Interactive ART Cases From the Clinic(ians): Case-Based Panel Discussion

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Panelists

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Learning Objectives

After attending this presentation, learners will be able to select antiretroviral therapy in patients who:

- Are starting initial therapy
- Have persistently low-level viremia
- Have a baseline M184V mutation
- Are pregnant
- Develop renal apparent renal impairment

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Question

Seems like we are now starting ARV therapy for about everyone, what about starting therapy immediately at time of diagnosis?

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Case 1

- 30 yo Female was diagnosed with HIV infection 4 hours ago in the ER
- Asymptomatic
- **Initial:** HIV RNA ***pending***
  CD4 count ***pending***
- Other labs are normal; HLA-B57 ***pending***
- Genotype is ***pending***
- No prior medical history.
- Ok to start therapy if you think she should

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ARS Question 1: When would you choose to start therapy?

1. Right now in the ER
2. Within 1 - 2 days (outpt Clinic)
3. In the next 2 weeks (outpt Clinic)
4. Within 2 – 4 weeks
5. Some other option

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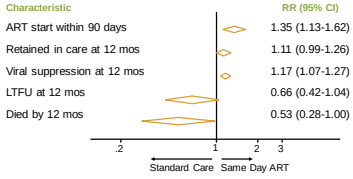
Improved Clinical Outcomes With Rapid ART Initiation

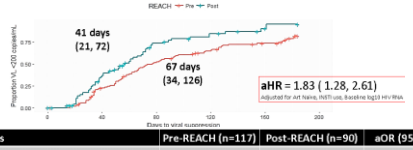
- Universal recommendations for treating all HIV-infected persons
- Systematic review of 22 studies of rapid ART initiation (including 4 RCTs)



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

Expedited ART– Experience in Atlanta

- Grady reduced barriers, with goal to begin ART within 72hrs
- Pre-intervention days to ART = 22, Post-intervention days to ART= 4.



Outcomes	Pre-REACH (n=117)	Post-REACH (n=90)	aOR (95% CI)
Attended 1st scheduled appointment[†]	85 (73)	73 (81)	1.63 (0.82, 3.22)
Achieved viral suppression[¥]	87 (74)	61 (68)	0.77 (0.39, 1.52)

[†]Adjusted for age, race, sex and being ART Naïve
[¥]Adjusted for age, race, baseline HIV RNA & INSTI use

Colasanti #1109

Question

What regimen should I use as initial therapy?

Case 2

- 48 yo Male presents with newly diagnosed HIV infection
- Asymptomatic
- **Initial:** HIV RNA 28,000 c/ml
  CD4 count 650 cells/ul
- Other labs are normal; HLA-B57 positive
- Genotype is Wild-type virus
- No prior medical history. Normal renal function
- Ok to start therapy if you think he should

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ARS Question 2: At this point which regimen would you choose?

1. TDF / 3TC / low dose (400mg) EFV (fdc; generic)
2. ABC/ 3TC / DTG (fdc)
3. TAF/ FTC (fdc) + DTG
4. TAF / FTC/ ELV / cobi (fdc)
5. TAF/ FTC / BIC (fdc)
6. TAF / FTC (fdc) + RAL (once daily)
7. TAF / FTC / RPV (fdc)
8. TAF/ FTC (fdc) + DRV/r (or cobi / fdc)
9. Some other option (e.g., DRV/r + DTG or …)

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JAMA | Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults
2018 Recommendations of the International Antiviral Society-USA Panel

Michael S. Saag, MD; Constance A. Benson, MD; Rajesh T. Gandhi, MD; Jennifer F. Hoy, MBBS; Raphael J. Landovitz, MD; Michael J. Mugavero, MD, MHSc; Paul E. Sax, MD; Davey M. Smith, MD; Melanie A. Thompson, MD; Susan P. Buchbinder, MD; Carlos del Rio, MD; Joseph J. Eron Jr, MD; Gerd Fätkenheuer, MD; Huldrych F. Günthard, MD; Jean-Michel Molina, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MD

IMPORTANCE Antiretroviral therapy (ART) is the cornerstone of prevention and management of HIV infection.

Editorial page 1
Author Audio Interview
Related article page 1

Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2018;320(4):1-18.

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Recommended Initial Regimens: InSTI Plus 2 nRTIs

- Bictegravir/TAF/emtricitabine
- Dolutegravir/abacavir/lamivudine
- Dolutegravir plus TAF/emtricitabine

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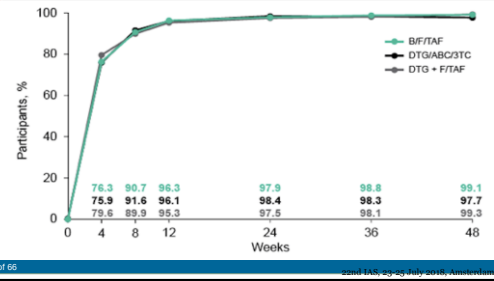
Saag, Benson, Gandhi, et al, *JAMA*, 2018

Virologic Response by Visit (FAS)

HIV-1 RNA <50 copies/mL, Missing=Excluded Analysis



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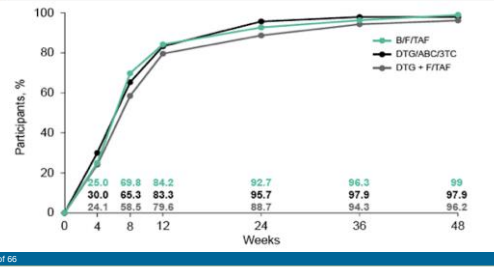
22nd IAS, 23-26 July 2018, Amsterdam, Netherlands

Virologic Efficacy:
HIV-1 RNA <50 copies/mL, Missing=Excluded Analysis

Baseline HIV-1 RNA >100,000 copies/mL



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Recommended Initial Regimens: If an InSTI Is Not Available

- Darunavir/cobicistat/TAF (or TDF)/emtricitabine*
- Darunavir boosted with ritonavir plus TAF (or TDF)/emtricitabine
- Efavirenz/TDF/emtricitabine
- Elvitegravir/cobicistat/TAF (or TDF)/emtricitabine
- Raltegravir plus TAF (or TDF)/emtricitabine
- Rilpivirine/TAF (or TDF)/emtricitabine (if pretreatment HIV RNA level is <100,000 c/mL and CD4 cell count is >200/µL)
- Fixed-dose Dor/TDF/3TC tablet approved July 2018

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Saag, Benson, Gandhi, et al, *JAMA*, 2018.

ARS Question 3: Would you use DTG / 3TC as initial therapy?

1. Yes
2. No
3. Not sure

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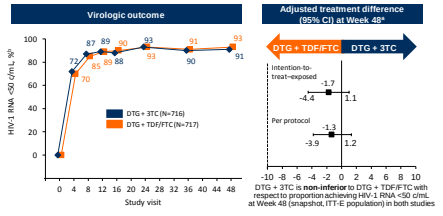
Gemini Studies: DTG plus 3TC vs. DTG plus TDF/FTC in Treatment Naïve patients.



[a]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/mm^3). [b]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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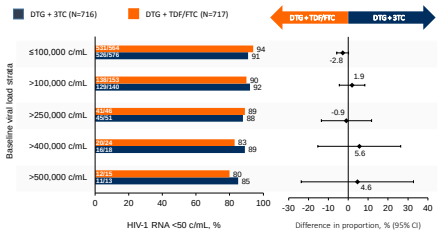
Eron et al. HIV DART and Emerging Viruses 2018; Miami, FL. Slides 7.

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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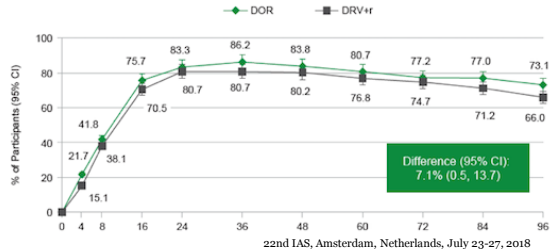
Figure 3. Proportion of Participants With HIV-1 RNA <50 c/mL†



22nd IAS, Amsterdam, Netherlands, July 23-27, 2018

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ARS Question 4:

Which ARV drug is most likely to cause a 0.1 mg/dl jump in serum creatinine 1 week after starting Rx?

1. Bictegravir
2. Tenofovir DF
3. Tenofovir AF
4. Atazanavir
5. Emtricitabine

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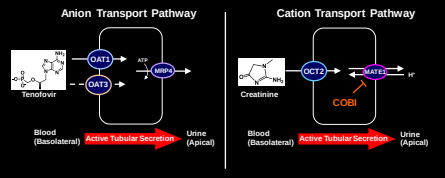
Tenofovir and COBI Interact with Distinct Renal Transport Pathways



- The active tubular secretion of tenofovir and the effect of COBI on creatinine are mediated by distinct transport pathways in renal proximal tubules

Ray A, et al. Antimicro Agents Chemo 2006;3297-3304
Lepist E, et al. ICAAC 2011; Chicago. #A1-1724

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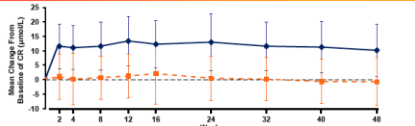
Renal Safety



	DTG 50 mg+ABC/3TC QD	EFV/FTC/TDF QD
Urine albumin/creatinine Median change (IQR) from baseline (mg/mmol CR) to Week 48	0.00 (-0.30, 0.30)	+0.05 (-0.20, 0.30)

- **Small increase in creatinine due to blockade of Cr secretion[1]**
- **DTG does not affect actual glomerular filtration rate (GFR)[1]**

1. Koteff, J. et al. Br J Clin Pharmacol. In press; 2012 Aug.
Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

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Question

Seems like we are now starting ARV therapy for about everyone, what about starting therapy for an **Elite Controller**?

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Case 3

- 30 yo Female was diagnosed with HIV infection 4 years ago
- Asymptomatic
- **Initial:** HIV RNA < 50 c/ml (HIV DNA positive)
  CD4 count 870 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype determined from DNA is wild-type
- No prior medical history.
- Ok to start therapy if you think she should

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ARS Question 5: Would you choose to start therapy at this time?

1. Yes
2. No
3. Maybe

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Question

Should I change a regimen when low level detectable virus is present?

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Case 4

- 55 yo male referred to you for evaluation
- Diagnosed 18 years ago with HIV infection
- **Initial:** HIV RNA 936,000c/ml
  CD4 count 70 cells/ul
- **Current:** HIV RNA 85 c/ml (prior value 62 c/ml)
  CD4 count 525 cells/ul
- Started on NEL/D4T/3TC; subsequently treated with
  - LOP-r / TDF/FTC,
  - EFV/ FTC/ TDF (fdc).
  - Now **DTG / DRV/c / 3TC**
- No historical resistance tests are available

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ARS Question 6: Should you change ARV therapy now?

1. Yes
2. No
3. Not sure

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Virologic Failure, Low Level Viremia, and Blips

Clinical characteristics

	≤6 months n=5,776	>6 to 12 months n=6,858	>12 months n=4,360
Pre-ART viral load *median*	**28000**	**62457**	**82713**
Year of ART initiation *median*	2011	2011	2011
ART anchor drug(s)			
NNRTI	40%	50%	46%
PI	32%	36%	45%
InSTI	**31%**	**16%**	**13%**
CD4 count, cells/μL *median*	440	460	460
AIDS diagnosis	**12%**	**14%**	**20%**
Hepatitis B co-infection	3%	4%	5%
Hepatitis C co-infection	**10%**	**9%**	**15%**

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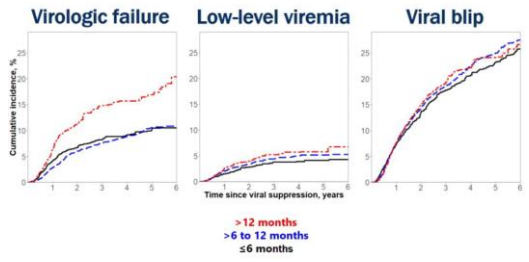
Lee, J et al NA-ACCORD, CROI 2019 Abst #97

Virologic Failure, Low Level Viremia, and Blips



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Lee, J et al NA-ACCORD, CROI 2019 Abst #97

Question

What regimen should I use as initial therapy in a women who desires to become pregnant?

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Case 5

- 30 yo Female who is on ARV Rx informs you she'd like to become pregnant HIV infection
- Asymptomatic; No prior medical history.
- **Initial:** HIV RNA 28,000 c/ml
  CD4 count 650 cells/ul
- Other labs are normal; HLA-B57 neg
- Pre-Rx genotype is Wild-type virus
- She is currently on DTG / ABC / 3TC (fdc) with undetectable HIV RNA

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ARS Question 7: At this point you would…

1. **Keep her on her current Rx** (ABC/ 3TC / DTG)
   Or Switch her to:
2. TDF / FTC / EFV (fdc)
3. TAF / FTC/ ELV / cobi (fdc)
4. TDF / FTC / RPV (fdc)
5. TDF/ FTC (fdc) / DRV/r
6. TAF/ FTC / ATV/r
7. TDF / FTC / ATV/r
8. Some other option

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TAF PK - Fetus

- Intracellular concentration of Tenofovir-DP is 4-5 times higher for TAF compared to TDF
- Does this expose the fetus to a higher risk of birth abnormalities?
- Does this lower the risk of vertical transmission?

Andrew Hill, 2016 WHO meeting

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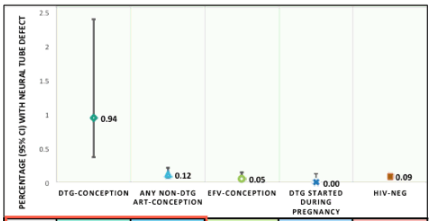
NTD Prevalence Difference by Exposure



	DTG-CONCEPTION	ANY NON-DTG ART-CONCEPTION	EFV-CONCEPTION	DTG STARTED DURING PREGNANCY	HIV-NEG
NTDs/ Exposures	4/426	14/11,300	3/5,787	0/2,812	61/66,057
% with NTD (95% CI)	0.94% (0.37%, 2.4%)	0.12% (0.07%, 0.21%)	0.05% (0.02%, 0.15%)	0.00% (0.00%, 0.13%)	0.09% (0.07%, 0.12%)
Prevalence Difference (95% CI)	ref	-0.82% (-0.24%, -2.3%)	-0.89% (-0.31%, -2.3%)	-0.94% (-0.35%, -2.4%)	-0.85% (-0.27%, -2.3%)

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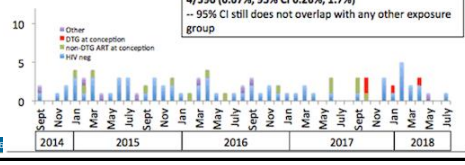
Update since 1 May 2018

- From 1 May-15 July, there were **2 more NTDs;** 1 in an infant exposed to **DTG *started during pregnancy*** (8 weeks GA) and 1 birth to an **HIV-uninfected** woman
  - NTDs in DTG started in pregnancy: 1/3104 (0.03%, 95% CI 0.01%, 0.18%)

Updated prevalence of DTG exposure at conception is 4/596 (0.67%, 95% CI 0.26%, 1.7%)
-- 95% CI still does not overlap with any other exposure group



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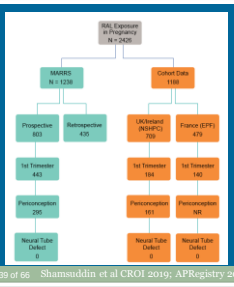
Neural tube Defects with RAL and EVG/cobi



- **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:**
  - N = 630 pregnancies with EVG exposure identified
    - No prospectively identified NTD cases
    - n = 2 retrospectively identified NTD cases (anencephaly, myelomeningocele; (TAB))

Slide 39 of 66 Shamsuddin et al CROI 2019; APRegistry 2018; Farrow T, et al. Glasgow 2018. Abstract P030

ARS Question 8: Can she breastfeed if VL undetectable (U=U)?

1. Yes
2. No
3. I don't know

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Question

What regimen should be used as initial therapy when an M184V mutation is present?

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Case 6

- 30 yo Female presents with newly diagnosed HIV infection
- Asymptomatic
- **Initial:** HIV RNA 128,000 c/ml
  CD4 count 350 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype shows **M184V and K103N mutation**
- No prior medical history. No children. Does not plan to become pregnant.
- Ok to start therapy if you think she should

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ARS Question 9: At this point which regimen would you choose?

1. TDF / 3TC / low dose (400mg) EFV (fdc; generic)
2. DTG / 3TC (fdc)
3. ABC/ 3TC / DTG (fdc)
4. TAF/ FTC (fdc) + DTG
5. TAF / FTC/ ELV / cobi (fdc)
6. TAF/ FTC / BIC (fdc)
7. TAF / FTC (fdc) + RAL (once daily)
8. TAF / FTC / RPV (fdc)
9. TAF/ FTC (fdc) + DRV/r (or cobi / fdc)
10. Some other option (e.g., DRV/r + DTG or …)

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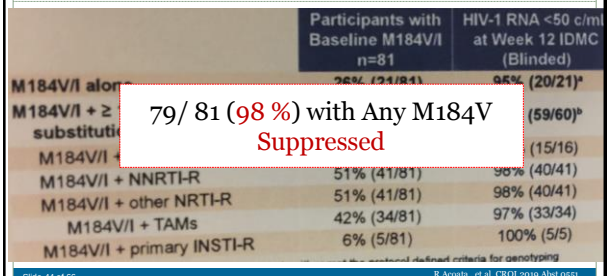
Pre-existing M184V Prior to Switch to InSTI Regimen: 4030



	Participants with Baseline M184V/I n=81	HIV-1 RNA <50 c/ml at Week 12 IDMC (Blinded)
M184V/I alone	26% (21/81)	95% (20/21)[a]
M184V/I + ≥ substituti		(59/60)[b]
M184V/I +		(15/16)
M184V/I + NNRTI-R	51% (41/81)	98% (40/41)
M184V/I + other NRTI-R	51% (41/81)	98% (40/41)
M184V/I + TAMs	42% (34/81)	97% (33/34)
M184V/I + primary INSTI-R	6% (5/81)	100% (5/5)

79/ 81 (98 %) with Any M184V Suppressed

[a] This analysis defined criteria for genotyping

R Acoata , et al, CROI 2019 Abst 0551

Question

Does InSTI therapy cause weight gain?

Case 7

- 47 year old woman starts on BIC/FTC/TAF 12 months ago from her original ARV regimen (TDF/FTC/DRV/r)
- Diagnosed 4 years ago
- **Initial:** HIV RNA 28,000 c/ml (Wildtype virus)
  CD4 count 450 cells/ul
- **Current:** HIV RNA <20 c/mL / CD4+ count 930 /uL
- Since starting her current regimen her weight has increased from **145 lbs to 171 lbs**

ARS Question 10: At this point you would…

1. **Keep her on her current Rx** (TAF/FTC/BIC)
   Or Switch her to:
2. TDF/ FTC (fdc) / DRV/r
3. TAF/ FTC / DRV/c (fdc)
4. TDF / FTC / RPV (fdc)
5. DTG / RLP (fdc)
6. TAF / FTC / ATV/c
7. Some other option

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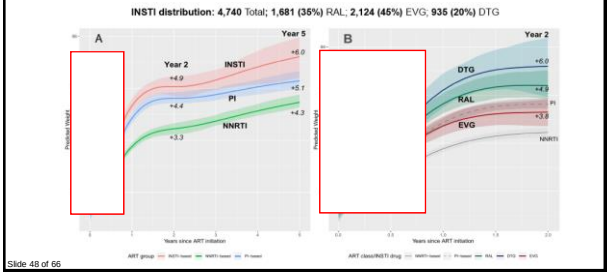
Change in Weight Overtime – NA-ACCORD

Bourgi et al CROI 2019



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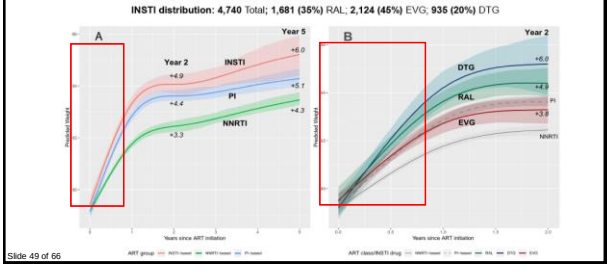
Change in Weight Overtime – NA-ACCORD

Bourgi et al CROI 2019



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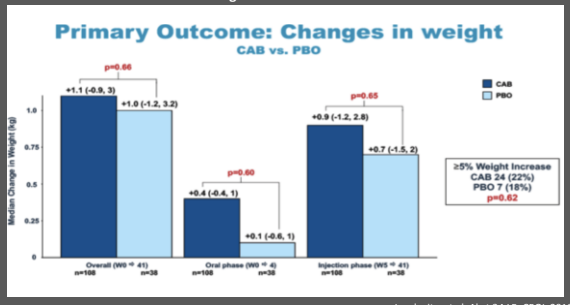
Cabotegravir vs Placebo for PrEP



Landovitz, et al, Abst 34 LB, CROI 2019

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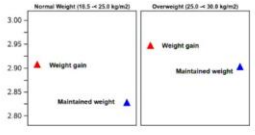
CROI 2019: The Impact of Inflammation on Weight Gain Following Initiation of ART

- ART-naïve ACTG trials A5202 and A5257
- Higher pre-ART IL-6, sTNFαR2, IP-10, and sCD163 in those who gained weight over 96 weeks
- Sex difference: women who gained weight had smaller declines in biomarkers compared to men

Adjusted pre-ART soluble CD136 levels in patients who gained weight vs. maintained weight



Does higher BMI promote inflammation in PLWH, or does inflammation promote weight gain?

Barros, SH. et al. CROI 2019. Poster 673

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Question

Should I simplify an "older" complex regimen?

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Case 9

- 57 year old man transfers to your care; no prior resistance tests are available
- He diagnosed with HIV in 2001; prior opportunistic infections and complains of 'Pill Fatigue'
- Has taken most existing antiretroviral drugs available; no exposure to DTG, ELV, or BIC
- Currently on TDF / FTC / ETV / DRV-r /Ral (twice daily)
- CD4+ count 430 /uL (nadir CD4 = 6)
  - HIV RNA <20 c/mL (max VL 667,000)

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ARS Question 12: At this point which regimen would you choose?

1. Continue current therapy (7 pills)

OR switch to:

2. TAF / FTC/ ELV / c (fdc) /DRV (2 pills)
3. ABC/ 3TC / DTG (fdc) / DRV/c (2 pills)
4. TAF / FTC / RAL / DRV/c (4 pills)
5. TAF / FTC / DTG / DRV/c (3 pills)
6. TAF/FTC/BIC (1 Pill)
7. TAF / FTC / DTG (2 pills)
8. Some other regimen

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Question

What regimen should I start when a patient returns after a long absence?

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Case 10

- 55 yo male returns after being “Lost to Follow Up” for 2 years
- Diagnosed 7 years ago with HIV infection
- Initial Rx: **TDF /FTC / RPV** (Tolerated well)
- **Initial:** HIV RNA 86,000 c/ml (wildtype virus)
  CD4 count 70 cells/ul
- **Status at last visit (2 years ago):**
  HIV RNA 26 c/ml / CD4 count 325 cells/ul
- Now returns and wants to re-engage in care
- Lab results pending

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ARS Question 13: What ARV therapy should you use now?

1. Same regimen as originally on
2. Start an InSTI-based regimen
3. Start a PI-based regimen
4. Wait for repeat resistance test, then choose regimen based on results
5. Some other answer

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Question

Should I stop abacavir in older patients?

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Case 11

- 62 yo male started on ARV Rx years ago (resistance history: wild type virus) **returns to you for care after 4 years** (Rx'd elsewhere)
- Has been through several regimens; now on ABC/ 3TC / DTG (fdc)
- **Now:** HIV RNA < 20 c/ml (persistently)
  CD4 560 cells/ul
  Cholesterol 180 mg/dl (HDL 52 / LDL 100)
  Creat 1.3 / eCrCl = 80 cc/min
- Smoker
- PMHx negative (No cardiac history)
- On atorvastatin and daily low-dose ASA

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ARS Question 14: Besides asking him to quit smoking, what would you do?

1. Continue his current ARV Rx
2. Change his ABC/3TC to TAF / FTC containing Rx
3. Change his ABC/3TC to DRV/rit (continue DTG)
4. Some other option

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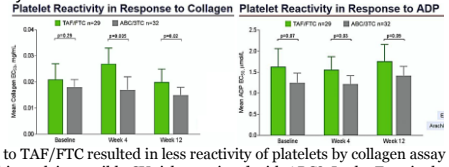
ABC → TAF – Effect on Platelets

- 61pts on ABC/3TC containing regimen randomized to continue or to switch to TAF/FTC. Platelet aggregation measured by platelet reactivity



- Switch to TAF/FTC resulted in less reactivity of platelets by collagen assay
- Does this explain possible CV risk associated with ABC? In the Framingham study ADP response was much more predictive for CVD than collagen response

(MK Puurunen, JAHA 2018)

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Conclusions

- ARV therapy should be initiated with an InSTI-based regimen (unless otherwise indicated), as close to time of Dx as possible
- Do not change Rx in setting of low-level viremia
- Use DTG, BIC, TAF and Cobi cautiously in women who are contemplating pregnancy
- M184V mutation does not have much impact on InSTI based Rx
- Weight gain is associated with initiation of ARV Rx, with more weight gain observed in InSTI regimens

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Question-and-Answer

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