AETC AIDS Education & Training Center Program Mountain West

Antiretroviral Therapy and Pregnancy

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Disclosures

Merck: serve on a case adjudication panel

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Antiretroviral Therapy and Pregnancy

Outline

- Review of vertical transmission of HIV
- Early data on the effect of ART on vertical transmission
- ART safety and the DTG story
- Current preferred regimens and guidelines
- Drugs and regimens for which there are not sufficient data
- Odds and ends

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Antiretroviral Therapy and Pregnancy

Vertical transmission of HIV-1

- Without ART the risk of mother to child transmission (MTCT) is estimated to be 15-30% during pregnancy plus an additional 10—20% associated with breast feeding
- Throughout pregnancy the risk of transmission increases with time:
  - Weeks 0-28: 6% of attributable transmissions
  - Weeks 28-36: 14%
  - Weeks 36-labor: 50%
  - During labor: 30%

(Nduati, JAMA, 2000, Kourtis, Lancet Infec Dis, 2006)

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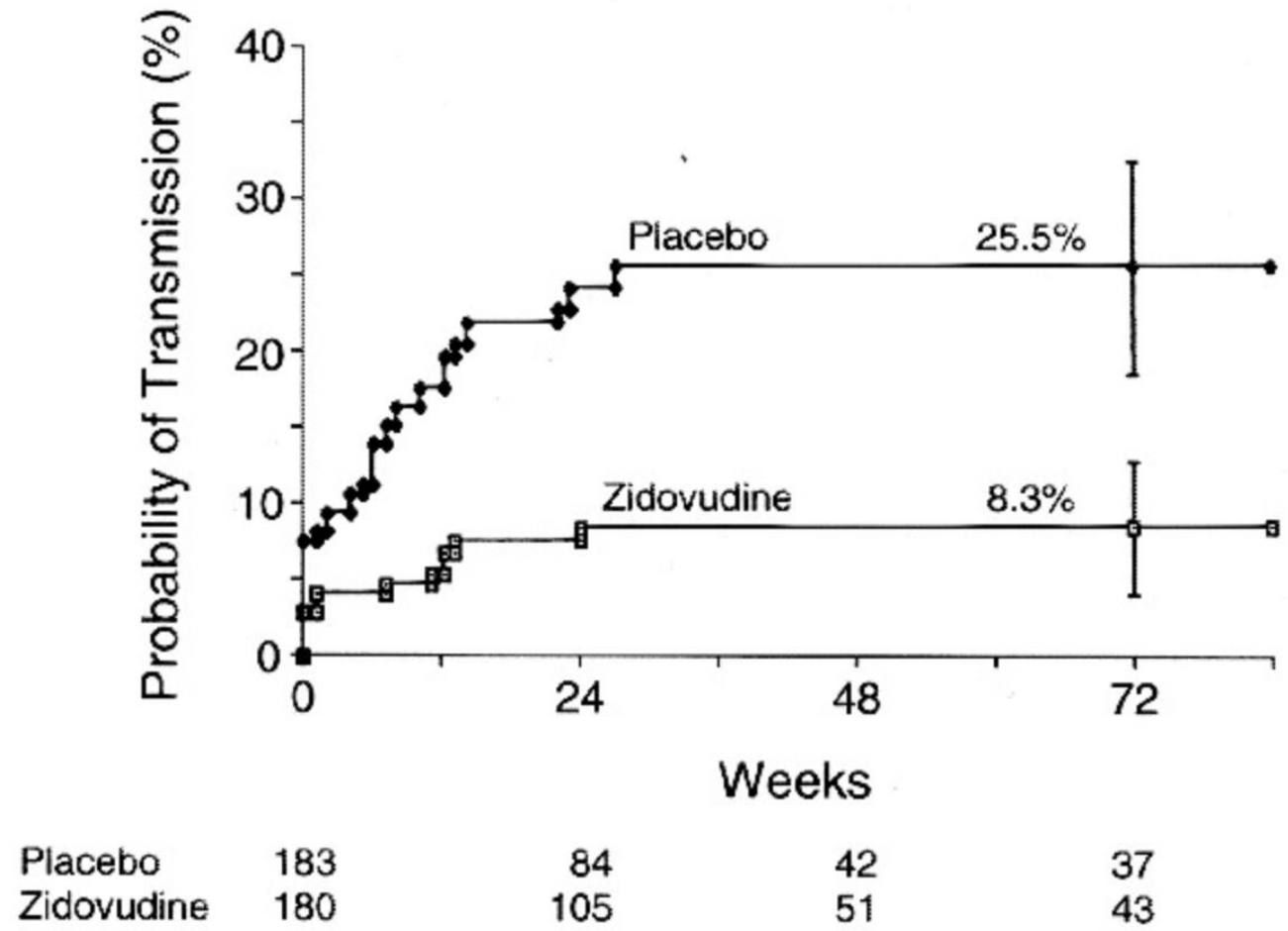
Antiretroviral Therapy and Pregnancy

Vertical transmission of HIV-1: PACTG 076

- ART dramatically reduces the rate of MTCT
- The landmark study, PACTG-076, a randomized, PC study of zidovudine (AZT) monotherapy enrolled 477 pregnant women who were randomized to antepartum (b/n 14-34 weeks) and intrapartum AZT plus AZT to the newborn
- AZT treatment led to a 67.5% reduction in MTCT



Connor, NEJM, 1994

Antiretroviral Therapy and Pregnancy

ART to prevent MTCT

- Subsequent studies with combination ART have demonstrated that the earlier in pregnancy that ART is initiated the more effective it is at preventing MTCT:
  - ART started prior to conception: 0.2% MTCT
  - ART started in the first trimester: 0.4% MTCT
  - ART started in the second trimester: 0.9% MTCT
  - ART started in the third trimester: 2.2% MTCT
- In one study of 2651 infants born to women on suppressive ART at conception and throughout pregnancy there were no MTCT events

Nesheim, Pediatrics, 2012; Mandelbrot, CID, 2015

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Antiretroviral Therapy During Pregnancy: *Safety*

DOES ART CAUSE CONGENITAL MALFORMATIONS?
Meta-analysis of 30 studies

Populations: pregnant women with HIV at any gestational age

Intervention: any ART taken for at least 1 month

Comparators: Women without HIV, women with HIV but not taking ART

Outcomes: congenital anomalies

Study designs: RCTs, quasi-experimental (controlled before and after time-series), observational cohorts

Alemu, Epidemiology and Health, 2021

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Antiretroviral Therapy During Pregnancy: *Safety*

DOES ART CAUSE CONGENITAL MALFORMATIONS?

Results

- Pooled relative risk demonstrated that those exposed to ART had a 10% increased risk of congenital malformations
- Subgroup analyses
  - No increased risk of anomalies in children born to women on efavirenz
  - A 10% increased risk among infants exposed to AZT and PI-based ART
  - A 60% increased risk among infants exposed to integrase inhibitors

Alemu, Epidemiology and Health, 2021

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Antiretroviral Therapy During Pregnancy: *Safety*

IMPAACT 2010/VESTED

- Multi-center, randomized, open-label, controlled, phase III trial
- DTG/TDF/FTC - DTG/TAF/FTC – EFV/TDF/FTC
- Africa, India, Thailand, USA
- Most (83%) on ART at entry for a median of 6 days
- Randomized by blocks of gestational age (14-18, 19-23, 24-28)

Lockman, Lancet, 2021

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Antiretroviral Therapy During Pregnancy: *Safety*

IMPAACT 2010/VESTED

- Outcomes
  - HIV RNA < 200 at or around delivery
  - Safety outcomes:
    - Adverse pregnancy outcome (pre-term delivery, small for gestational age, stillbirth or abortion)
    - ≥ Grade 3 adverse event in mother or infant

Lockman, Lancet, 2021

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Antiretroviral Therapy During Pregnancy: *Safety*

IMPAACT 2010/VESTED

	DTG-TAF-FTC	DTG-TDF-FTC	EFV-TDF-FTC	P-value
HIVRNA < 200 at delivery	95%		80%	<0.0001
Composite adverse pregnancy outcome	24%	33%	33%	0.043 and 0.047
Pre-term delivery	6%	9%	12%	0.16 and 0.023
Grade 3 AE (including congenital anomalies)				No difference
Neonatal mortality (birth to 28 days)	1%	2%	5%	0.05

Lockman, Lancet, 2021

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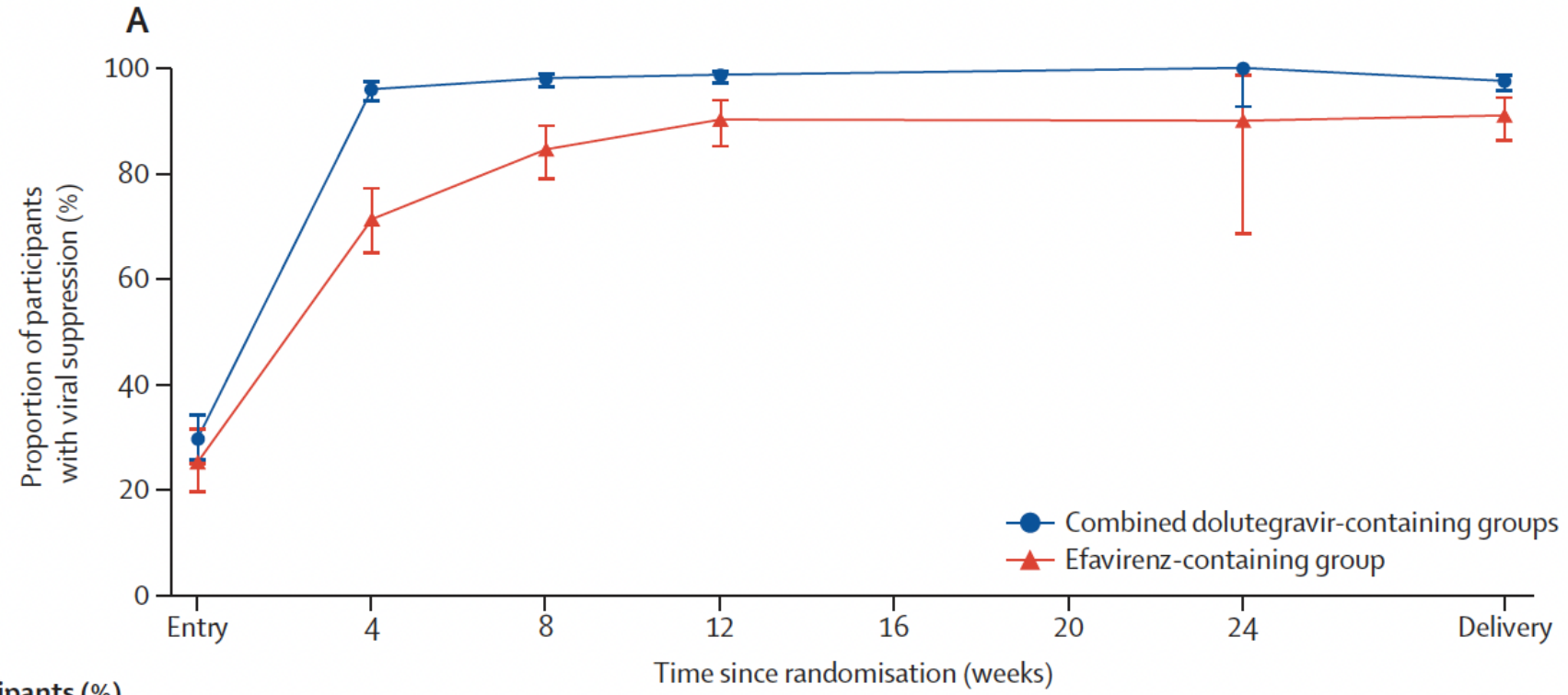
Antiretroviral Therapy During Pregnancy: *Safety*

IMPAACT 2010/VESTED



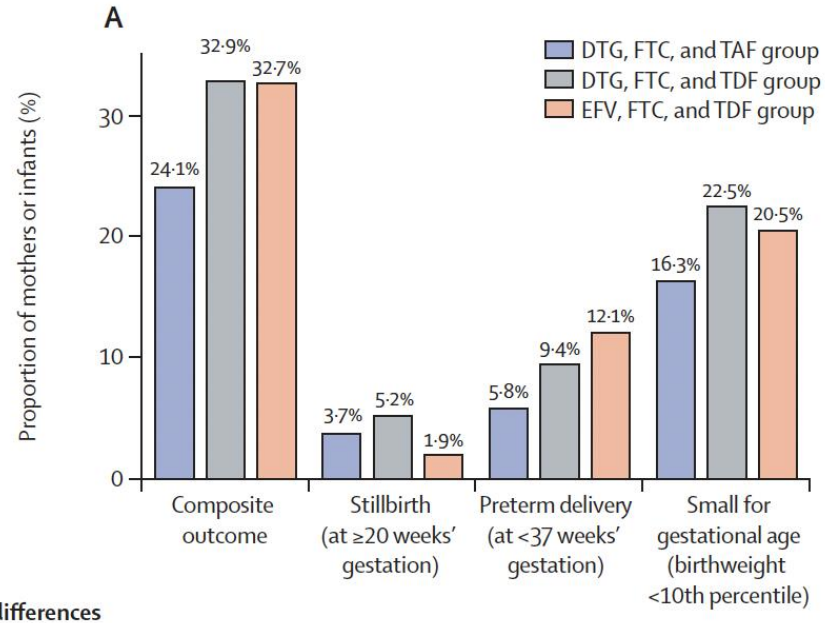
Proportion of participants (%)							
Combined dolutegravir-containing groups	129/432 (30%)	404/421 (96%)	404/412 (98%)	382/387 (99%)		47/47 (100%)	395/405 (98%)
Efavirenz-containing group	53/209 (25%)	147/206 (71%)	170/201 (85%)	166/184 (90%)		18/20 (90%)	182/200 (91%)

Lockman, Lancet, 2021

Antiretroviral Therapy During Pregnancy: *Safety*

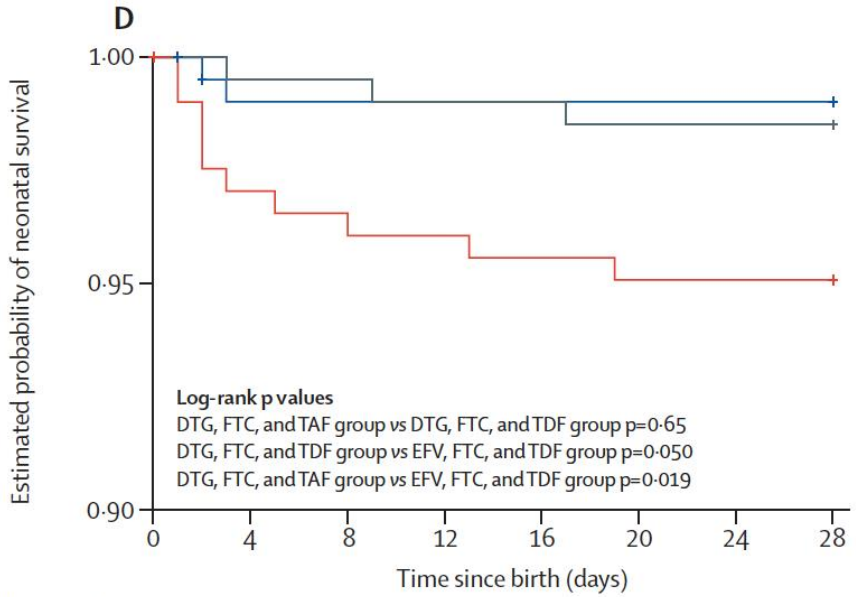
IMPAACT 2010/VESTED

Adverse Pregnancy Outcomes



Group differences (95% CI)	Composite outcome	Stillbirth (at ≥20 weeks' gestation)	Preterm delivery (at <37 weeks' gestation)	Small for gestational age (birthweight <10th percentile)
DTG, FTC, and TAF group *vs* DTG, FTC, and TDF group	−8·8% (−17·3% to −0·3%)	−1·5% (−5·4% to 2·4%)	−3·6% (−8·8% to 1·5%)	−6·2% (−13·9% to 1·5%)
DTG, FTC, and TDF group *vs* EFV, FTC, and TDF group	0·2% (−8·8% to 9·1%)	3·3% (−0·2% to 6·8%)	−2·7% (−8·7% to 3·3%)	2·0% (−6·0% to 10·0%)
DTG, FTC, and TAF group *vs* EFV, FTC, and TDF group	−8·6% (−17·1% to −0·1%)	1·8% (−1·3% to 4·9%)	−6·3% (−11·8% to −0·9%)	−4·2% (−11·7% to 3·4%)

Neonatal Survival



Number at risk (number censored)								
DTG, FTC, and TAF group	208 (0)	201 (5)	201 (5)	201 (5)	201 (5)	201 (5)	201 (5)	201 (206)
DTG, FTC, and TDF group	202 (0)	200 (1)	200 (1)	199 (1)	199 (1)	198 (1)	198 (1)	198 (199)
EFV, FTC, and TDF group	207 (0)	197 (4)	196 (4)	195 (4)	194 (4)	193 (4)	193 (4)	193 (197)

Lockman, Lancet, 2021

Antiretroviral Therapy During Pregnancy: *Safety*

Antiretroviral therapy and pregnancy: Dolutegravir

- 2018: FDA Warning Regarding the Use of Dolutegravir in Pregnancy

September 2018

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

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[**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.

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Antiretroviral Therapy During Pregnancy: *Safety*

Antiretroviral therapy and pregnancy: Dolutegravir

- FDA Warning Regarding the Use of Dolutegravir in Pregnancy

September 2018

- Concern stemmed from a preliminary unscheduled analysis of an NIH-funded birth surveillance study in Botswana
- 4 cases of neural tube defects (NTDs) out of 426 infants born to women who **initiated dolutegravir prior to pregnancy and were taking it at the time of conception**
- Rate of 0.94% compares to 0.12% among infants born to women taking non-dolutegravir-based regimens at time of conception
- No NTDs seen in 116 women who initiated dolutegravir during the first trimester of pregnancy

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Antiretroviral Therapy During Pregnancy: *Safety*

Dolutegravir: Updated Data from Tsepamo Study

Neural Tube Defects According to Maternal HIV Status and ART

	DTG at Conception	Non-DTG ART at Conception	EFV at Conception	DTG Started During Pregnancy	HIV-Negative
# of NTD	5	15	3	1	70
# of exposures	1,683	14,792	7,959	3,840	89,372
% with NTD (95% CI)	**0.30** (0.13-0.69)	**0.10** (0.06-0.17)	0.04 (0.01-0.11)	0.03 (0.00-0.15)	0.08 (0.06-0.10)
Difference in prevalence (95% CI)	Reference	0.20 (0.01-0.59)	0.26 (0.07-0.66)	0.27 (0.06-0.67)	0.22 (0.05-0.62)

Zash R et al. N Engl J Med. 2019 Jul 22. and IAS 2019, Mexico City.

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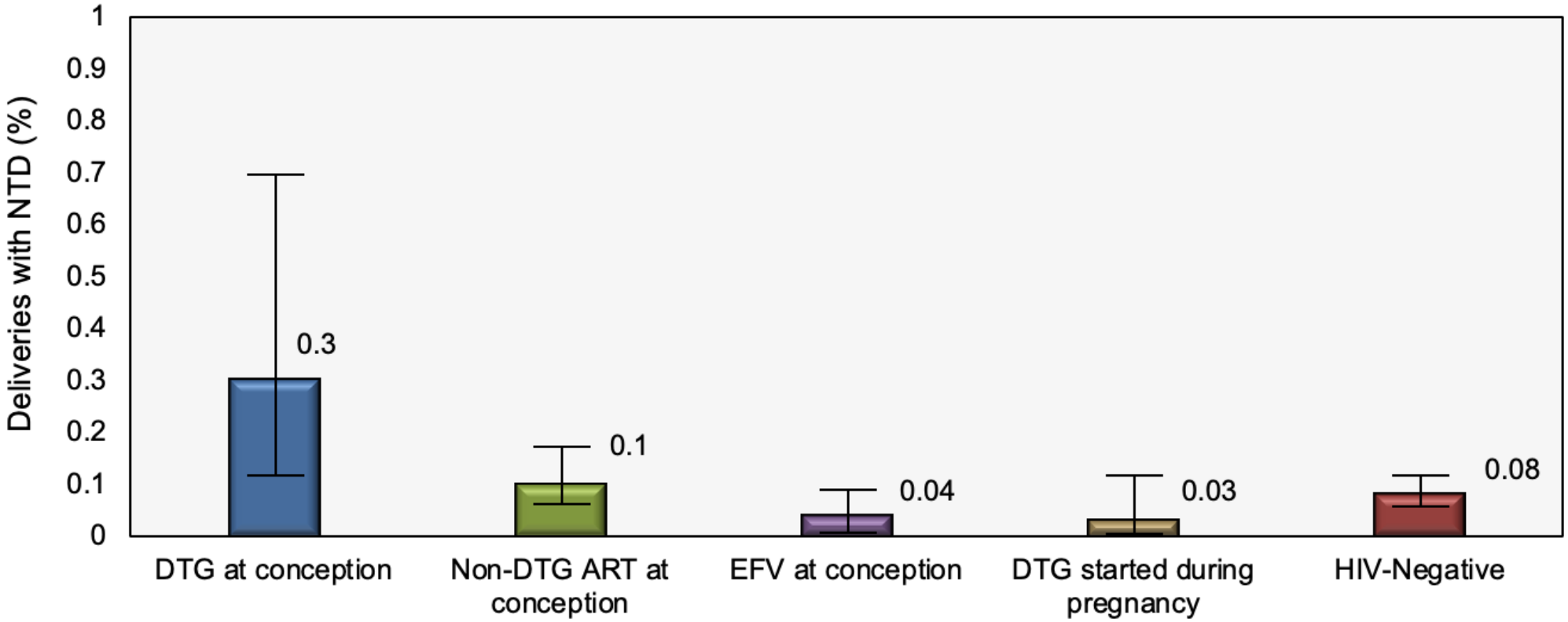
Antiretroviral Therapy During Pregnancy: *Safety*

Dolutegravir: Updated Data from Tsepamo Study

Neural Tube Defects According to Maternal HIV Status and ART



Zash R et al. N Engl J Med. 2019 Jul 22. and IAS 2019, Mexico City.

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Antiretroviral Therapy During Pregnancy: *Safety*

Dolutegravir: WHO Recommendation July 2019

WHO recommends dolutegravir as preferred HIV treatment option in all populations

22 July 2019 | News release | Mexico City

Based on new evidence assessing benefits and risks, the WHO recommends the use of the HIV drug dolutegravir (DTG) as the preferred first-line and second-line treatment for all populations, including pregnant women and those of childbearing potential.

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Antiretroviral Therapy During Pregnancy

DHHS Guidelines: 2022

- When choosing an antiretroviral (ARV) drug regimen for use in pregnant people, providers and patients should consider multiple factors, including adverse effects, drug interactions, pharmacokinetics (PKs), convenience of the individual drugs and drug combinations in the regimen, available pregnancy safety and outcome data, virologic efficacy in nonpregnant adults, and the patient's resistance test results and comorbidities **(AIII)**.
- The same regimens that are recommended for the treatment of nonpregnant adults should be used in pregnant people when sufficient data suggest that appropriate drug exposure is achieved during pregnancy (**AII)**.

Recommendations for the use of ARV during pregnancy: clinicalinfo.hiv.gov

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Antiretroviral Therapy During Pregnancy

DHHS Guidelines: 2022

- In most cases, people who present for obstetric care on fully suppressive ARV regimens should continue their current regimens **(AIII)**.
- PK changes in pregnancy may lead to lower plasma levels of some ARV drugs and necessitate increased doses, more frequent dosing, boosting, more frequent viral load monitoring, or a change in ARV regimen; **(AII)**.

Recommendations for the use of ARV during pregnancy: clinicalinfo.hiv.gov

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Preferred ARVs (DHHS Guidelines 2022)

Class	Preferred Agents	Considerations
NRTI	TDF-FTC or 3TC	
	TAF-FTC or 3TC	TAF/FTC is associated with fewer adverse birth outcomes and slightly higher gestational weight gain
	ABC-3TC	Use only if HLA-B*5701 negative; ABC/3TC not recommended in combination with EFV or boosted ATV if HIV RNA >100,000 copies/mL
INSTI	DTG	DTG preferred over RAL in acute HIV. DTG may be associated with a small (not significant) increase in NTD when taken during conception
	RAL	Twice daily dosing (400mg bid) is required during pregnancy
PI	ATV + RTV	Monitoring neonatal bilirubin levels is recommended
	DRV + RTV	Twice daily dosing is required during pregnancy

Source: 2021 HHS Perinatal Treatment Guidelines. AIDS Info (clinicalinfo.hiv.gov)

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Alternative ARVs (DHHS Guidelines 2022)

Class	Alternative Agents	Considerations
NRTI	AZT-3TC	Long experience but is BID and with hematologic toxicities
NNRTI	EFV + TDF + 3TC or FTC EFV + preferred dual NRTI backbone	Useful for patients who need a single tablet regimen and who cannot take an INSTI
	RLP + FTC + TDF or TAF RLP + preferred dual NRTI backbone	Do not use RLP in those with pVL > 100,000 or CD4 < 200. Avoid with PPIs, take with food RLP may reach low levels in 2nd or 3rd trimester – monitor pVL

Source: 2021 HHS Perinatal Treatment Guidelines. AIDS Info (clinicalinfo.hiv.gov)

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ARVs: Insufficient Data or Not Recommended

Insufficient Data to Recommend (DHHS Guidelines 2022)

Class	Agents	Considerations
INSTI	Bictegravir (BIC)/TAF/FTC	Only limited experience in pregnancy
NNRTI	Doravirine (DOR)	No data on use in pregnancy
Entry inhibitor	Ibalizumab (binds CD4)	No data on use in pregnancy. Reversible CD4 depletion in infant monkeys born to mothers receiving this agent

Not Recommended (DHHS Guidelines 2022)

Class	Agents	Considerations
Boosting agent	Any Cobicistat boosted drug	Inadequate levels of boosted drug in later stages of pregnancy leading to viral breakthroughs
Long-acting drugs	Cabotegravir and rilpivirine	Limited data on use in pregnancy

2021 HHS Perinatal Treatment Guidelines. AIDS Info (clinicalinfo.hiv.gov)

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Alternative ARVs in *Treatment experienced Patients in certain circumstances* (DHHS Guidelines 2022)

Drug	Considerations
Etravirine	Not recommended for use in nonpregnant ART-naive populations. Data about the use of ETR in pregnancy are limited.
Fostemsavir	Not recommended for use in nonpregnant ART-naive populations. Data about the use of FTR in pregnancy are limited.
LPV/r	Increased incidence of pre-term delivery. Must be dosed bid. More nausea
Maraviroc	Not recommended for use in nonpregnant ART-naive populations. Data about the use of MVC in pregnancy are limited.
Neviripine	More adverse effects (rash, hepatitis), low barrier to resistance
T-20	Not recommended for use in nonpregnant ART-naive populations.

Source: 2021 HHS Perinatal Treatment Guidelines. AIDS Info (clinicalinfo.hiv.gov)

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Odds and Ends: Other Important Guidance (DHHS Guidelines 2022)

Situation	Considerations
Presents pregnant on a suppressive 2 drug regimen	Continue 2 drug regimen with more frequent pVL monitoring (q1-2 months)
Presents pregnant on a drug regimen for which there are insufficient data on use in pregnancy	Continue the regimen with more frequent pVL monitoring (q1-2 months)
Presents pregnant on LA-CAB/RLP	Change ART
Develops acute HIV while pregnant	DTG-anchored regimen is preferred r/DRV-anchored regimen is an alternative
Care of F->M TG pregnant person	May experience heightened gender dysphoria and depression Testosterone can be teratogenic
Breast feeding (in the US)	Not recommended If breast feeding will occur – should infant be on ART > 4 weeks (of AZT) if mother is suppressed? Controversial

2021 HHS Perinatal Treatment Guidelines. AIDS Info (clinicalinfo.hiv.gov)

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