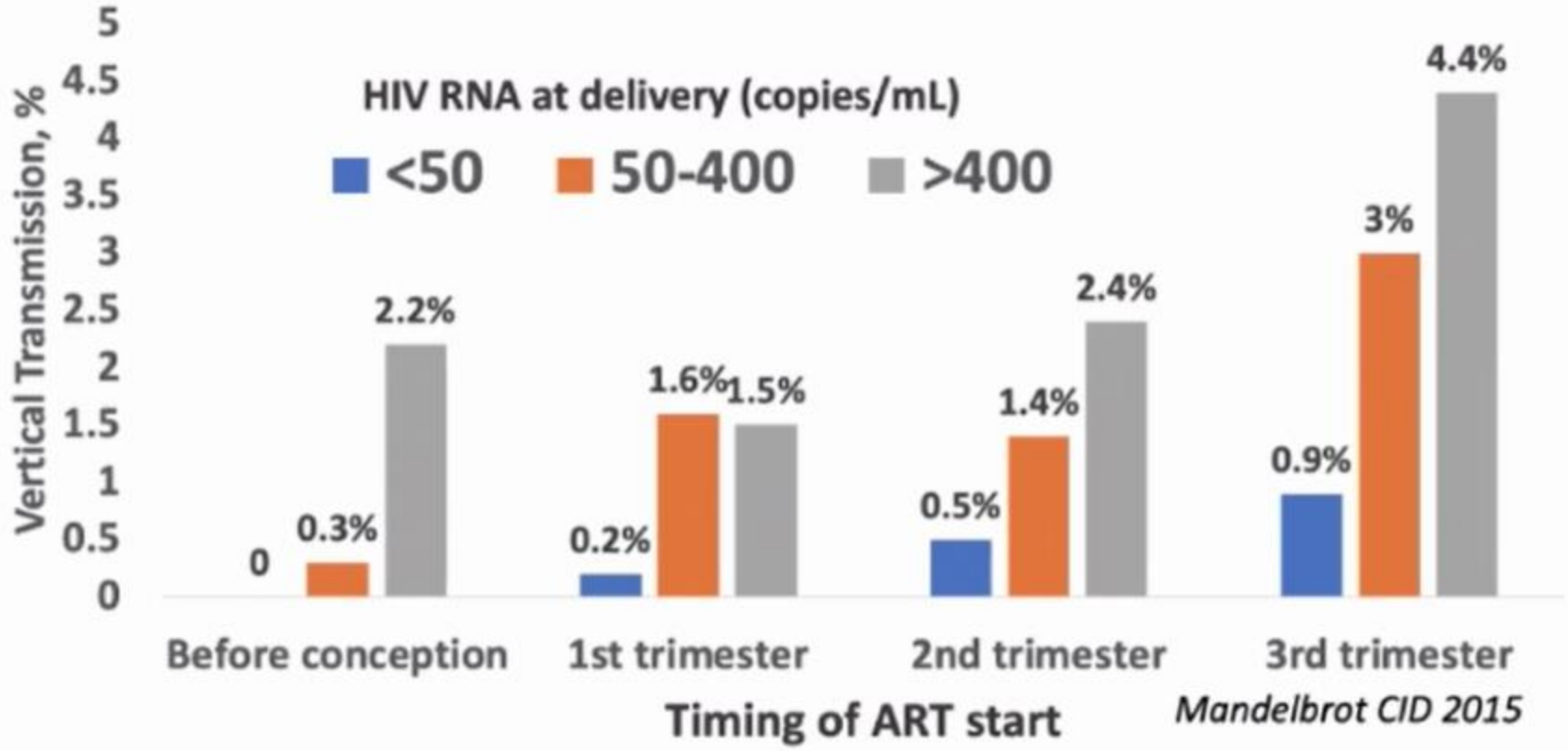
Vertical Transmission Prevention



Plenary session; HIV treatment in pregnancy: beyond prevention of vertical transmission; CROI 2021

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



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So How Do We Prevent Maternal to Child Transmission??

Key Points

- Earlier ART start = 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
- Bottom line: increase ART coverage and maternal HIV re-testing (to diagnose incidental HIV); reduce HIV incidence; and better support retention in care and ART adherence

Plenary session; HIV treatment in pregnancy: beyond prevention of vertical transmission; CROI 2021

Thank You!

sgudipa2@hfhs.org