LMAP 2020

LIVERPOOL MASTERCLASS IN ANTIVIRAL PHARMACOLOGY

Drug Disposition in Pregnancy and Lactation

Catriona Waitt

cwaitt@liverpool.ac.uk

@CatrionaWaitt

Case 1: Diagnosis of HIV in late pregnancy

A 32 year-old journalist has recently moved to the UK from Spain.

She is approximately 6 months into her third pregnancy; she has had no antenatal care yet since her previous pregnancies were uncomplicated and she was busy with the international move.

At her first antenatal appointment (estimated 28 weeks gestation) she is diagnosed with HIV

What else do you wish to know clinically?
What tests would you do?
What would you tell her?
What would you start?

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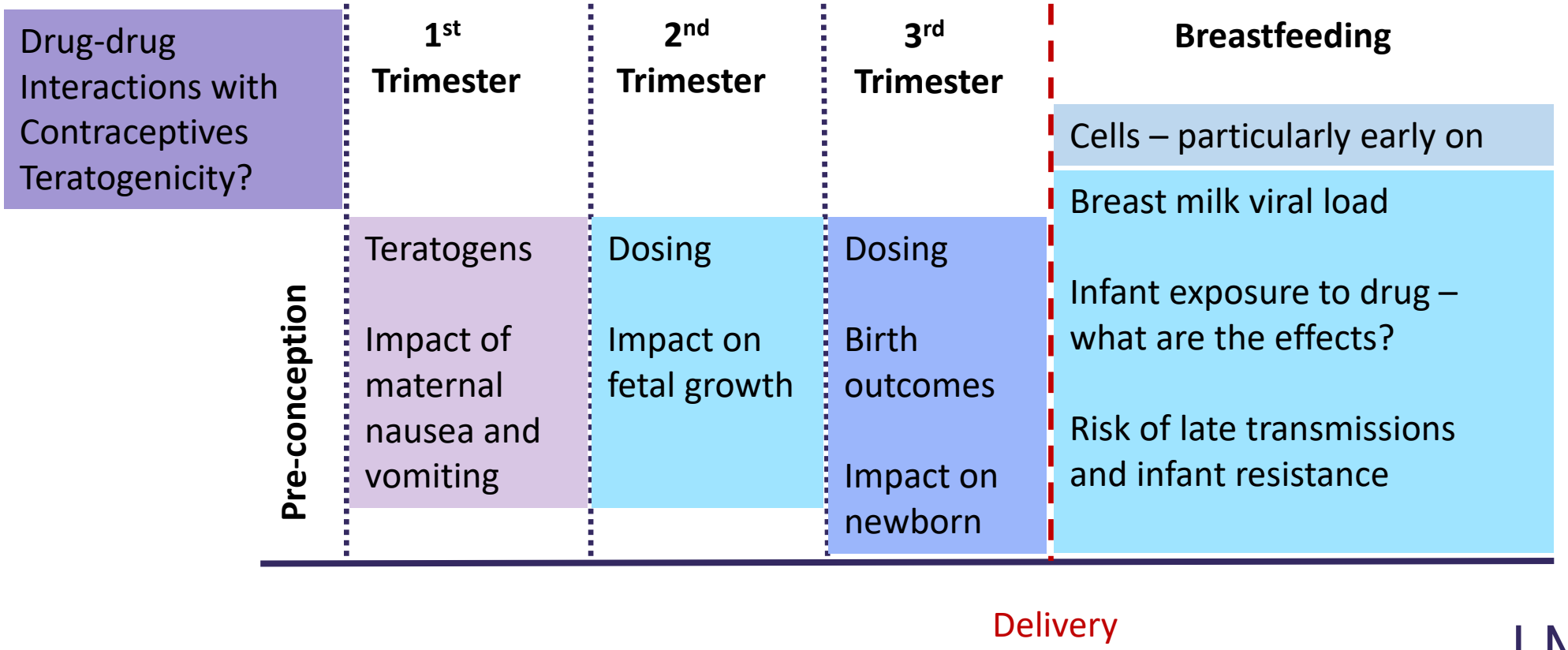
Different phases in reproductive life-cycle bring different risk-benefit considerations



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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

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

BHIVA
British HIV Association

British HIV Association guidelines for the management of HIV in pregnancy and postpartum 2018 (2020 third interim update)

For a comprehensive overview, refer to:

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

Hodel EM, Marzolini C, Waitt C, Rakhmanina N.

Curr Pharm Des. 2019;25(5):556-576. doi: 10.2174/1381612825666190320162507.

PMID: 30894103 Review.

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What to start and how to monitor

5.1.1	Sexual health screening is recommended for pregnant women newly diagnosed with HIV.	1B
5.2.4	In women who commence cART in pregnancy, a CD4 cell count should be performed as per routine initiation of cART with the addition of a CD4 count at delivery even if starting at CD4 >350 cells/mm^3.	1C
5.2.5	In women who commence cART in pregnancy, an HIV viral load should be performed 2–4 weeks after commencing cART, at least once every trimester, at 36 weeks and at delivery.	1C
5.2.6	In women commencing cART in pregnancy, liver function tests (LFTs) should be performed as per routine initiation of cART and then with each routine blood test.	1C
6.3.1	Women are recommended to start tenofovir DF or abacavir with emtricitabine or lamivudine as a nucleoside backbone.	2C
6.3.2	It is recommended that the third agent in cART should be efavirenz or atazanavir/r, as these are agents with the most safety data in pregnancy.	1C
	Rilpivirine (25 mg od), raltegravir (400 mg bd) or darunavir/r (600/100 mg bd) may be used as alternatives.	1C

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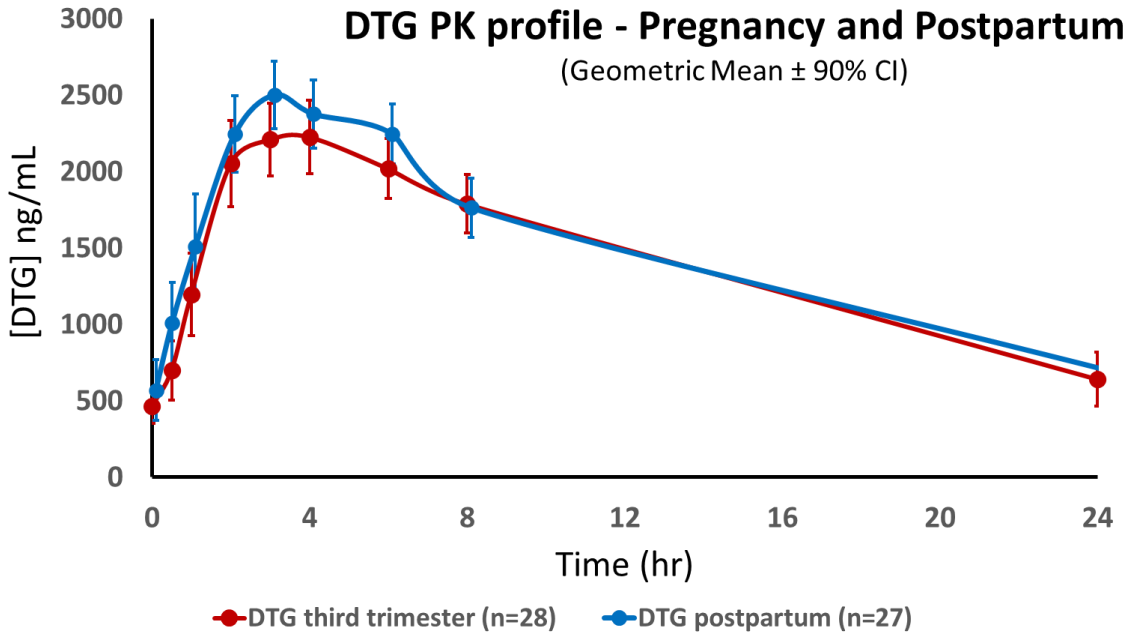
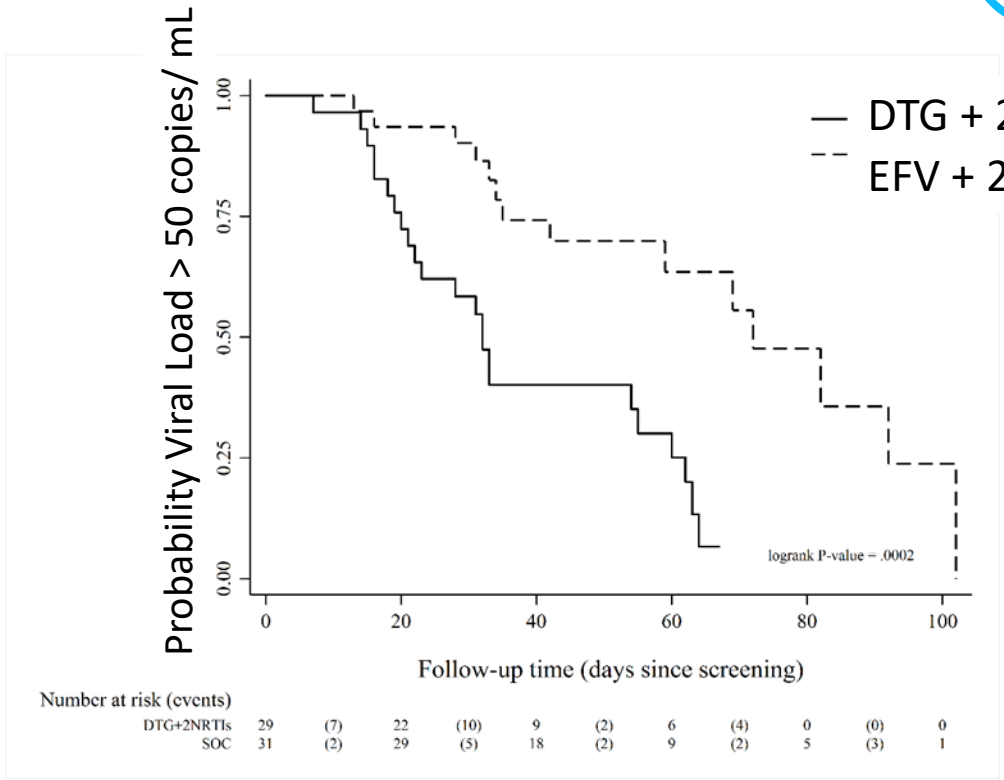
DolPHIN

1. Is the standard 50mg once daily dose sufficient in late pregnancy?
2. Is the rapid viral load reduction seen in non-pregnant adults also seen in pregnancy?
3. Is it safe?





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

Waitt et al, PLoS Med. 2019 Sep 20;16(9):e1002895

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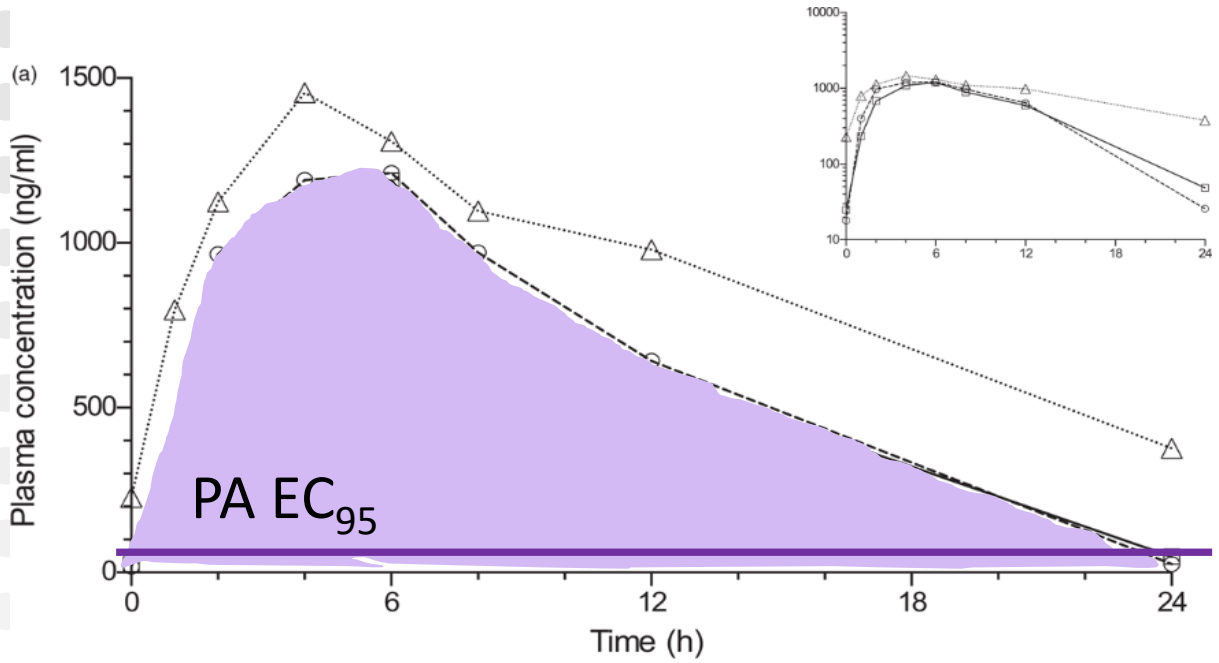
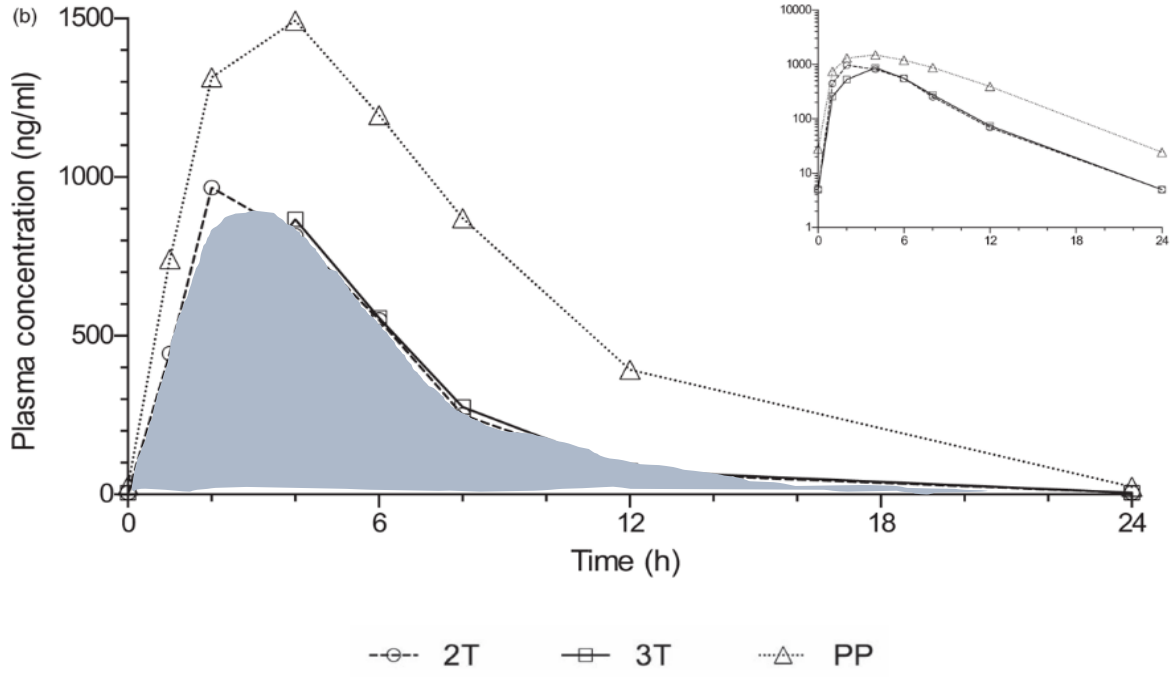
Are any regimens unsuitable in pregnancy?

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

Elvitegravir



Cobicistat



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

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

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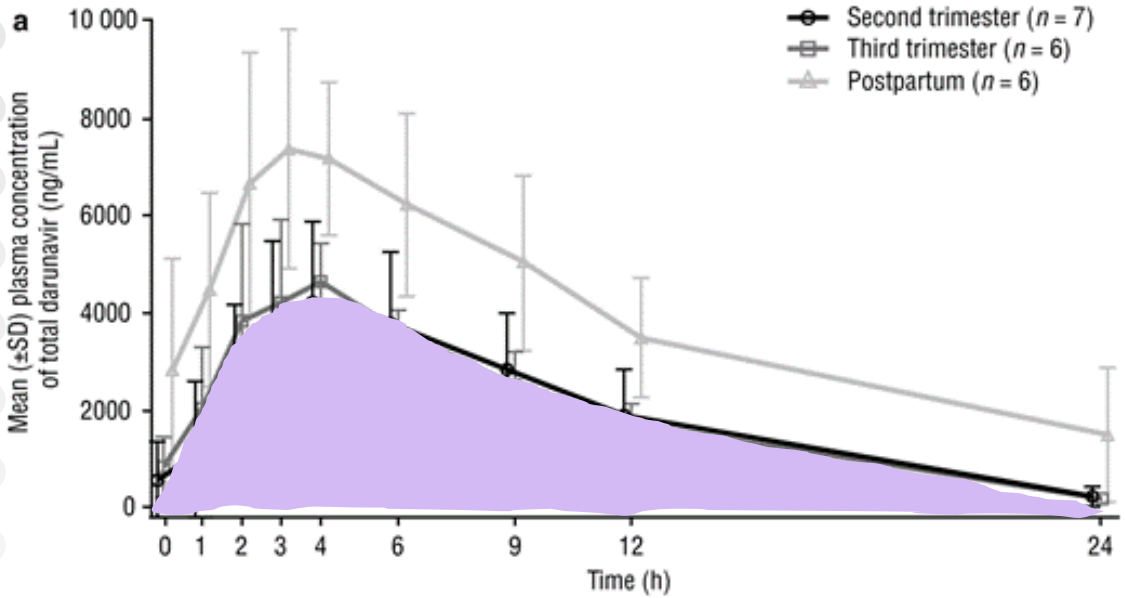
Crauwels 2019, HIV Med ; epub ahead of print

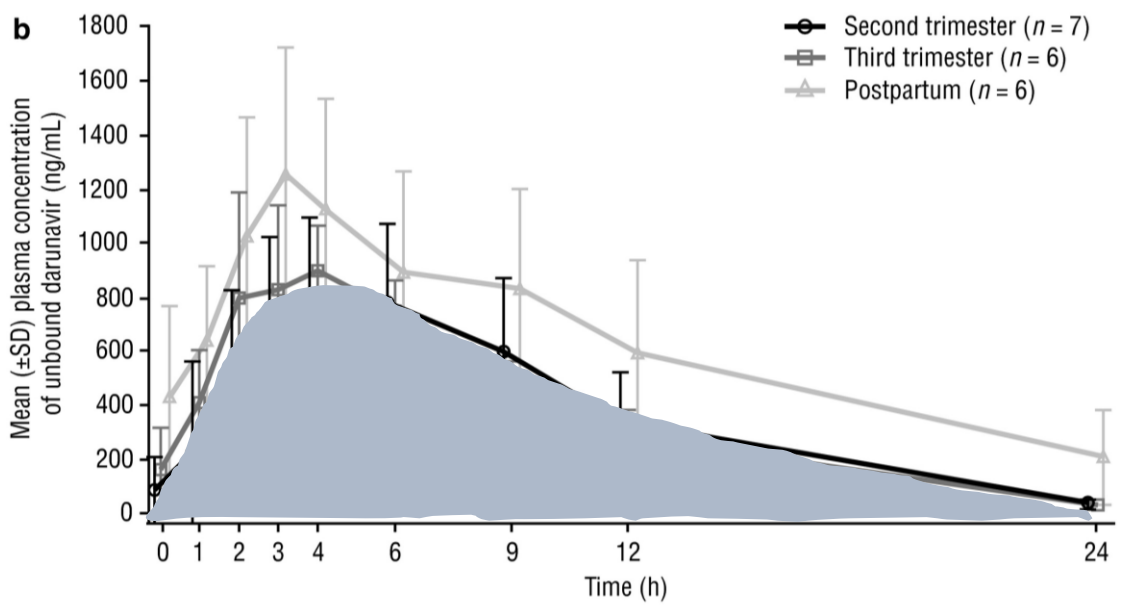
Reduced exposure to darunavir and cobicistat in HIV-1-infected pregnant women receiving a darunavir/cobicistat-based regimen

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

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Case 2: Decision to breastfeed in a high-income country

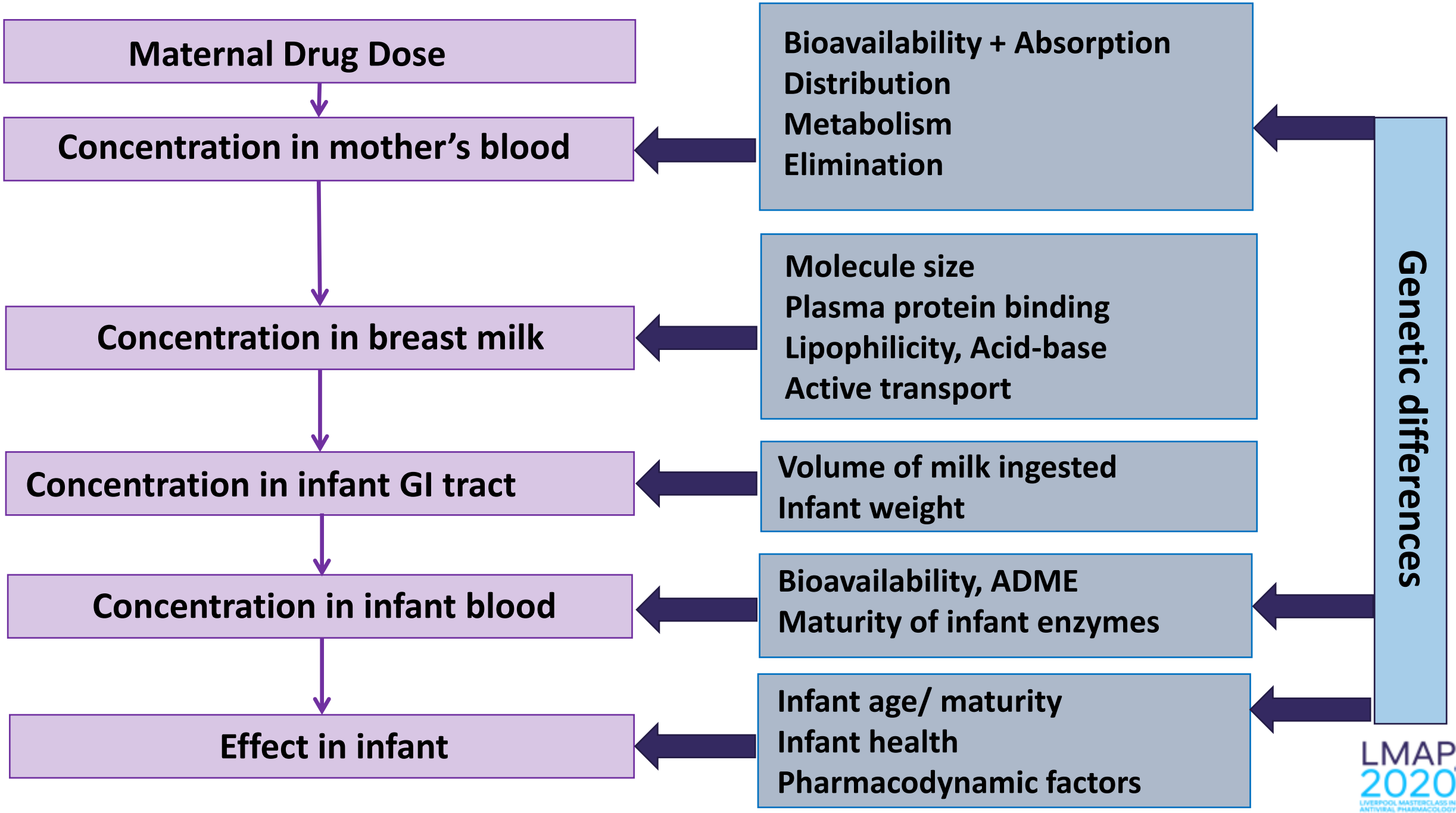
A 32 year old Ugandan doctor is doing her PhD in London. She was diagnosed with HIV at the age of 13 (presumed vertical transmission) and is currently virologically suppressed on atazanavir-ritonavir, lamivudine and tenofovir disoproxil fumarate. She is approaching her EDD with her first child and has expressed a desire to breastfeed.

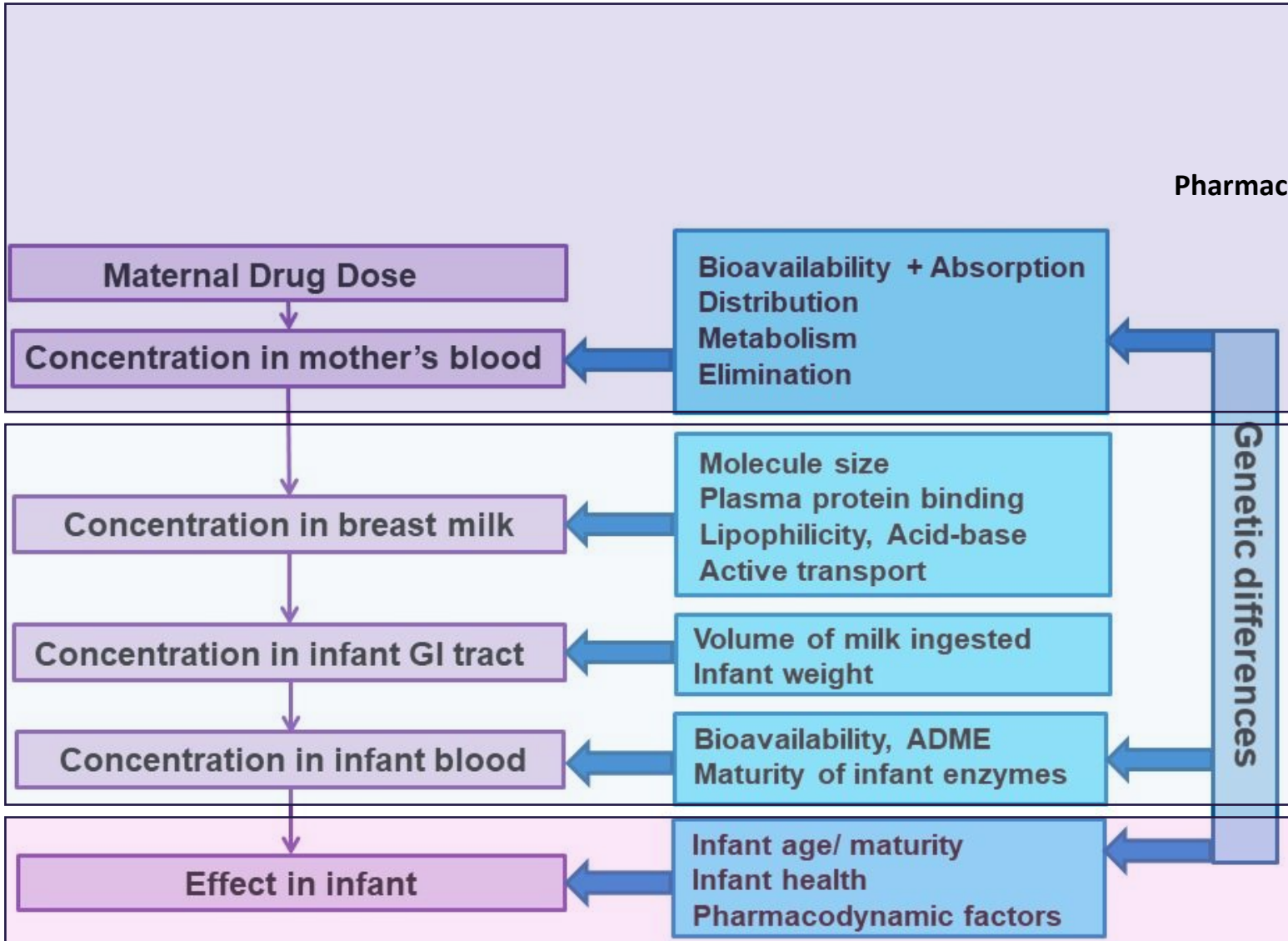
Is there anything else you wish to know?
Do you want to do any tests?
Are you happy with her current regimen?
What will you discuss with her?

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


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



BHIVA guidelines for the management of HIV in pregnancy and postpartum 2018

Pharmacokinetics, placental and breastmilk transfer of antiretroviral drugs in pregnant and lactating women living with HIV
Hodel et al 2019
Curr Pharm Des, epub ahead of print

Is infant exposure to antiretroviral drugs during breastfeeding quantitatively important? A systematic review and meta-analysis of pharmacokinetic studies
Waitt et al 2015
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 in high-income countries
Waitt et al 2018
Lancet HIV. 2018 Sep;5(9):e531-e536

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What is Known

- NRTI and NNRTI enter the breastmilk and can be measured in the infant
- If HIV infection occurs, the infant may develop drug resistance as a result of low-level drug exposure
- Even with 'perfect' adherence and maternal plasma VL <50, occasional vertical transmissions can occur

What is Not Known

- The exact rate of MTCT when adherence is good and VL <50
- Optimal frequency of maternal plasma and breast milk VL
- Any subtle, longer-term risks or benefits to the breastfed infant exposed to maternal ART
- Risk – benefit ratio has not been fully defined

COMES INTO EFFECT 9 NOVEMBER 2020

Guidance on professional standards and ethics for doctors

Decision making and consent

General Medical Council

Working with doctors Working for patients

Principle **one**	All patients have the right to be involved in decisions about their treatment and care and be supported to make informed decisions if they are able.
Principle **two**	Decision making is an ongoing process focused on meaningful dialogue: the exchange of relevant information specific to the individual patient.
Principle **three**	All patients have the right to be listened to, and to be given the information they need to make a decision and the time and support they need to understand it.
Principle **four**	Doctors must try to find out what matters to patients so they can share relevant information about the benefits and harms of proposed options and reasonable alternatives, including the option to take no action.
Principle **five**	Doctors must start from the presumption that all adult patients have capacity to make decisions about their treatment and care.