Interactive ART Cases From the Clinic: Is There One Right Answer?

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Learning Objectives

After attending this presentation, learners will be able to:

- Be able to list at least three regimens that are recommended as first line therapy for MOST patients with HIV infection
- Describe the prevalence of transmission of resistance to the different classes of antiretroviral agents (e.g.) NNRTI, NRTI, PI and integrase inhibitors) and how they impact initial treatment choice.
- Describe potential disadvantages or adverse effects on initial antiretroviral therapy with integrase inhibitors

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Initial Antiretroviral Therapy

- LR is a 35 yo MSM who was recently diagnosed with HIV infection
- His CD4 cell count is 535 and his HIV RNA is 87,000 c/mL
- He has no co-morbid conditions,
- His ALT is normal, cr = 0.90 and total cholesterol is 150
- His husband is HIV negative (recently tested) and accompanies him to the visit
- His HCV Ab, HBV surface Ab and Ag, HLA B5701 and HIV RT/pro genotype are pending

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Would you start antiretroviral therapy now

1. Yes
2. No
3. Not Sure

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What regimen would you start

1. Bictegravir/TAF/FTC
2. Darunavir/cobi/TAF/FTC
3. Dolutegravir/abacavir/3TC
4. Dolutegravir plus TAF/FTC
5. Dolutegravir plus TDF/3TC (generic)
6. Dolutegravir/3TC
7. Doravirine/TDF/3TC
8. Efavirenz (400)/TDF/3TC (generic)
9. Raltegravir plus 2NRTI
10. Rilpivirine/TAF/FTC
11. Something else

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Recommended First-line ART for Most Patients With HIV

Class	DHHS[1]	IAS-USA[2]
INSTI	▪ BIC/FTC/TAF* ▪ DTG/ABC/3TC* ▪ DTG + FTC/(TAF or TDF) ▪ RAL + FTC/(TAF or TDF)	▪ BIC/FTC/TAF* ▪ DTG/ABC/3TC* ▪ DTG + FTC/TAF

- Integrase inhibitor-based therapy is recommended for most (all?) patients
- Regimens with Boosting agents are not longer recommended
- Other regimens may be considered in certain clinical situations
- Is an abacavir-containing regimen appropriate for **most** patients?

*Single-tablet regimens.

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1. DHHS ART. Oct 2018. 2. Saag MS, et al. JAMA. 2018;320:379.

DHHS recommendations
Certain Clinical Situations (October 2018)

NOTES:

- Doravirine plus TDF/3TC or TAF/FTC has been added
- Generic EFV/TDF/3TC has been added (400 mg EFV is in the text but not in the table)
- 3TC is listed as an appropriate substitute for FTC and use of generic formulations is discussed
- Three regimens for PLWH for whom tenofovir and abacavir cannot be used or are not optimal
  - DTG plus 3TC **(BI)**
  - DRV/r plus RAL BID **(CI)—if HIV RNA <100,000 copies/mL and CD4 cell count >200 cells/mm3**
  - DRV/r once daily plus 3TC **(CI)**

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Initial Antiretroviral Therapy

- LR is a 35 yo MSM who was recently diagnosed with HIV infection
- His CD4 cell count is 535 and his HIV RNA is 87,000 c/mL
- He has no co-morbid conditions,
- His ALT is normal, cr = 0.90 and total cholesterol is 150
- He has multiple partners some of whom are HIV +
- HCV Ab +, HBV surface Ab +, HLA B5701 negative
- HIV RT/pro and integrase resistance testing shows
  - M41L, K103N, T215D in RT
  - L90M in protease
  - T97A in integrase

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Does your baseline resistance testing include integrase?

1. Yes
2. No
3. Not Sure

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What regimen would you start

1. Bictegravir/TAF/FTC
2. Darunavir/cobi/TAF/FTC
3. Dolutegravir/abacavir/3TC
4. Dolutegravir once daily plus TAF/FTC
5. Dolutegravir twice daily plus TAF/FTC
6. Dolutegravir/3TC
7. Doravirine/TDF/3TC
8. Raltegravir plus 2NRTI
9. Rilpivirine/TAF/FTC
10. Something else

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Transmitted integrase resistance in NC

Menza et al AIDS 2017 31:2235

840 PLWH who had resistance testing within 3 months of diagnosis
Two individuals had major integrase resistance mutations (0.2%)

Subject	Year	Age	Sex	Race	Risk	HIV VL, (copies/ml)	CD4+ (cells/μl)	Days to genotype	INSTI mutations	Reverse transcriptase/ protease mutations
1	2012	24	Male	Black	MSM	ND	ND	34	L74M	None
2	2014	22	Male	Black	MSM	600	387	24	T97A	None
3	2015	45	Male	Black	HET	141 910	666	42	T66A, S147G	G190A
4	2015	40	Male	Black	HET	6450	486	30	T97AT	K103N
5	2015	22	Male	Black	MSM	54 635	702	12	T97AT	None
6	2015	42	Male	White	NIR	6 856 570	5	35	E138K	None
7	2015	20	Male	Black	NIR	5410	805	23	L74M	None
8	2015	32	Male	Black	MSM	288 872	383	34	T97A	None
9	2015	37	Male	Hispanic	MSM	11 676	775	54	T97A	None
10	2015	26	Male	Black	MSM	46 326	155	23	T97AT	None
11	2015	24	Male	Hispanic	MSM	847	760	74	T97AT	None
12	2015	24	Male	Black	MSM	324 720	656	53	T97A	K103N
13	2015	19	Male	Black	MSM	15 200	836	13	T97A	None
14	2015	52	Female	Black	HET	23 400	964	39	L74M	K103N
15	2016	32	Female	Black	NRR	46 630	572	15	L74M	K103N
16	2016	29	Male	Black	MSM	29 800	538	68	L74LM	None
17	2016	24	Female	White	HET	1450	1148	14	T97A	None
18	2016	65	Male	Black	NRR	224 380	13	59	T97A	None
19	2016	42	Female	Black	NRR	8828	732	4	L74M	K103N
20	2016	25	Male	Black	MSM	30 554	760	20	N155H	D67N, M184V

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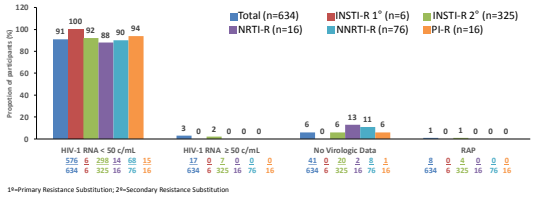
Treatment Response to B/F/TAF

In patients with pre-Therapy

Week 48 Virologic Outcome of B/F/TAF-treated Participants Stratified by Baseline Resistance Category



1°=Primary Resistance Substitution; 2°=Secondary Resistance Substitution

White et al CROI 2018 Abstract 532

Should we continue to do baseline resistance testing?

1. Yes
2. No
3. Not Sure

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The cost-effectiveness ratio for resistance testing remained less than 50,000 dollars per quality-adjusted life-year gained unless the prevalence of resistance was < or =1% -- Sax P, et al CID 2005

Antiretroviral therapy initiation

- LR is a 35 yo MSM who was recently diagnosed with HIV infection
- His CD4 cell count is 335 and his HIV RNA is **187,000 c/mL**
- He has Type 1 diabetes since age 15 with initial poor control, now well controlled on insulin. Fam Hx is + for DM and MI (father age 48)
- His ALT is normal, cr = 2.96 (CrCl = 38) and total cholesterol is 150 on atorvastatin
- He is in a stable relationship with an HIV+ man
- HCV Ab +, HBV surface Ab +, HLA B5701 negative
- RT/pro genotype is wild type

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What regimen would you start

1. Bictegravir or dolutegravir plus TAF/FTC
2. Darunavir/cobi/TAF/FTC
3. Darunavir/boosted plus INSTI
4. Darunavir/boosted plus 3TC
5. Dolutegravir plus abacavir/3TC
6. Dolutegravir plus 3TC
7. Raltegravir plus TAF/FTC
8. Rilpivirine/TAF/FTC
9. Rilpivirine/dolutegravir
10. Something else

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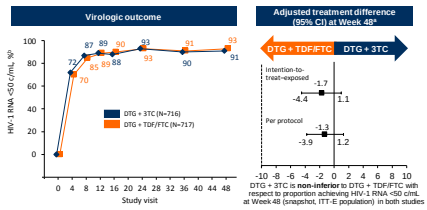
Gemini Studies: DTG plus 3TC vs. DTG plus TDF/FTC in Treatment Naïve patients.



*Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm³). †Calculated from a repeated measures model adjusting for study, treatment, visit (repeated factor), baseline plasma HIV-1 RNA, baseline CD4+ cell count, treatment and visit interaction, and baseline CD4+ cell count and visit interaction.

Cahn et al. *Lancet*. 2018 [Epub ahead of print].

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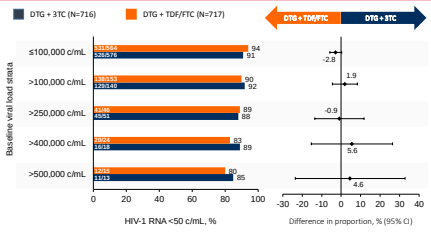
Eron et al. HIV DART and Emerging Viruses 2018; Miami, FL. Slides 7.

Proportion of Participants With Plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Analysis) by Baseline Plasma HIV-1 RNA



Cahn et al. *Lancet*. 2018 [Epub ahead of print].

Eron et al. HIV DART and Emerging Viruses 2018; Miami, FL. Slides 7.

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DHHS recommendations
Certain Clinical Situations (October 2018)

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  - DRV/r once daily plus 3TC **(CI)**

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Antiretroviral therapy initiation

- LR is a 35 yo woman who was recently diagnosed with HIV infection
- Her CD4 cell count is 535 and his HIV RNA is 87,000 c/mL
- She has no co-morbidities and is only on an oral contraceptive
- Her ALT and cr are normal, total cholesterol is 150
- She is in a stable relationship with an HIV negative man. Her husband accompanies her to the visit. She would like to become pregnant as soon as safety possible
- HCV Ab negative, HBV surface Ab +, HLA B5701 negative
- RT/pro genotype is wild type

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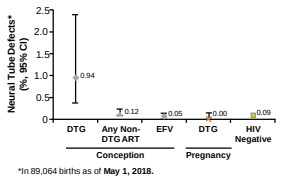
What regimen would you start?

1. Bictegravir/TAF/FTC
2. Darunavir/cobi/TAF/FTC
3. Dolutegravir/abacavir/3TC
4. Dolutegravir plus 2NRTI
5. Doravirine/TDF/3TC
6. Efavirenz/TDF/3TC
7. Raltegravir plus 2NRTI
8. Rilpivirine/TAF/FTC
9. Ritonavir-boosted PI plus 2 NRTI
10. Something else

Tsepamo Interim Analysis: DTG Exposure at Conception and During Pregnancy

- Tsepamo: ongoing birth outcomes surveillance study among Botswanan women ± HIV infection[1,2]

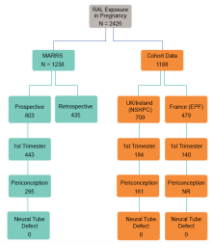


*In 89,064 births as of **May 1, 2018.**

- At latest analysis on **July 15, 2018**[2]
  - NTD prevalence with DTG exposure at conception: 4/596 (0.67%; 95% CI: 0.26% to 1.70%)
  - NTD prevalence with DTG started **during pregnancy**: 1/3104 (0.03%; 95% CI: 0.01% to 0.18%)
- ARV Pregnancy Registry (7/31/18): No NTDs in women with first trimester or any DTG, EVG, or RAL exposure reported to Antiretroviral Pregnancy Registry[4]

1. Zash. NEJM. 2018;379:979. 2. Zash. AIDS 2018. Abstr TUSY15.
3. Zash Lancet Global Health 2018 6:e804-810. ARV Pregnancy Registry Interim Report 7/31/2018.

Neural tube Defects with RAL and EVG/cobi



- No NTDs with first trimester EVG or RAL exposure in Antiretroviral Pregnancy Registry (APR) as of July 2018
- Gilead global safety database assessed for NTDs in infants exposed to EVG in utero:
  - database includes pregnancy outcomes from clinical trials, APR, spontaneous post-marketing and solicited cases, literature
  - N = 630 pregnancies with EVG exposure identified
    - No prospectively identified NTD cases
    - n = 2 retrospectively identified NTD cases (anencephaly, myelomeningocele; (TAB))
- 4 retrospective reports in Merck database
  - 1 preconception live birth

Shamsuddin et al CROI 2019; APRegistry 2018; Farrow T, et al. Glasgow 2018. Abstract P030

Antiretrovirals in Pregnancy

- Pregnancy testing should be preformed in women of child-bearing potential prior to starting ART
- Cobicistat based regimens should not be used and should be switched
- No current data on TAF, doravirine, bictegravir
- "The chemical structure of BIC is similar to DTG. There are no safety data on the use of BIC around the time of conception. For those who are of childbearing potential, but who are not pregnant, an approach similar to that outlined for DTG should be discussed before considering the use of BIC-containing ART **(AIII)**."
- For RAL, "the rate of fetal malformations is within the expected range for pregnancy outcomes in the US; however, data on RAL in 1st trimester is limited (< 300 deliveries). As it is currently not known whether the association between DTG and NTDs represents a class effect, this potential risk should be discussed with WOCB potential who prefer an INSTI-containing regimen."

DHHS guidelines Oct 2018

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Initial Antiretroviral Therapy

- LR is a 25 yo B MSM who is being seen in the emergency department for purulent urethritis on Wednesday evening
- He has had multiple partners in the last month including receptive anal sex
- Only a few labs are back: His ALT is normal, his creatinine is 0.68
- No other data are available
- A 4th generation HIV test is + but antibody GEENIUS assay is negative
- You call the lab and the signal to cut-off ratio is 10
- HIV RNA assay will be back early next week

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Would you start therapy in this man before his HIV RNA comes back?

1. Yes
2. No
3. Not sure

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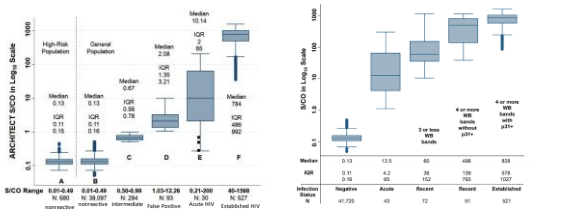
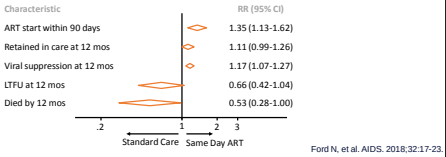
4th Generation HIV Assay S/CO ratio



Improved Clinical Outcomes With Rapid ART Initiation

- Universal recommendations for treating all HIV-infected persons
- Systematic review of 22 studies of rapid ART initiation (including 4 RCTs)
  - In the 4 RCTs, compared with standard care, same day ART increased likelihood of ART initiation in first 90 days, patient retention and viral suppression at 12 mos



Ford N, et al. AIDS. 2018;32:17-23.

What regimen would you start?

1. Bictegravir/TAF/FTC
2. Darunavir/cobi/TAF/FTC
3. Dolutegravir/abacavir/3TC
4. Dolutegravir plus TXF/XTC
5. Dolutegravir/3TC
6. Doravirine plus TXF/XTC
7. Efavirenz (400)/TDF/3TC (generic)
8. Raltegravir plus 2NRTI
9. Rilpivirine/TAF/FTC
10. Something else

Antiretroviral Therapy Intolerance

- LR is a 35 yo BMSM who was recently diagnosed with HIV infection
- His CD4 cell count is 535 and his HIV RNA is 87,000 c/mL
- He has no co-morbid conditions, and weighs 86 kg (BMI 28.5)
- His ALT is normal, cr = 0.90 and total cholesterol is 150
- His HCV Ab, HBV surface Ab and Ag, HLA B5701 and HIV RT/pro genotype is wild type
- He is started on DTG plus TAF/FTC
- After 12 week his HIV RNA is < 40 c/mL and TND, CD4 is 643

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Antiretroviral Therapy Intolerance

- He returns at month 6 and feels relatively well. His HIV RNA remains TND and CD4 is 680. His creatinine and ALT are normal
- He has some trouble sleeping and is a little more anxious than in the past but his job is stressful. He weighs 88 kg.
- He is happy to continue his current therapy.
- At month 12 he continues to do well with suppressed HIV and no lab abnormalities. However his sleep and anxiety have not improved. He now weighs 91 kg
- He says he is exercising and has not had substantial changes in his diet.

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What will you do at this point?

1. Continue current therapy – and treat anxiety with counseling +/- an SSRI and refer to nutrition for diet review and advice
2. Consider changing his therapy to address both his CNS symptoms and weight gain
3. Not sure

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You opt for counseling, SSRI and nutrition but he returns in 4 months with persistent CNS symptoms and now weighs 93 kg
You decide to change therapy – what anchor agent will you choose

1. Bictegravir
2. Dolutegravir but change NRTI
3. Raltegravir
4. Doravirine
5. Rilpivirine
6. Darunavir/boosted
7. Something else

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Would you

1. Continue TAF/FTC
2. Change to TDF/FTC
3. Change to ABC/3TC
4. Change to 3TC alone
5. Consider NRTI sparing
6. Something else

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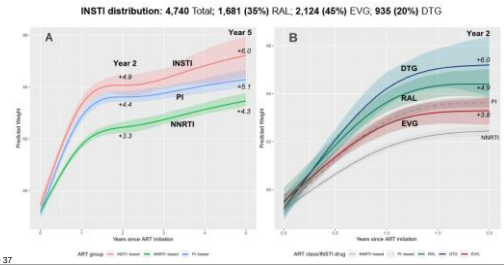
Change in Weight Overtime – NA-ACCORD

Bourgi et al CROI 2019



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Virologic failure on Dolutegravir

ponent atest Ref Rng & Units	8/5/2015	2/3/2016	5/4/2016	9/14/2016
RNA Quant Result ot Detected	Not Detected	Not Detected	Detected	Detected
RNA Dcopies/mL			<40	<40
RNA Log10 0.00 log copies/mL				
RNA Comment	-	-		

ponent atest Ref Rng & Units	5/10/2017	2/28/2018	11/7/2018	11/30/2018
RNA Quant Result ot Detected	Not Detected	Detected (A)		
RNA Dcopies/mL		<40 (H)	146 (H)	1,588 (H)
RNA Log10 0.00 log copies/mL			2.16 (H)	3.20 (H)
RNA Comment				

ponent atest Ref Rng & Units	1/3/2019
RNA Quant Result ot Detected	
RNA Dcopies/mL	79 (H)
RNA Log10 0.00 log copies/mL	1.90 (H)
RNA Comment	

- 45 yo woman diagnosed during pregnancy in 2007 with "high CD4 and low viral load" and treated with AZT/3TC LPV/r. Suppressed by her report. Child HIV negative. Out of care for 7 years
- Started on DTG/ABC/3TC in 2015. HIV RNA 14,600 and CD4 453. She is HBV sAb+, HCV negative, with nl creatinine and ALT
- She is undocumented from Mexico and lives 60 miles from clinic. Her adherence to clinic visits has been sporadic and she has missed some refills. HIV RNA as in the table
- Resistance testing from 1588 c/ml sample:
  - Integrase RAMs*: L74L/M, T97A, G140S, Q148H pan resistant
  - PR RAMS RAMs*: L10I, I54V, V82V/A; RTV resistant
  - NRTI RAMs*: M41L, M184V; 3TC, FTC resistant, ABC, ZDV intermediate
  - K103N (presumed transmitted)

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How would you manage antiretroviral therapy in this patient?

1. Bictegravir/TAF/FTC
2. Darunavir/cobi/TAF/FTC
3. Dolutegravir twice daily plus TAF/FTC
4. Doravirine plus TXF/XTC
5. Rilpivirine/TAF/FTC
6. Darunavir/cobi plus doravirine or rilpivirine
7. Darunavir/cobi/TAF/FTC plus doravirine or rilpivirine
8. Something else

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Therapy Switch in Complex Medical Patient

- 60 yo HIV + woman who has been treated for HIV since the mid 1990's. Her first regimen was ZDV/3TC for 2 years and she was subsequently exposed to multiple agents including indinavir and efavirenz.
- Her first HIV RNA < 400 was on LPV/r plus TDF and 3TC and her HIV RNA has been < 50 and < 20 (detected) on a series of PI-based therapy – now FDC darunavir/cobi/TAF/FTC. CD4 658
- She has hyperlipidemia, diabetes controlled on metformin, obesity (BMI 35) and severe DJD of her knees (L > R). She is HBV Sab+, HCV -, cr 1.8 and ALT 68. Cr cl = 45
- She has a triamcinolone injection of her L knee with marked improvement but her orthopedist became aware of an DDI.
- She is very reluctant to have a knee replacement and asks about a change in therapy.
- You have no resistance testing data.

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Would you order an HIV DNA (archive) resistance test?

1. Yes
2. No
3. Not sure

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Archive DNA resistance results

- NRTI: M41M/L, K70K/R, M184M/V, T215T/Y
- NNRTI: K103N
- PI: L33L/F, M46M/L, I54I/V, V82V/A
- INSTI: none

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How would you manage her antiretroviral therapy?

1. Continue her DRV/c/TAF/FTC and urge her to have knee replacement
2. Switch to bictegravir or dolutegravir plus TAF/FTC
3. Switch to dolutegravir plus 3TC
4. Switch to dolutegravir/rilpivirine FDC
5. Switch to dolutegravir or raltegravir plus doravirine
6. Switch to DTG/RPV plus TAF/FTC
7. Switch to DTG or RAL plus doravirine plus TAF/FTC
8. Something else

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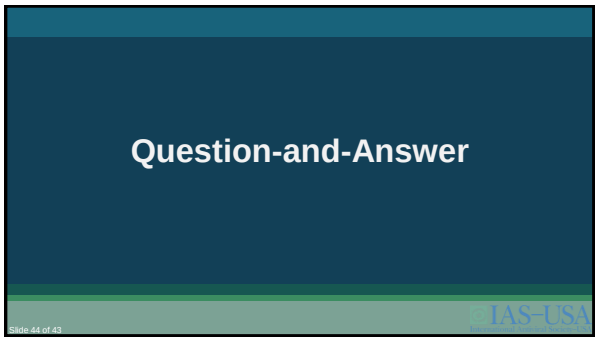
Question-and-Answer
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IAS-USA