Guideline Controversies
An Infectious Diseases Physician Prospective

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Case 1

- TM is a 30 year-old woman who presents to your office very delighted as just found out she is pregnant.
- She was diagnosed 2½ years ago with HIV-1 and started on efavirenz/TDF/FTC. She has had an undetectable HIV RNA viral load for the past 2 years.
- She has no co-morbidities, is without other sexually transmitted infections, and takes no medications. Her only complaint is intermittent nausea.
- Estimated gestation is 8 weeks

Labs	Result
HIV-1 RNA, copies/ml at diagnosis	47,800
Current HIV-1 RNA, copies/ml	<20
CD4+ cell count, cell/mm^3 at diagnosis	305
Current CD4+ cell count, cell/mm^3	678
HLA-B 5701	Negative
HIV genotype at diagnosis	Wild type
Hepatitis B	Immune
Hepatitis C	Negative
CBC, renal, liver function tests	Normal

Case 1 – What would you do?

- Continue EFV/TDF/FTC/
- Change ART regimen to EVG/Cobi/TDF/FTC
- Change ART regimen to EFV+AZT+3TC
- Change ART regimen to RAL+TDF+FTC
- Change ART regimen to DTG+ABC+3TC
- Discontinue ART and restart during the second trimester
- Something else

Safety of Efavirenz in 1st Trimester Pregnancy Metanalysis of 21 Studies

- 2026 live births among women with 1st trimester efavirenz exposure.
  - 44 congenital anomalies giving pooled proportion of 1.63% (95% CI) 0.78–2.48].
    - One neural tube defect.
- Twelve studies reported birth outcomes of women exposed to efavirenz or nonefavirenz-containing regimens during 1st trimester.
  - Pooled analysis found no differences in overall risks congenital anomalies between these two groups (relative risk 0.78, 95% CI 0.56–1.08).
  - Incidence of neural tube defects was low, 0.05%
  - Results of overall analysis were not statistically different to the raw proportion of congenital anomalies reported by the Antiretroviral Pregnancy Registry (2.3%, 95% CI 1.3–3.7).

Ford N, Mofenson L, et al. AIDS. 2014; 28 (Suppl 2): S123-S131

Controversy on whether TDF+FTC associated with adverse neonatal outcomes

Table 1. Results from Siemieniuk R et al. BMJ. 2017; 358;j3961

Outcome	TDF+FTC cART	AZT+3TC cART
Premature Births (<34 weeks)	74	32
Stillbirth/neonatal mortality (Low/medium resource settings)	304	69
Stillbirth/neonatal mortality (High resource settings)	66	15

Promise Study Investigators Response

- Rates of spontaneous abortion & stillbirth not significantly different between AZT alone, AZT-cART and TDF-cART arms
- Both AZT-cART and TDF-cART regimens associated with increased preterm delivery <37 weeks compared to AZT-alone
- Preterm delivery <37 weeks during Period 2 was not significantly different between AZT-ART and TDF-ART (p=0.77).
- Only preterm delivery (<34 weeks) was different, with a higher rate of very preterm delivery observed in TDF-ART compared to AZT-ART arm (p=0.04), though TDF-ART very preterm rate not significantly different than AZT-alone arm
- Botswana Observational study compared birth outcomes (2014-2016), among HIV-infected women starting ART Compared with a regimen of TDF-FTC-EFV, all other regimens, including AZT-based ART had higher risk of adverse outcome.

Case 1B

- TM is a 30 year-old woman who presents to your office very delighted as just found out she is pregnant.
- She was diagnosed 1 years ago with HIV-1 and started on dolutegravir/ ABC/3TC shortly after diagnosis. She has had an undetectable HIV RNA viral load for the last 10 months.
- She has no co-morbidities, is without other sexually transmitted infections, and takes no medications. Her only complaint is nausea.
- Estimated gestation is 8 weeks

Labs	Result
HIV-1 RNA, copies/ml at diagnosis	47,800
Current HIV-1 RNA, copies/ml	<20
CD4+ cell count, cell/mm^3 at diagnosis	305
Current CD4+ cell count, cell/mm^3	678
HLA-B 5701	Negative
HIV genotype at diagnosis	Wild type
Hepatitis B	Immune
Hepatitis C	Negative
CBC, renal, liver function tests	Normal

Case 1B – What would you do?

- Continue DTG/TDF/FTC
- Change ART regimen to EVG/Cobi/TDF/FTC
- Change ART regimen to EFV+AZT+3TC
- Change ART regimen to RAL+TDF+FTC
- Change ART regimen to DRV/r+TDF+3TC
- Change ART regimen to DRV/r+TAF+FTC
- Discontinue ART and restart during the second trimester
- Something else

DHHS Recommendations: Women on Suppressive ART who Become Pregnant

- “It is recommended that women conceiving on a cART regimen should continue this. “
  - “Exceptions are: non-standard regimens, for example protease inhibitor (PI) monotherapy, regimens that have been demonstrated to show lower pharmacokinetics in pregnancy and protease inhibitors demonstrated to increase risk of pre-term delivery. “(BHIVA)
- *“In general, HIV-infected pregnant women receiving ART who present for care during the first trimester should continue treatment during pregnancy, assuming the regimen is tolerated and effective in suppressing viral replication*” (DHHS)

Case 2

- SL is a 25 year-old woman referred from the obstetrical clinic when HIV test (4th generation) was found to be positive
- She has no co-morbidities, is without other sexually transmitted infections, and takes no medications. Her only complaint is nausea. She is delighted with the pregnancy.
- Estimated gestation is 9 weeks
- You discuss initiating ART, and SL asks "what would you do?"

Labs	Result
HIV-1 RNA, copies/ml	8,300
CD4+ cell count, cell/mm^3	595
HLA-B 5701	Negative
HIV genotype	Pending
Hepatitis B	Immune
Hepatitis C	Negative
CBC, renal, liver function tests	Normal

Case 2 – What would you do?

- Immediately start ART and adjust the regimen, if necessary, when the genotype returns
- Wait until results of the genotype are available and then select a regimen
- Wait to start ART until well into the second trimester
- Start ART at 24 weeks
- Something else

Guideline Controversy
When to Start Antiretroviral Rx in Pregnancy

BHIVA[1]	DHHS[2]	WHO[3]
Start ART as soon as they are able to do so in 2nd trimester, BUT within the 1st trimester if VL >100,000 copies/mL and/or CD4 <200. cell. All women should have commenced ART by week 24 of pregnancy.	All pregnant women living with HIV should receive ART, initiated as early in pregnancy as possible to prevent perinatal transmission regardless of plasma HIV RNA or CD4.	ART should be initiated in all pregnant and breastfeeding women living with HIV, regardless of WHO clinical stage and at any CD4 cell count and continued lifelong

[1] British HIV Association, Consultation Draft 2018.
[2] DHHS Perinatal Guidelines. November 2017
[3] WHO Guidelines. 2016

Congenital Malformation Rates with ART

STATUS WITH REGARD TO CONGENITAL MALFORMATION	ANTIRETROVIRAL AGEND	
Congenital malformation rates in expected range; > 2-fold higher than general population excluded	Darunavir Efavirenz Indinavir	Raltegravir Rilpivirine
Congenital malformation rates in expected range; >1.5-fold higher than general population excluded	Abacavir Atazanavir Emtricitabine Lamivudine	Nevirapine Ritonavir Tenofovir disoproxil fumarate Zidovudine
Insufficient data available to assess	Cobicistat Dolutegravir Elvitegravir Enfuvirtide Etravirine	Fosamprenavir Maraviroc Saquinavir Tonofovir alafenamide Tipranavir

BHIVA guidelines and Antiretroviral Pregnancy Registery

Impact of ART Initiation Timing on Perinatal Transmission

Timing of ART Initiation	% Perinatal Transmission (95% CI)	No with Transmission/ Total	Adjusted Odd Ratio of Transmission (95% CI)
3rd Trimester ≥ 28 weeks	2.2 (1.4-3.3)	23/1051	7.8 (2.1-28.8)
2nd Trimester 14-27 weeks	0.9 (0.5-1.3)	24/2810	6.0 (1.7-20.7)
1st Trimester < 14 weeks	0.4 (0.09-1.2)	3/709	2.9 (0.6-17.7)
Before Conception	0.2 (0.06-0.4)	6/3505	1

Mandelbrot L, Tubiana R, Le Chenadec J, et al. for the ANRS-EPF Study Groupa. Clin Inf Dis 2015. 61:1715-25

DHS Perinatal Guidelines on waiting for Genotype

- “In pregnant women not already receiving ART, ART should be initiated before results of drug-resistance testing are available because earlier viral suppression has been associated with lower risk of transmission. If ART is initiated before results are available, the regimen should be modified, if necessary based on the resistance assay results.”

Case 2 – Continued

- After discussion, SL agrees that she wants to initiate treatment as soon as possible.
- She admits to really disliking taking pills but feels that she could take pills once a day as her concern is to protect her baby.

Labs	Result
HIV-1 RNA, copies/ml	8,300
CD4+ cell count, cell/mm^3	595
HLA-B 5701	Negative
HIV genotype	Pending
Hepatitis B	Immune
Hepatitis C	Negative
CBC, renal, liver function tests	Normal

What Regimen do you Recommend?

- Raltegravir + Tenofovir (TAF) + FTC
- Raltegravir + Tenofovir (TDF) + FTC
- Darunavir/ritonavir + Tenofovir (TDF) + FTC
- Rilpivirine/TDF/FTC
- Efavirenz/TDF/FTC
- Dolutegravir/ABC/3TC
- Dolutegravir+Tenofovir (TDF) + FTC

Labs	Result
HIV-1 RNA, copies/ml	8,300
CD4+ cell count, cell/mm^3	595
HLA-B 5701	Negative
HIV genotype	Pending
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Guideline Controversy
What ART to Start for Pregnant Treatment-Naïve Patient

The only 2 things guidelines agree on:

USE
TDF or ABC with 3TC or FTC

DO NOT USE
DDI OR D4T

BHIVA Recommendations: Initial ART in Pregnancy

- "Women are recommended to start TDF or ABC with FTC or 3TC as a nucleoside backbone"
- "In the absence of specific contraindications, … third agent in cART should be in accordance with BHIVA adult ART guidelines, where sufficient clinical and pharmacokinetic data exist in pregnancy."
  - Boosted protease inhibitors are robust but have an increased risk of pre-term delivery.
  - There is good evidence for the use of efavirenz in pregnancy; however, it is no longer a preferred regimen for ART naïve patients in BHIVA and international guidelines.
- "Integrase inhibitor-based regimen is considered as third agent of choice in patients with high baseline viral load (>100,000 HIV RNA copies/mL), where cART is being started late in pregnancy or where it is failing to suppress the virus "

Guideline Status	NRTIs	PIs	Integrase Inhibitors	NNRTIs
Preferred	ABC OR TDF With 3TC + FTC		Raltegravir* ?Dolutegravir*	Rilpivirine
Alternative	3TC/ZDV	Atazanavir/RTV Darunavir/RTV		Efavirenz
NOT Recommended	D4T DDI			

*VL >100,000 copies/ml

DHHS Recommendations: Initial ART for Pregnant Women

Guideline Status	NRTIs	PIs	Integrase Inhibitors	NNRTIs
Preferred	3TC/ABC FTC/TDF 3TC + TDF	Atazanavir/RTV* Darunavir/RTV*†	Raltegravir* §	
Alternative	3TC/ZDV	Lopinavir/RTV*	Dolutegravir*	Efavirenz* Rilpivirine*‡
Insufficient data to recommend	FTC/TAF	Fosamprenavir (NOT recommended in naïve patients)		
NOT Recommended	D4T DDI ABC/3TC/AZT		EVG/COBI	

*In addition to 2-NRTI backbone. †Must be used twice daily in pregnancy. ‡Only if pretreatment HIV-1 RNA ≤ 100,000 copies/mL and CD4+ cell count ≥ 200 cells/mm^3. § If adherence concerns or potential for ART discontinuation postpartum, a PI is preferred over INSTI to reduce resistance risk.

DHHS Perinatal Guidelines. October 2016.

WHO Recommendations: Initial ART for Pregnant Women

Guideline Status	Regimen	NRTIs	PIs	Integrase Inhibitors	NNRTIs
Preferred	EFV/FTC (or 3TC)/ TDF				
Alternative		3TC/ZDV			Nevirapine
Insufficient data to recommend				Dolutegravir	
Not Recommended	DDI D4T				

What Regimen do you Recommend?

- Raltegravir + Tenofovir (TAF) + FTC
- Raltegravir + Tenofovir (TDF) + FTC
- Darunavir/ritonavir + Tenofovir (TDF) + FTC
- Rilpivirine/TDF/FTC
- Efavirenz/TDF/FTC
- Dolutegravir/ABC/3TC
- Dolutegravir+Tenofovir (TDF) + FTC

Labs	Result
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