# Clinical pharmacology of mother to child HIV transmission prevention: update for clinicians

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Necessity to study drugs in pregnancy and breastfeeding

European treatment guidelines

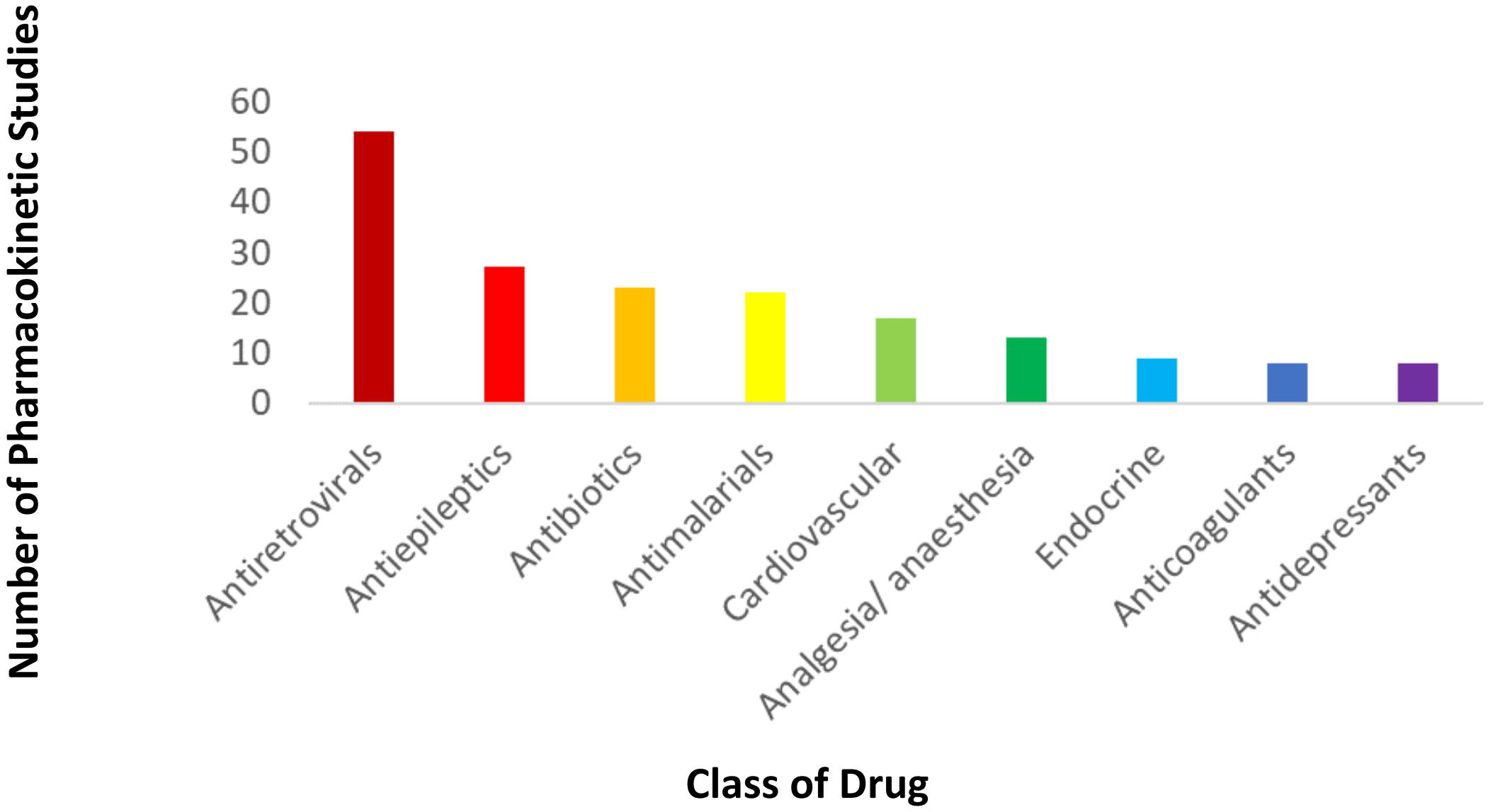
Clinically relevant pharmacokinetic changes in pregnancy

Antiretrovirals in breastfeeding

# Essential to study drug dosing and safety in the population who will be given those drugs

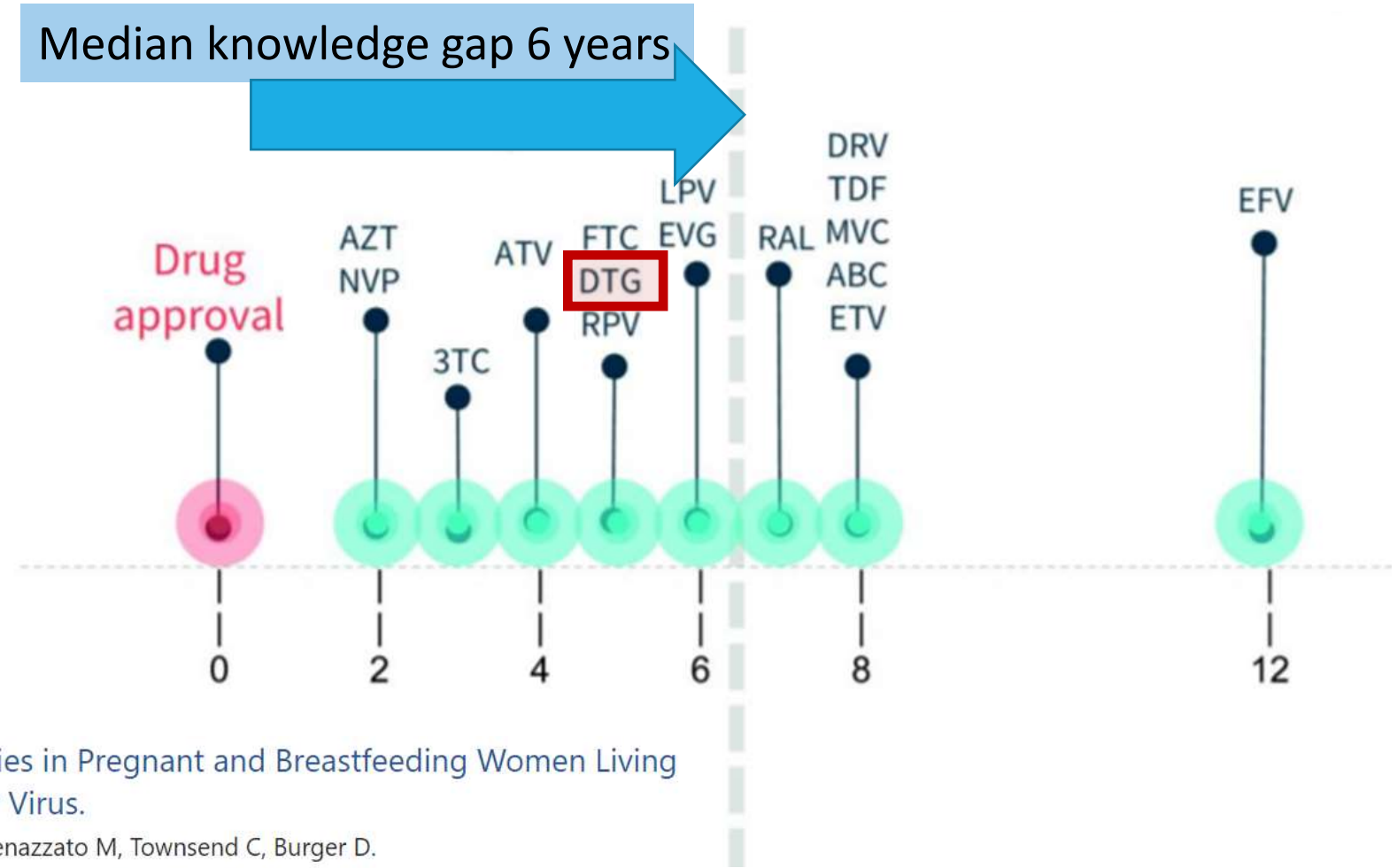
# Pariente 2016: Pregnancy-Associated Changes in Pharmacokinetics: A Systematic Review

PLoS Med 2016; 13(11): e1002160



# Long delay between licensing and pregnancy dosing data

Time to first published PK data in pregnancy

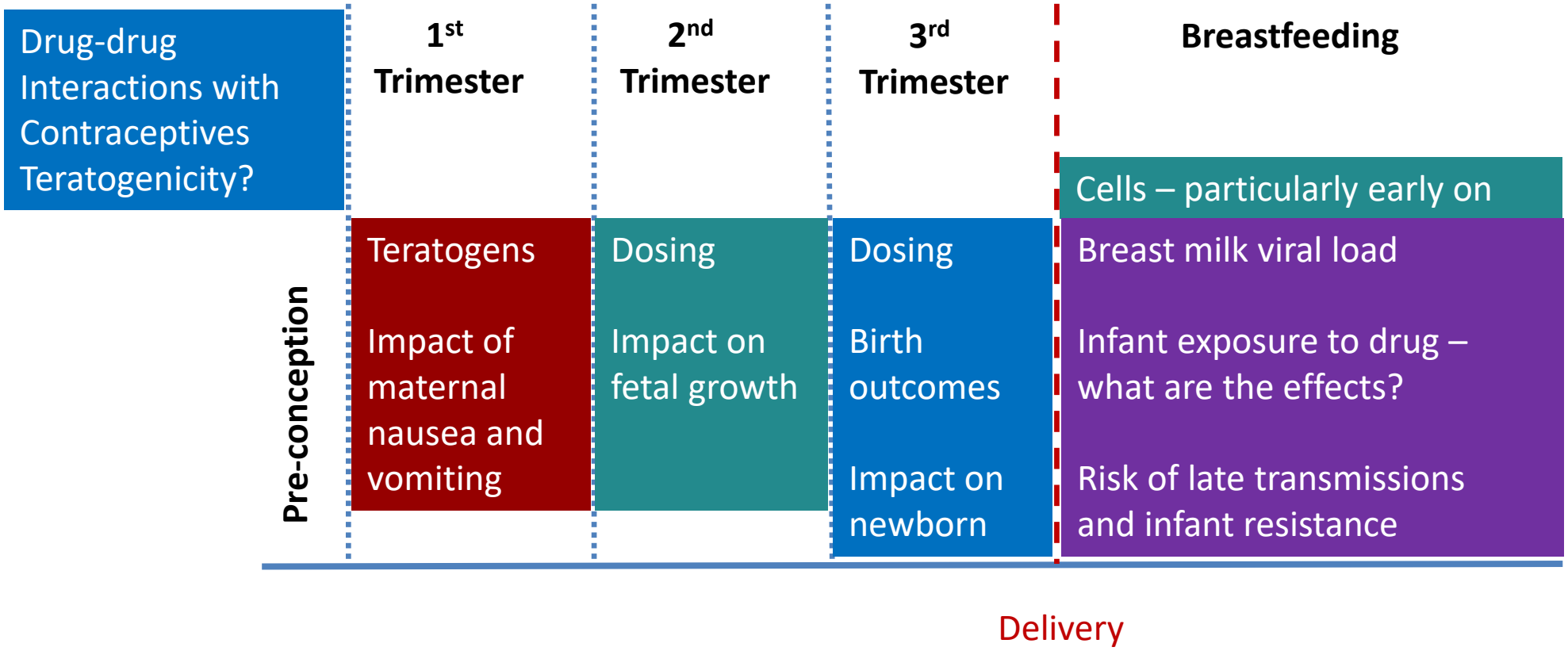



Importance of Prospective Studies in Pregnant and Breastfeeding Women Living With Human Immunodeficiency Virus.

Colbers A, Mirochnick M, Schalkwijk S, Penazzato M, Townsend C, Burger D.

Clin Infect Dis. 2019 Sep 13;69(7):1254-1258. doi: 10.1093/cid/ciz121.

# Different phases in reproductive life-cycle bring different risk-benefit considerations



## ABSORPTION

- Nausea = difficulty with adherence
- Vomiting = reduction in drug intake
- ↓ gastric emptying = ↓ maximal drug concentration
- ↑gastric pH = ↓absorption of weak acid and base molecules

## DISTRIBUTION

- ↑ total body water and expanded plasma volume = ↑volume of distribution of hydrophilic drugs
- ↑ body fat = ↑volume of distribution of lipophilic drugs
- ↓maternal albumin and albumin occupied by steroids/hormones = ↑ free drug fraction

Image by McGrath Creative: www.mcgrathcreate.com

## METABOLISM

- Enzyme induction/inhibition by progesterone/oestrogen = ↑↓ metabolism depending on drug
- Inhibited enzymes = CYP1A2, CYP2C19
- Induced enzymes = CYP2B6, CYP2C8, CYP2C9,CYP2D6, CYP2E1, CYP3A4, UGT

## ELIMINATION

- ↑ renal blood flow and ↑ glomerular filtration rate = ↑ elimination of renally eliminated drugs
- ↑hepatic blood flow = ↑ elimination of high hepatic extraction drugs

From Hazenberg et al 2021 Clinical Pharmacology and Therapeutics

# What ART is best for use in pregnancy?

Information from EACS guidelines 2021
https://eacs.sanfordguide.com/art/pregnancy-and-hiv

# Scenario 1: Women planning to become pregnant already on ART

Main aim: Continued viral load suppression

In some instances, may require temporary switch – individual clinical judgement

For DTG or regimens with insufficient data – needs full discussion and documentation

# Scenario 2: HIV diagnosed in early pregnancy

## Start ART as soon as possible

| Regimen | Main Requirements |
|---|---|
| **Recommended regimens** | |
| **2 NRTIs + INSTI (PREFERRED)** | |
| ABC/3TC + DTG or<br>ABC/3TC/DTG | DTG to be discussed with women considering to become pregnant or if to be used in first 6 weeks of pregnancy<br>HLA-B*57:01 negative<br>HBsAg negative |
| TDF/XTC or TAF/FTC<br>+ DTG | DTG to be discussed with women considering to become pregnant or if to be used in first 6 weeks of pregnancy.<br>TAF/FTC not recommended in first 14 weeks of pregnancy |
| TDF/XTC or TAF/FTC<br>+ RAL 400 mg bid | TAF/FTC not recommended in first 14 weeks of pregnancy |
| **2 NRTIs + PI/r** | |
| TDF/XTC or TAF/FTC<br>+ DRV/r 600 mg/100 mg bid | With food<br>TAF/FTC not recommended in first 14 weeks of pregnancy |

## Scenario 3: ART to start in late pregnancy

Consider integrase inhibitor-based regimen (faster virological reduction)

## Scenario 4: VL not suppressed in late pregnancy

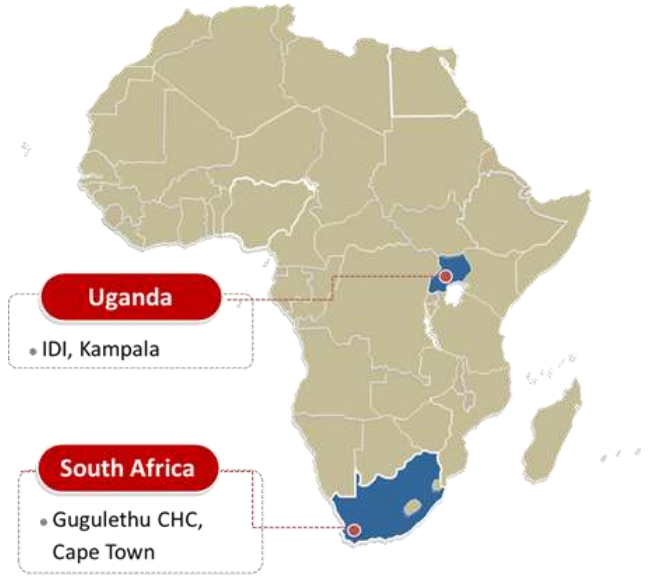
Consider intensification of regimen with integrase inhibitor

# Role of Integrase Inhibitors in Pregnancy
# Example: DolPHIN-1

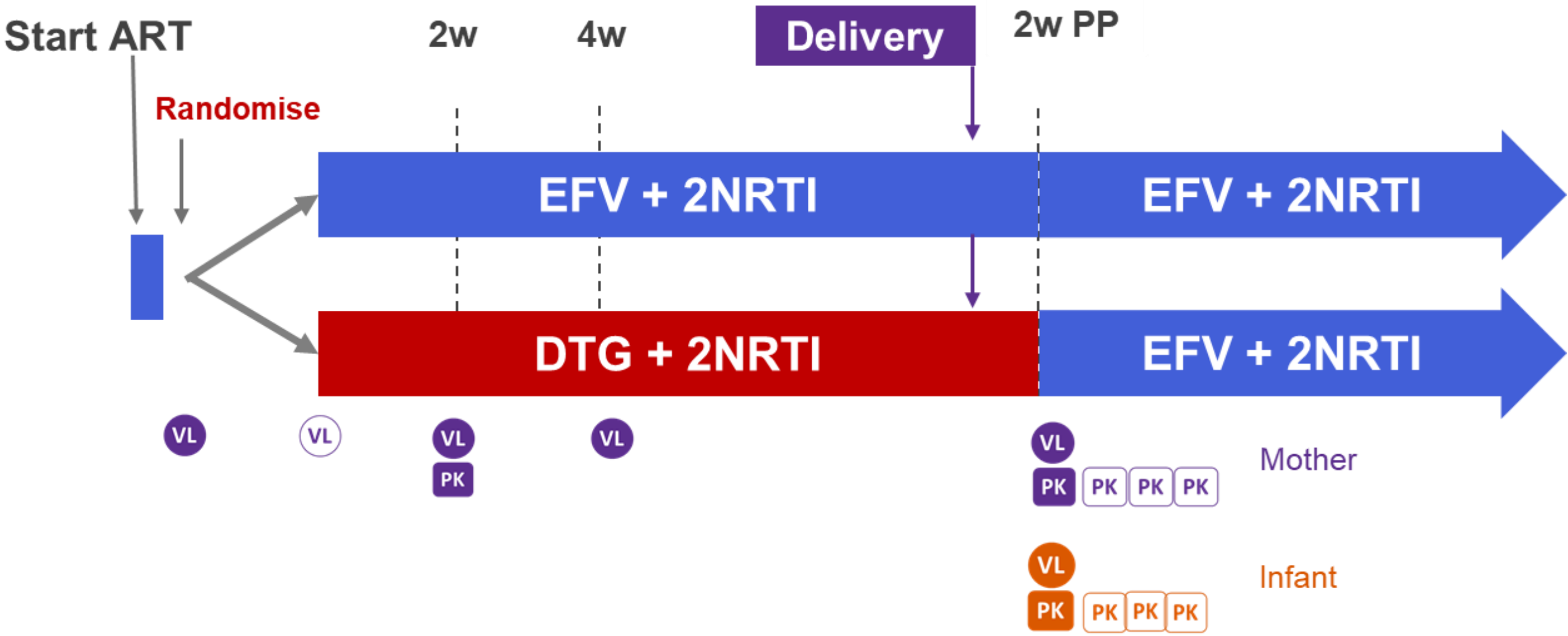
# Overall objectives of DolPHIN-1

The current EFV-based standard of care takes a median of 84 days to bring virologic suppression; in a mother in third trimester, this is too long

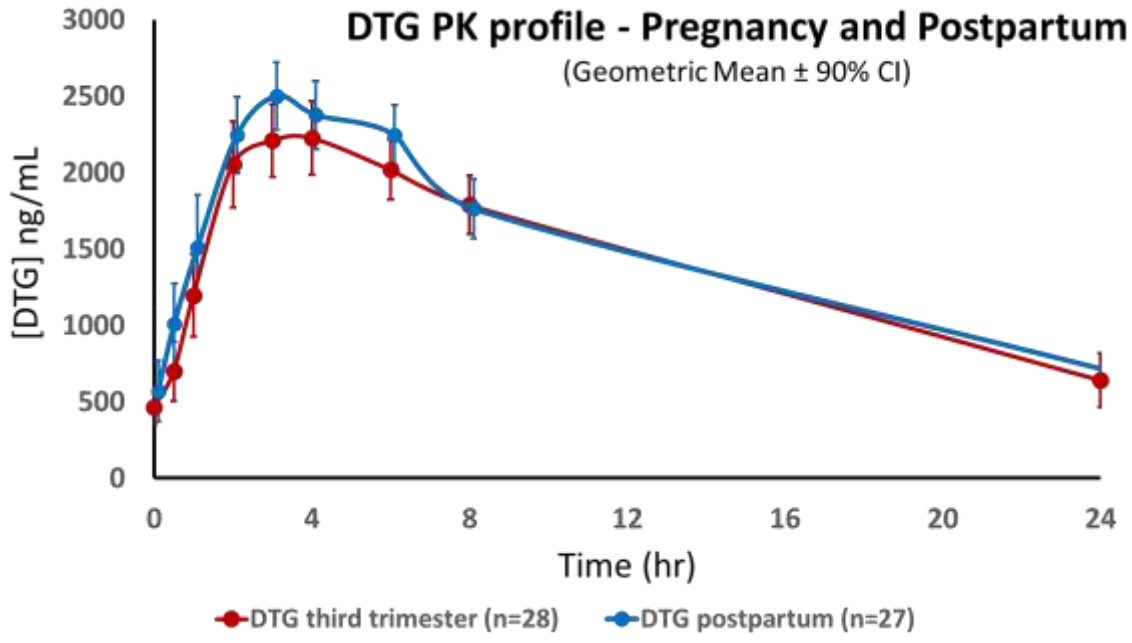
1. Is the 50mg once daily dose of DTG adequate in late pregnancy?
2. Is the virological suppression seen in non-pregnant adults also seen in pregnancy?
3. Is it safe?

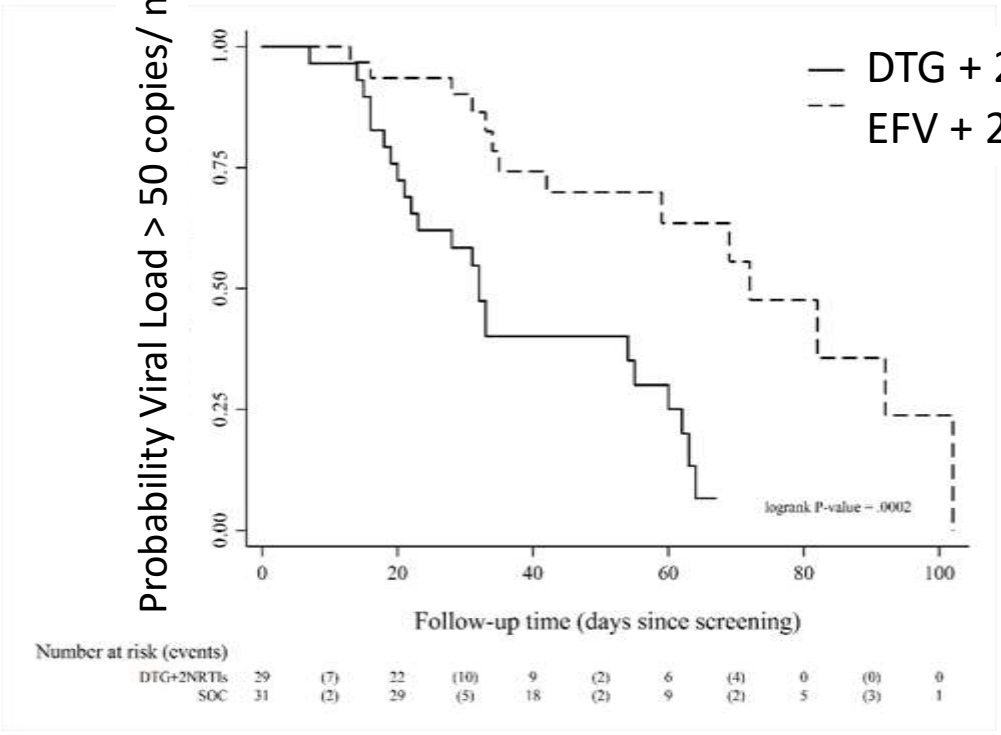


# Study Design



# Results and Impact




## British HIV Association Guidelines for HIV Treatment in Pregnancy

| | | |
|---|---|---|
| 6.4.1 | A woman who presents after 28 weeks should commence cART without delay. | 1B |
| 6.4.2 | If the viral load is unknown or >100,000 HIV RNA copies/mL, a three- or four-drug regimen that includes raltegravir 400 mg bd or dolutegravir 50 mg od is suggested | 2D |

## U.S. Dept. Health & Human Services HIV Rx Guidelines

**Recommendations for the Use of Antiretroviral Drugs During Pregnancy**

- 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.

World Health Organization

**Box 1. Recommendations: first- and second-line ART regimens**

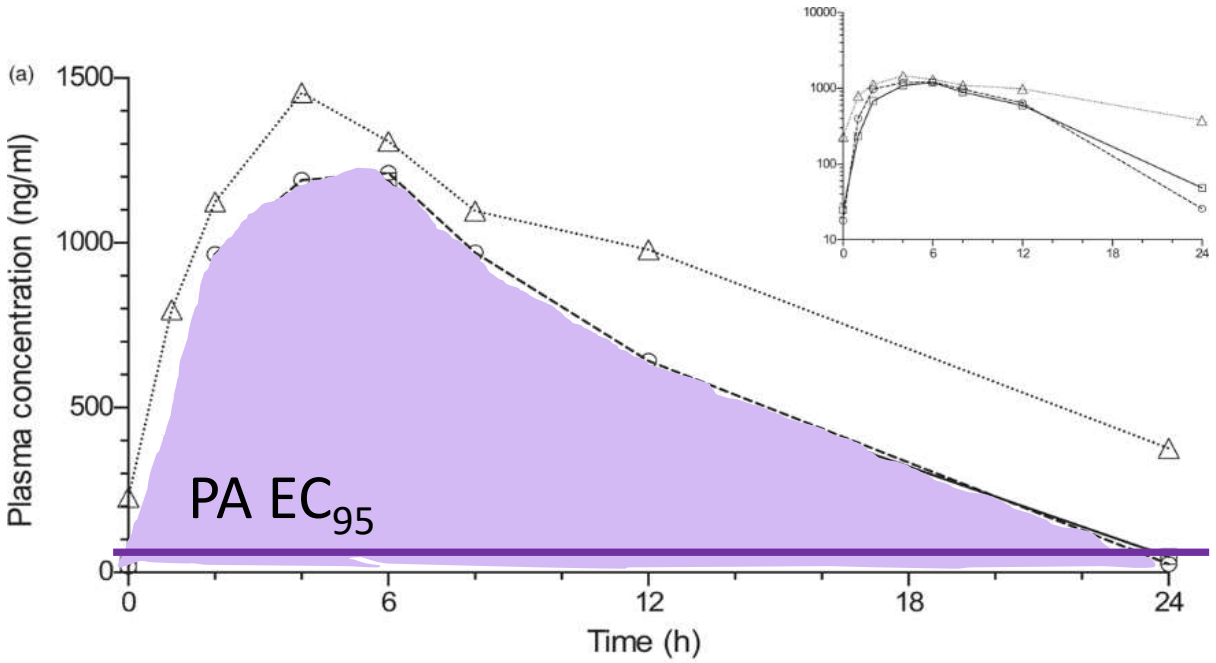
**First-line ART regimens[a]**

1. Dolutegravir (DTG) in combination with a nucleoside reverse-transcriptase inhibitor (NRTI) backbone is recommended as the preferred first-line regimen for people living with HIV initiating ART
   - Adults and adolescents[b] *(strong recommendation, moderate-certainty evidence)*
   - Infants and children with approved DTG dosing *(conditional recommendation, low-certainty evidence)*

Are any regimens unsuitable in pregnancy?

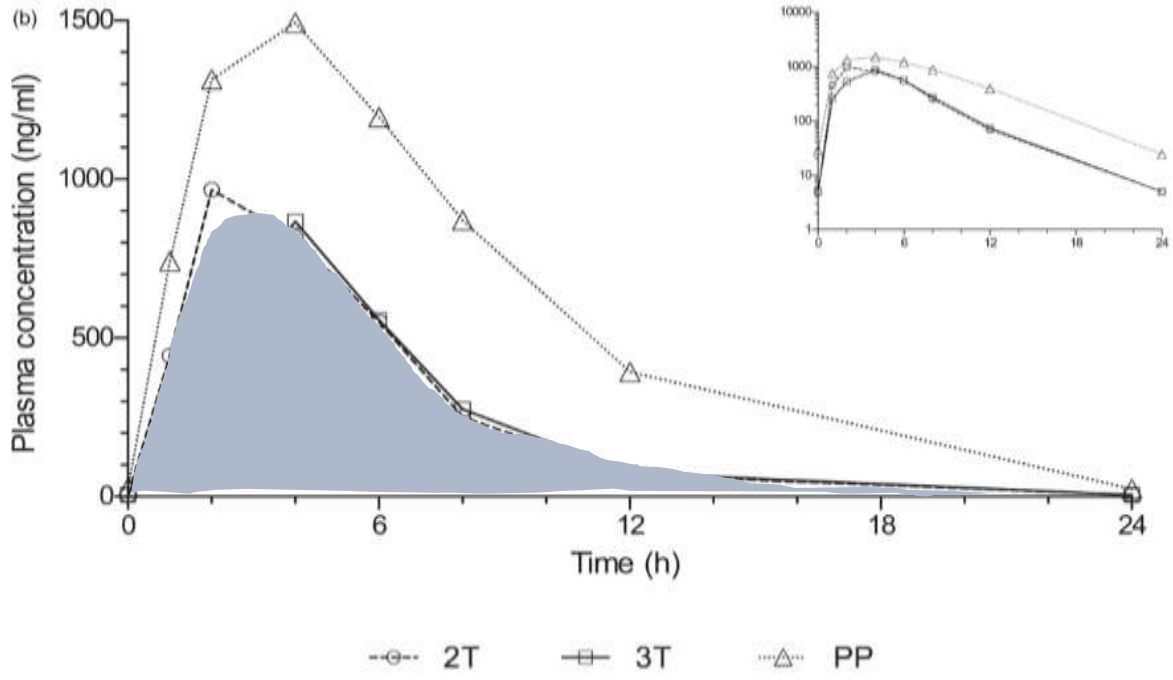
# Momper 2018, AIDS ; 32(17):2507-2516
# Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV

## Elvitegravir




$C_{24}$ 81% lower (T2) and 89% lower (T3) compared with paired postpartum

## Cobicistat

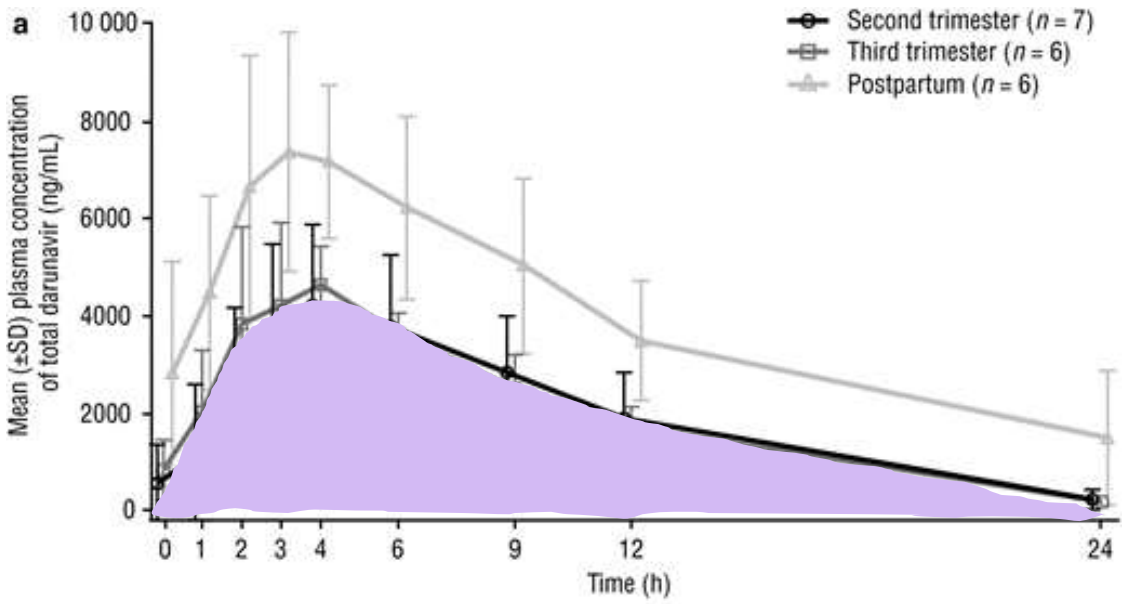



$C_{24}$ 60% lower (T2) and 76% lower (T3) compared with paired postpartum

Crauwels 2019, HIV Med ; 20(5):337-343.

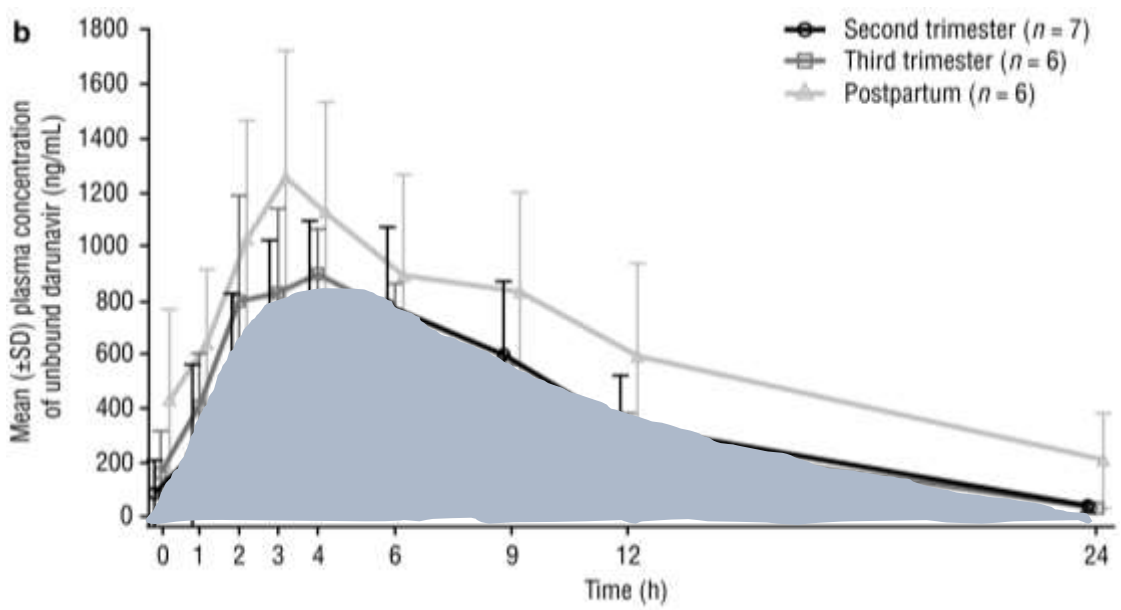
# Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant women receiving a darunavir/cobicistat-based regimen

## Darunavir




$C_{min}$ was 92% (T2) and 89% (T3) lower than in the postpartum period

## Cobicistat




$C_{min}$ was 83% (T2) and 83% (T3) lower than in the postpartum period

Similar, clinically significant changes for unbound DRV

# Decisions about breastfeeding can be complex

## Factors in Favour

Breastfeeding brings many benefits to both mother and infant[1]

Breastfeeding is often the socio-culturally acceptable choice[2]

Most ARVs (except PIs) transfer into milk and can be measured in the breastfed infant – but infant toxicities have never been reported[3]

## Factors of Concern

Risk of HIV transmission is not zero, even when mother is virologically suppressed[4]

Adherence can be challenging postpartum[5]

Infants who acquire HIV through breastfeeding whilst mother is on ART have high rates of drug resistance[6]

How much risk is acceptable? Who should choose?[7]

1. Infant morbidity, mortality, and **breast** milk immunologic profiles among **breast**-feeding HIV-infected and HIV-uninfected women in Botswana. Shapiro 2007, J Infect Dis. 2007 Aug 15;196(4):562-9

2. "Why aren't you breastfeeding?": How mothers living with HIV talk about infant feeding in a "breast is best" world Greene 2015, Health Women Int 26(8): 883-901

3. Waitt CJ, Garner P, Bonnett LJ, Khoo SH, Else LJ. Is infant exposure to antiretroviral drugs during breastfeeding quantitatively important? A systematic review and meta-analysis of pharmacokinetic studies. *J Antimicrob Chemother* 2015; **70**(7): 1928-41

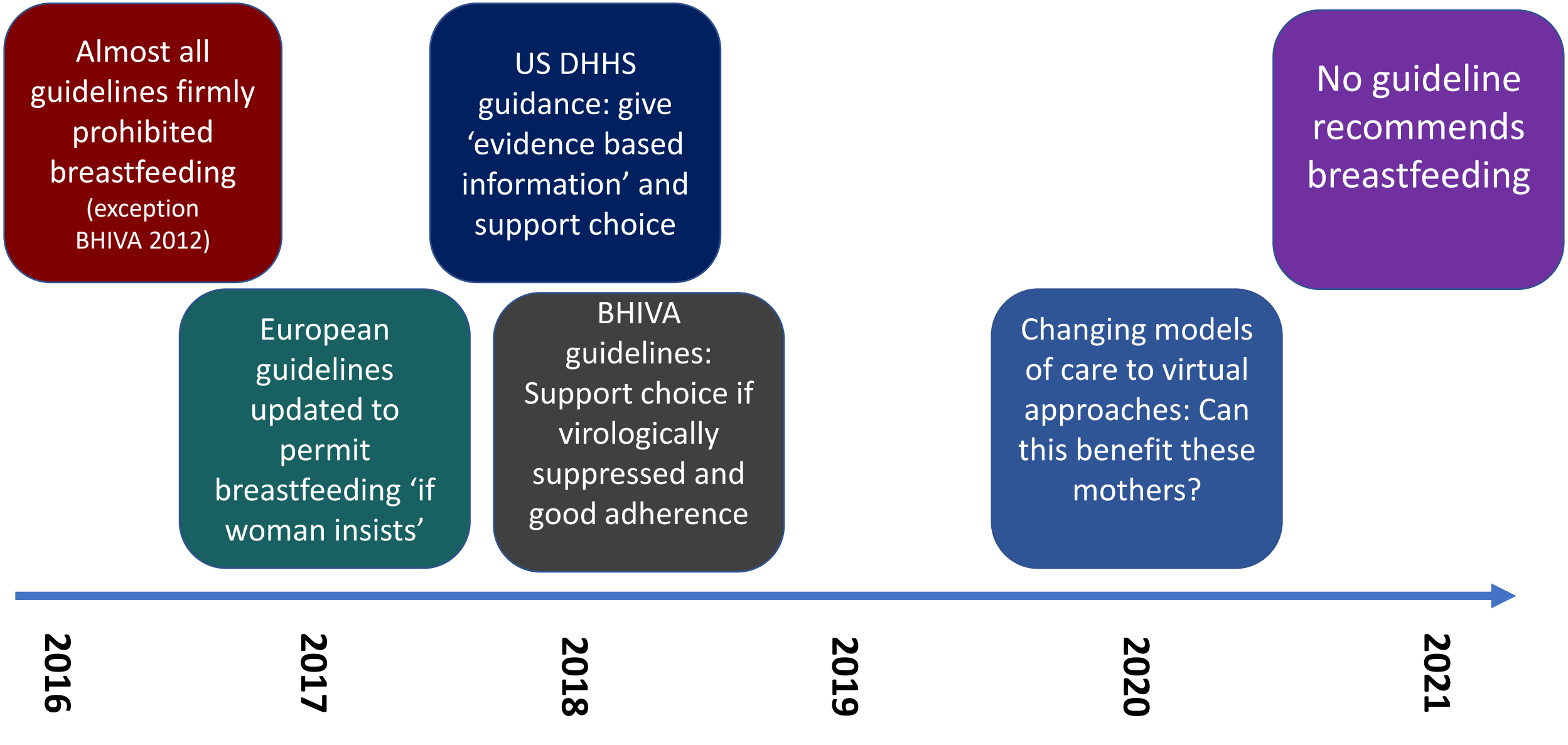
4. Van de Perre P, Rubbo PA, Viljoen J, et al. HIV-1 reservoirs in breast milk and challenges to elimination of breast-feeding transmission of HIV-1. *Science translational medicine* 2012; **4**(143): 143sr3

5. Nachega JB, Uthman OA, Anderson J, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. *AIDS* 2012; **26**(16): 2039-52

6. Fogel JM, Mwatha A, Richardson P, et al. Impact of maternal and infant antiretroviral drug regimens on drug resistance in HIV-infected breastfeeding infants. *Pediatr Infect Dis J* 2013; **32**(4): e164-9.

7. Does U=U for breastfeeding mothers and infants? Breastfeeding by mothers on effective treatment for HIV infection in high-income settings. Waitt 2018, *Lancet HIV* 5 (9): e531-536

# Guidelines from High Income Countries



# Mothers must remain at the centre of care

Adherence to maintain virological suppression more important than subtle differences between regimens

Patient-centred models important
More evidence need to define best practice
Support and regular discussion – start conversations early, respond to changing concerns and priorities

Absolute numbers small in all settings
Need to collaborative work to collect data and share learning

Regimens that support adherence likely to bring benefit – potential role of long-actings (and necessity to study these)

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# Questions?

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