ART and Pregnancy/Breastfeeding
Bournemouth 5th April 2019

Catriona Waitt

Senior Lecturer in Clinical Pharmacology, University of Liverpool

Wellcome Postdoctoral Clinical Training Fellow

@CatrionaWaitt

Declaration of interests relating to this presentation

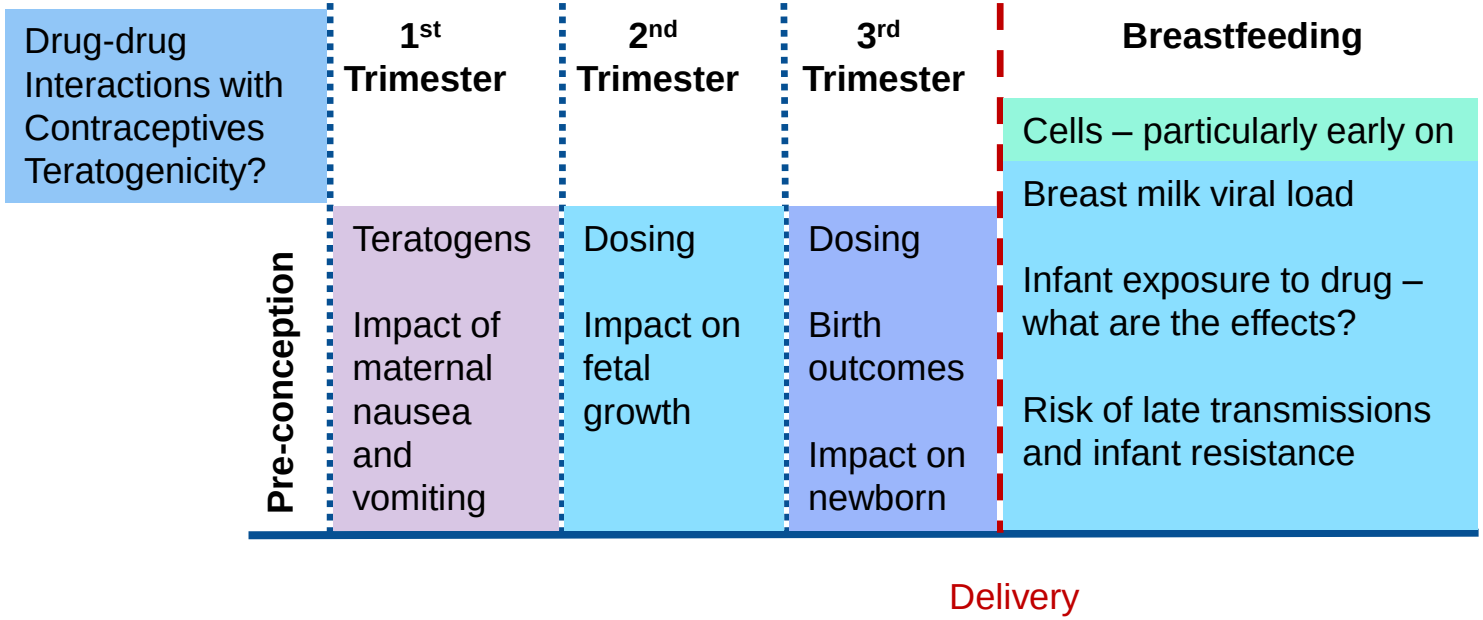
- None to declare

BHIVA
British HIV Association

Outline of Presentation

- Importance of research in pregnancy/ breastfeeding
- Pharmacokinetic changes in late pregnancy
- ARVs where PK differs in pregnancy
- Pharmacokinetics of drug transfer to breastfed infant
- ARV exposure to the breastfed infant
- Research gaps

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

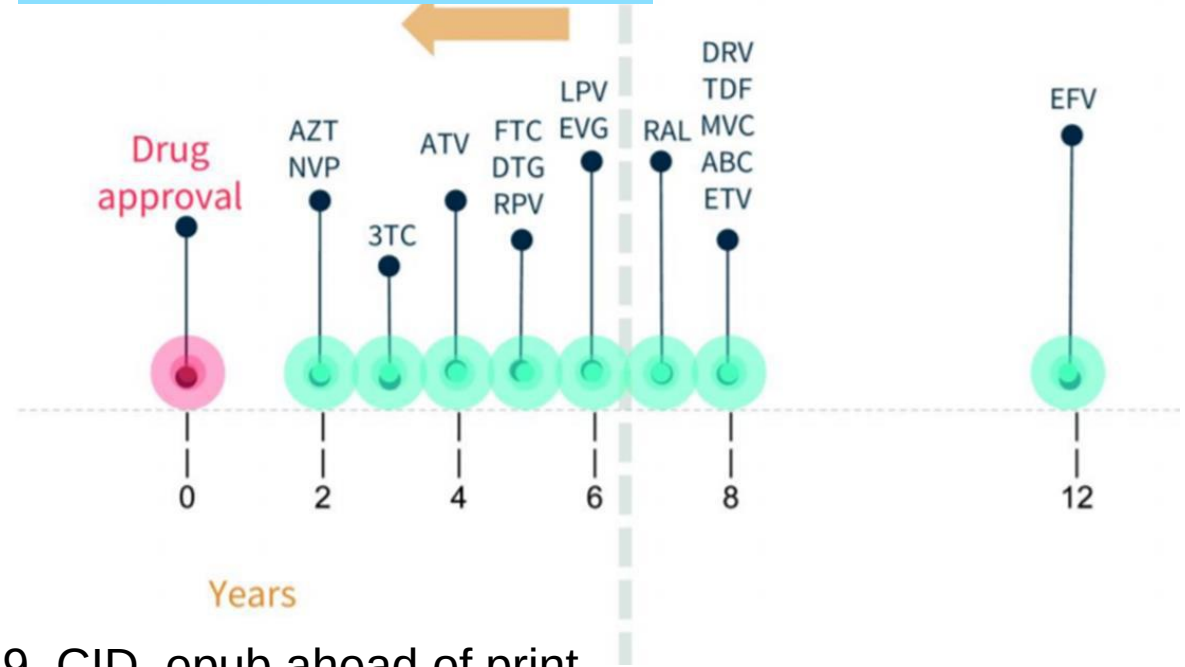


BHIVA
British HIV Association

Long delay between licensing and pregnancy dosing data

Time to first published PK data in pregnancy

Median knowledge gap 6 years



Colbers et al. 2019, CID, epub ahead of print

BHIVA British HIV Association

DOI: 10.1111/hiv.12720
HIV Medicine (2019), **20** (Suppl. 3), s2-s85

British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018

For a comprehensive overview, refer to:

Curr Pharm Des. 2019 Mar 20. doi: 10.2174/1381612825666190320162507. [Epub ahead of print]

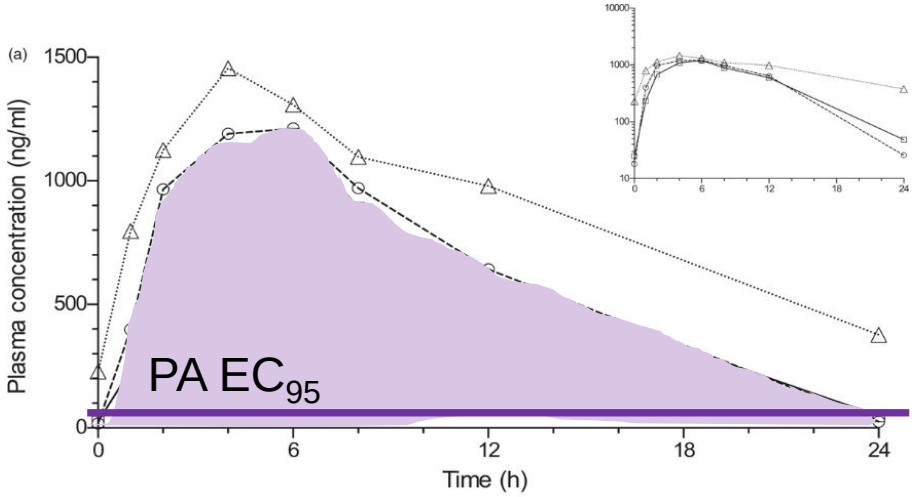
Pharmacokinetics, Placental and Breastmilk Transfer of Antiretroviral Drugs in Pregnant and Lactating Women Living with HIV.

Hodel EM[1], Marzolini C[1], Waitt C[1], Rakhmanina N[2].

BHIVA
British HIV Association

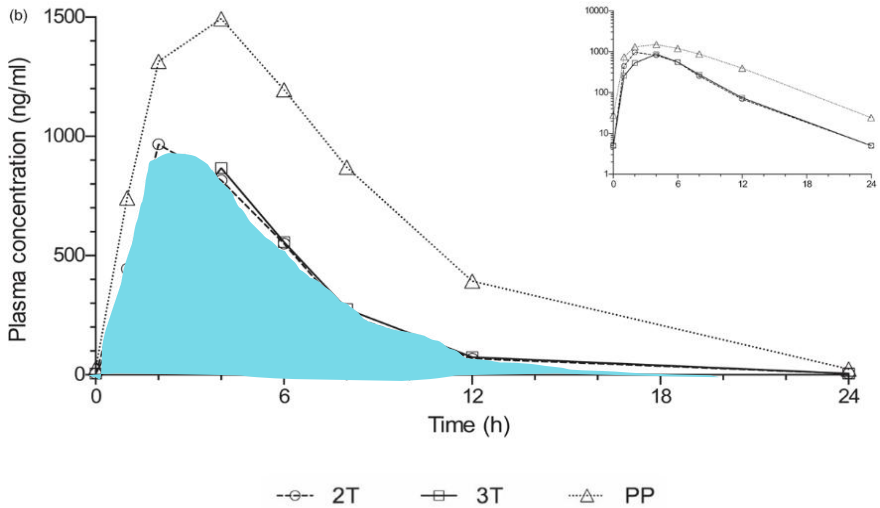
Momper 2018, AIDS ; 32(17):2507-2516
Elvitegravir/cobicistat pharmacokinetics in pregnant and postpartum women with HIV

Elvitegravir



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

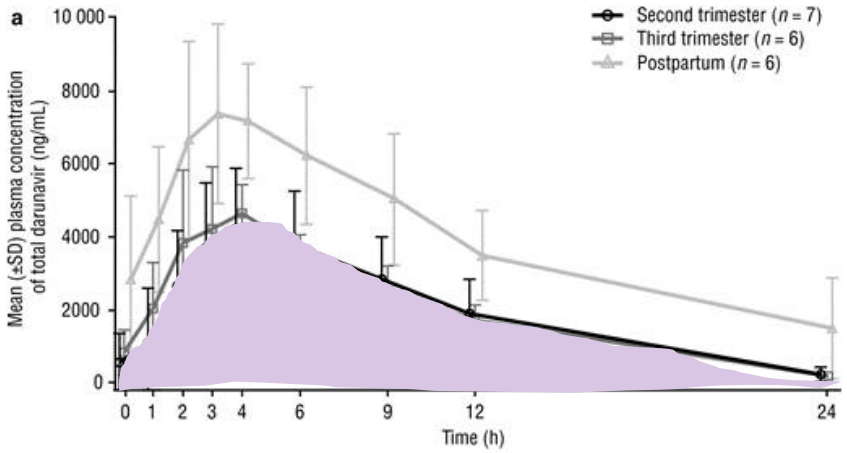
Cobicistat



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

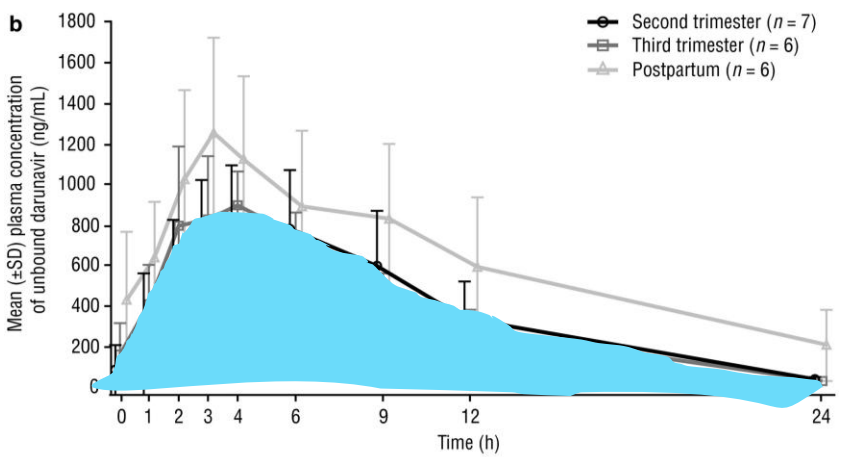
Crauwels 2019, HIV Med ; epub ahead of print
Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant women receiving a darunavir/cobicistat-based regimen

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

BHIVA
British HIV Association

DOI: 10.1111/hiv.12720
HIV Medicine (2019), **20** (Suppl. 3), s2-s85

British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018

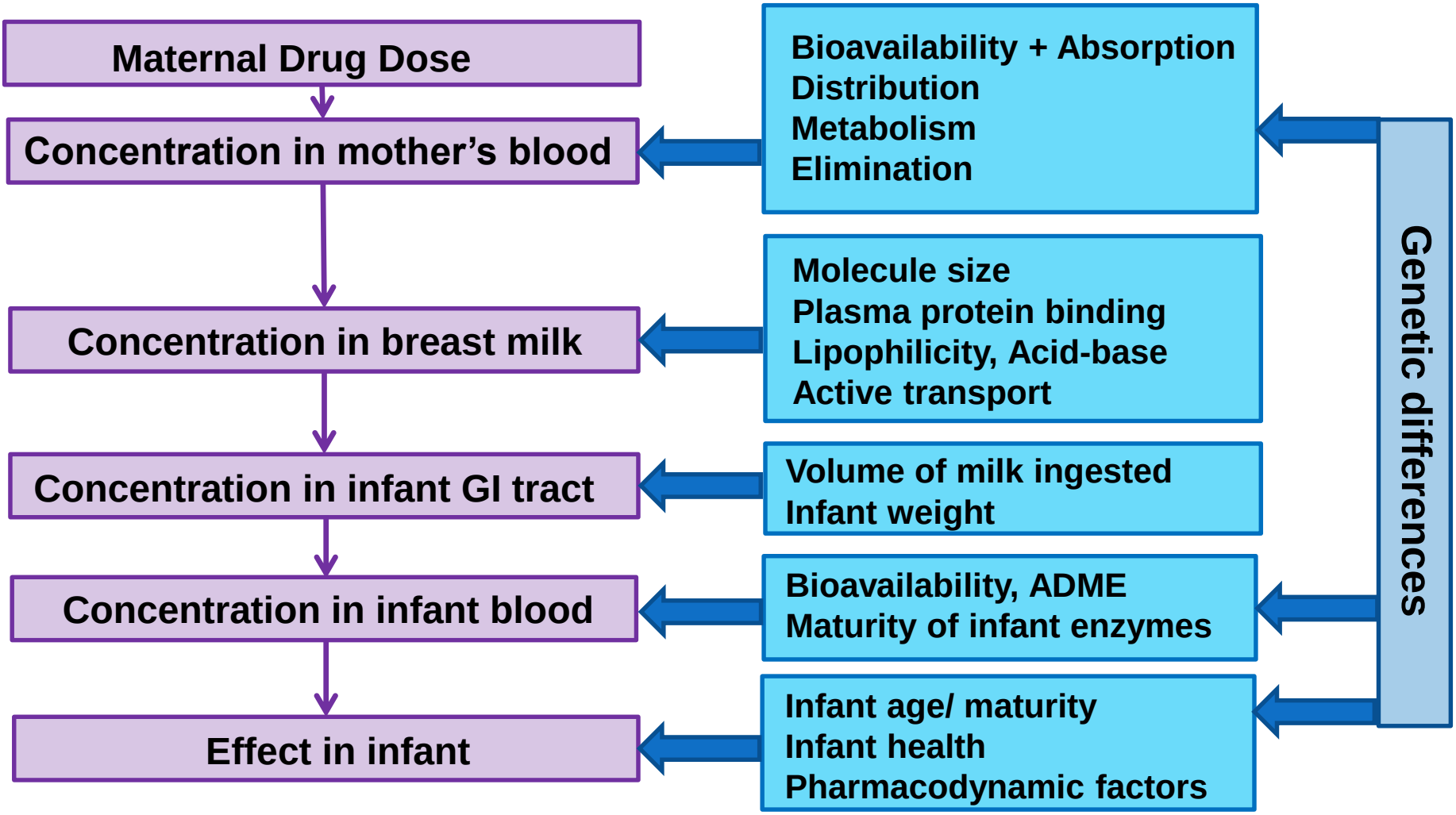
9.4.4	Women who are virologically suppressed on cART with good adherence and who choose to breastfeed should be supported to do so, but should be informed about the low risk of transmission of HIV through breastfeeding in this situation and the requirement for extra maternal and infant clinical monitoring.	1D
	When a woman decides to breastfeed, she and her infant should be reviewed monthly in clinic for HIV RNA viral load testing during and for 2 months after stopping breastfeeding.	1D
	Maternal cART (rather than infant pre-exposure prophylaxis [PrEP]) is advised to minimise HIV transmission through breastfeeding and safeguard the woman's health.	1D

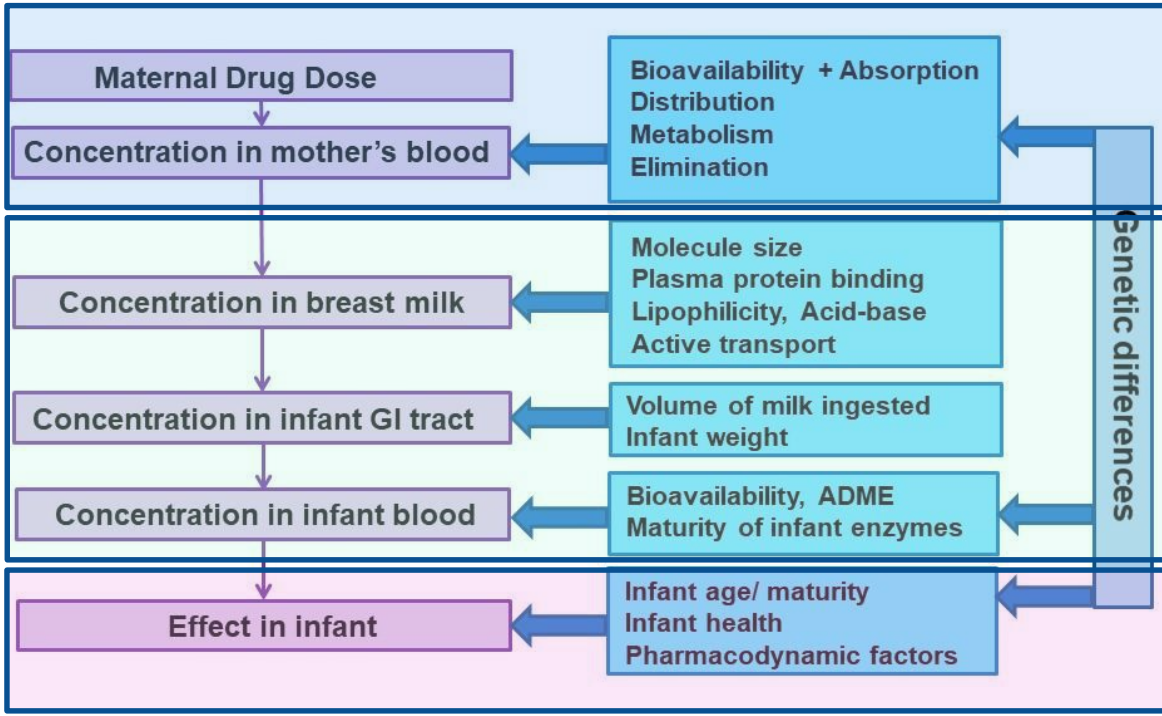
Pharmacokinetic lactation studies: FDA guidance

FDA recommendations for clinical studies in lactating women include the following situations:

- A drug under review for approval is expected to be used by women of reproductive age
- Marketed medications that are commonly used by women of reproductive age (e.g., antidepressants, antihypertensives, anti-infectives, diabetic and pain medications)

BHIVA
British HIV Association


Maternal Drug Dose
Concentration in mother's blood
Concentration in breast milk
Concentration in infant GI tract
Concentration in infant blood
Effect in infant
Bioavailability + Absorption
Distribution
Metabolism
Elimination
Molecule size
Plasma protein binding
Lipophilicity, Acid-base
Active transport
Volume of milk ingested
Infant weight
Bioavailability, ADME
Maturity of infant enzymes
Infant age/ maturity
Infant health
Pharmacodynamic factors
Genetic differences



British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018

Curr Pharm Des. 2019 Mar 20. doi: 10.2174/1381612825666190320162507 [Epub ahead of print]

Pharmacokinetics, Placental and Breastmilk Transfer of Antiretroviral Drugs in Pregnant and Lactating Women Living with HIV.

Hodel EM[1], Marzolini C[1], Waitt C[1], Rakhmanina N[2].

Is infant exposure to antiretroviral drugs during breastfeeding quantitatively important? A systematic review and meta-analysis of pharmacokinetic studies

Catriona John Waitt[1]*, Paul Garner[2], Laura Jayne Bonnett[3,4], Saye Hock Khoo[1] and Laura Jayne Else[1]

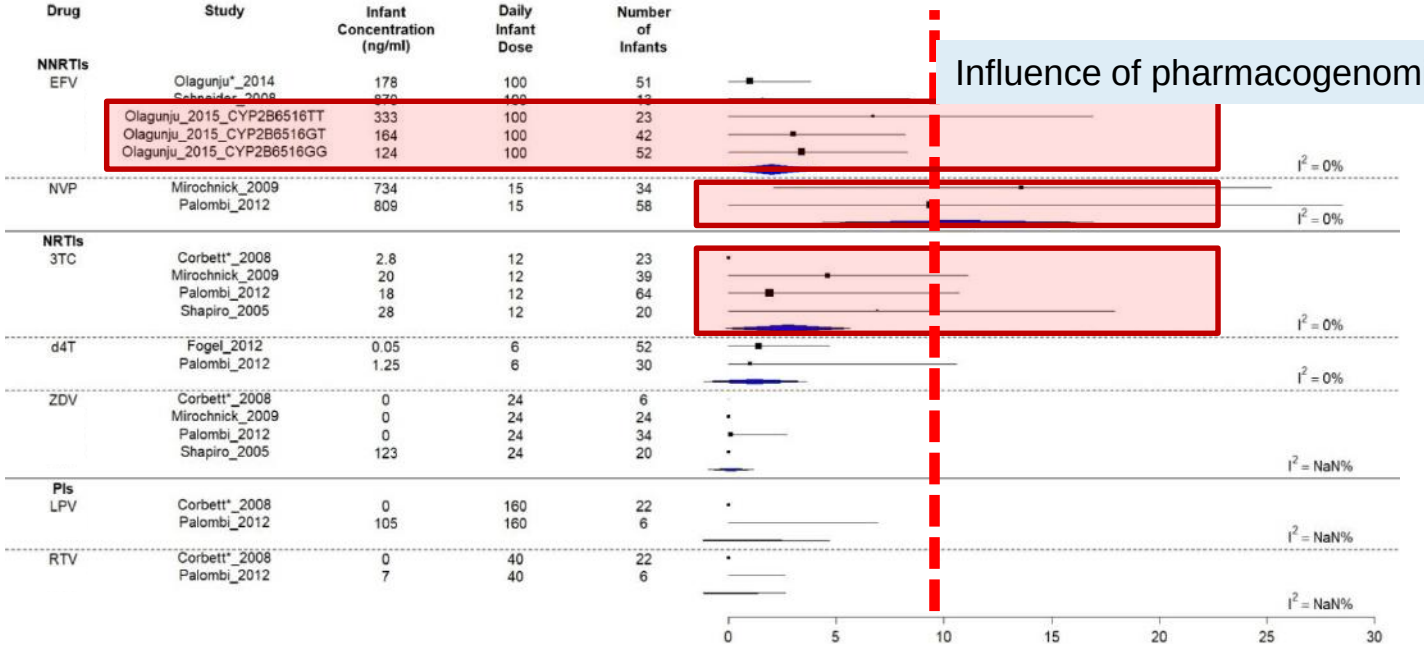
J Antimicrob Chemother. 2015 Jul;70(7):1928-41

Does U=U for breastfeeding mothers and infants?
Breastfeeding by mothers on effective treatment for HIV infection in high-income settings

Catriona Waitt, Nicola Low, Philippe Van de Perre, Fiona Lyons, Mona Loutfy, Karoline Aebi-Popp

BHIVA
British HIV Association

Interpretation of breast milk PK: ‘Relative Infant Dose’



[BM] as percentage of recommended paediatric dose

TFV (given as maternal TDF): Infant concentrations not detectable

DTG ~ 1% infant mg/Kg dose (note not recommended in infants)

Waitt and Bonnett, CROI 2018
Abstract 55

BHIVA British HIV Association

Questions about transmission risk:

- Does U=U in breastfeeding?
- What is transmission risk outside trial settings?
- What is significance of cell-associated DNA?
- What is the optimal frequency of VL monitoring?

Optimisation of Regimens

- What are the risks of infant HIV drug resistance and toxicity?
- Are any regimens safer for infant?
- Do any regimens have more pharmacokinetic forgiveness?

ART in Breastfeeding: Key Unanswered Questions And Research Perspective

Newer Drugs

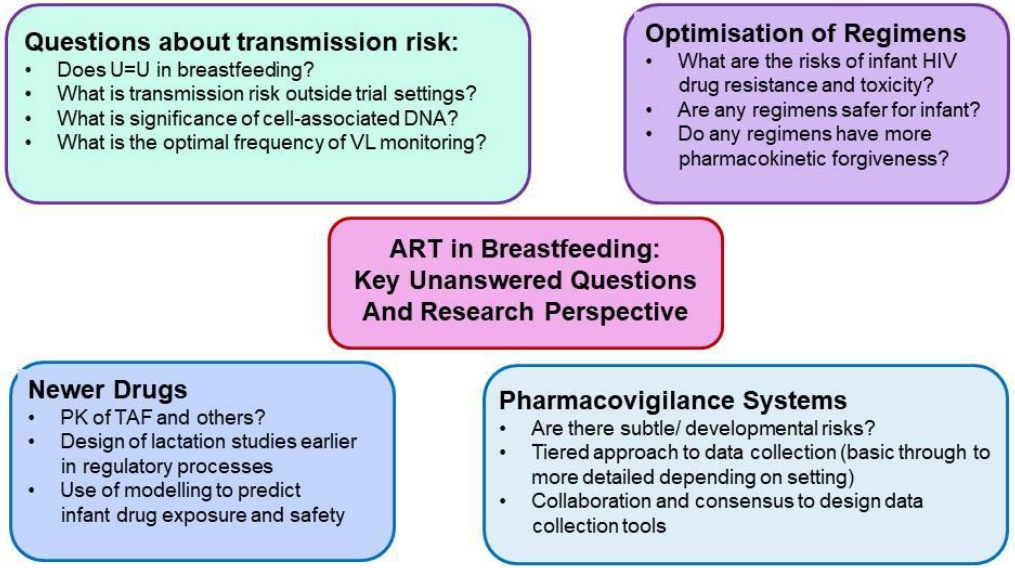
- PK of TAF and others?
- Design of lactation studies earlier in regulatory processes
- Use of modelling to predict infant drug exposure and safety

Pharmacovigilance Systems

- Are there subtle/ developmental risks?
- Tiered approach to data collection (basic through to more detailed depending on setting)
- Collaboration and consensus to design data collection tools

Transmission events increasingly rare
A single centre may not get meaningful sample size
Requires multi-centre, multi-national collaboration

Large safety studies will require international collaboration and consensus



Strengthened cross-disciplinary partnerships
Optimal design of PK studies
Use of sparse data from operational setting

Large sample sizes and extended follow-up
Consensus to determine priority drugs
Surveillance tools in routine clinical care

Waitt *et al*, Lancet HIV 2018

Questions and Discussion

BHIVA
British HIV Association