Treating and Preventing HIV in 2019: Interactive Cases From the Clinic(ians)

Michael S. Saag, MD
Professor of Medicine
Associate Dean for Global Health
Jim Straley Chair in AIDS Research
University of Alabama at Birmingham
Birmingham, Alabama

IAS–USA

Panelists

Gayle Balba
Henry Masur
Roy Gulick
Poonam Mathur
R. Douglas Bruce

IAS–USA

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
- Are eligible for PrEP

Slide 4 of 70

Question

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

Slide 5 of 70

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

Slide 6 of 70

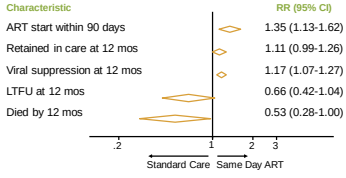
ARS 1: When would you choose to start therapy?

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

Slide 7 of 70

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)

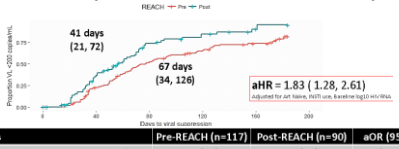


Ford N, et al. AIDS. 2018;32:17-23.

Slide 8 of 70

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[1]	85 (73)	73 (81)	1.63 (0.82, 3.22)
Achieved viral suppression[2]	87 (74)	61 (68)	0.77 (0.39, 1.52)

[1]Adjusted for age, race, sex and being ART Naive
[2]Adjusted for age, race, baseline HIV RNA & INSTI use

Colasanti #1109

Slide 9 of 70

Question

What regimen should I use as initial therapy?

Slide 10 of 70

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

Slide 11 of 70

ARS 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 …)

Slide 12 of 70

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.

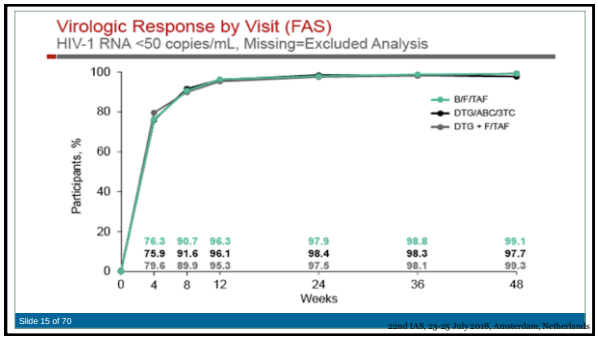
Slide 13 of 70

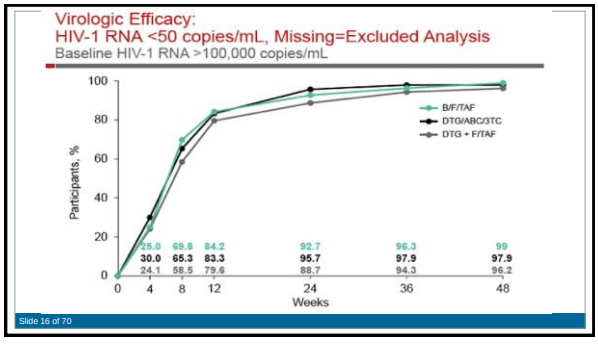
Recommended Initial Regimens: InSTI Plus 2 nRTIs

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

Slide 14 of 70

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





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

Slide 17 of 70

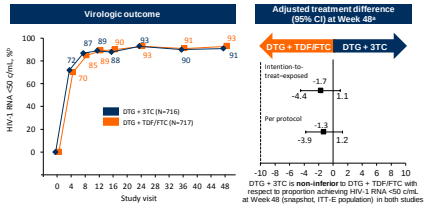
Saag, Benson, Gandhi, et al, *JAMA*, 2018.

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

1. Yes
2. No
3. Not sure

Slide 18 of 70

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



DTG + 3TC is **non-inferior** to DTG + TDF/FTC with respect to proportion achieving HIV-1 RNA <50 c/mL at Week 48 (snapshot, ITT-E population) in both studies

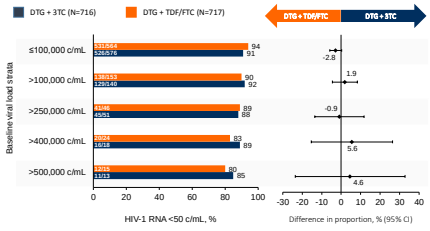
[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 vs >100,000 c/mL) and CD4+ cell count (≤200 vs >200 cells/mm[3]). [b]Calculated from a repeated measures model adjusting for study treatment, visit (repeated 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].

Slide 19 of 70

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

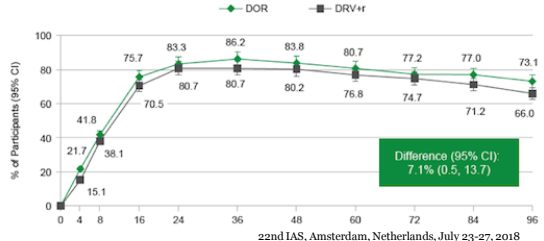


Cahn et al. *Lancet*. 2018 [Epub ahead of print].

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

Slide 20 of 70

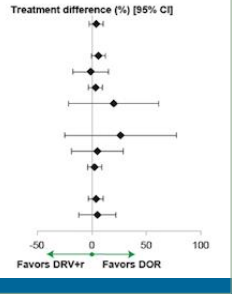
Figure 3. Proportion of Participants With HIV-1 RNA <50 c/mL†



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

Slide 21 of 70

	HIV-1 RNA <50 c/mL, % (N) DOR	DRV+r
All Participants	81.0 (342)	76.8 (323)
Baseline HIV-1 RNA, c/mL		
≤100,000	85.6 (264)	79.7 (282)
>100,000	65.4 (78)	65.2 (72)
≤500,000	81.8 (325)	78.1 (311)
>500,000	64.7 (17)	36.4 (11)
Baseline CD4+ T-cell Count, cells/mm³		
≤50	80.0 (5)	52.9 (17)
>50 and ≤200	71.0 (31)	65.8 (38)
>200	82.0 (306)	79.9 (268)
NRTI Component		
TDF/FTC	80.3 (295)	76.3 (283)
ABC/3TC	85.1 (47)	80.0 (40)



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

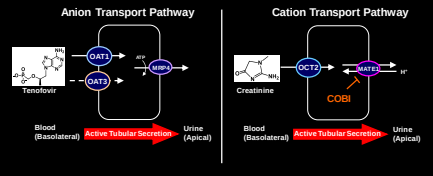
Slide 22 of 70

ARS 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

Slide 23 of 70

Tenofovir and COBI Interact with Distinct Renal Transport Pathways

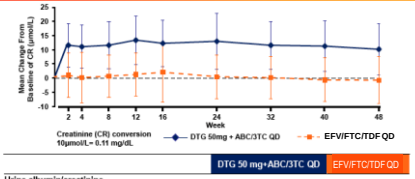


- The active tubular secretion of tenofovir and the effect of COBI on creatinine are mediated by distinct transport pathways in renal proximal tubules

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

Slide 20 of 70

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.
Wainberg S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b

Slide 25 of 70

Question

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

Slide 26 of 70

Case 3

- 30 yo Male 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 he should

Slide 27 of 70

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

1. Yes
2. No
3. Maybe

Slide 28 of 70

Question

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

Slide 29 of 70

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

Slide 30 of 70

ARS 6: Should you change ARV therapy now?

1. Yes
2. No
3. Not sure

Slide 31 of 70

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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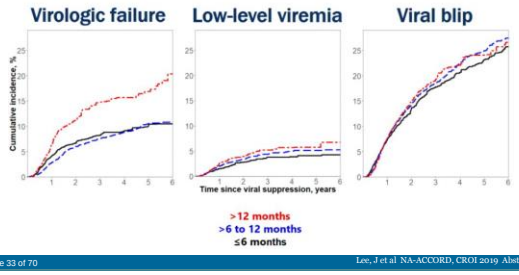
Slide 32 of 70

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

Virologic Failure, Low Level Viremia, and Blips



Slide 33 of 70

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?

Slide 34 of 70

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

Slide 35 of 70

ARS 7: At this point you would

A. Keep her on her current Rx (ABC/ 3TC / DTG)
B. Switch her to TDF / FTC / EFV (fdc)
C. Switch her to TAF / FTC/ ELV / cobi (fdc)
D. Switch her to TDF / FTC / RPV (fdc)
E. Switch her to TDF/ FTC (fdc) / DRV/r
F. Switch her to TAF/ FTC / ATV/r
G. Switch her to TDF / FTC / ATV/r
H. Some other option

Slide 36 of 70

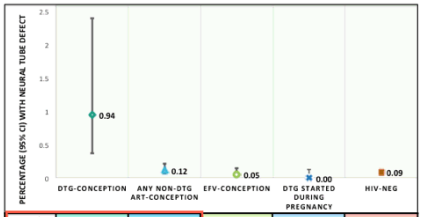
TAF PK - Fetus

- 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

Slide 37 of 70

NTD Prevalence Difference by Exposure



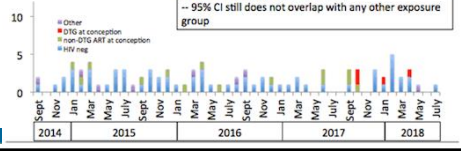
	DTG-CONCEPTION	ANY NON-DTG ART-CONCEPTION	EFV-CONCEPTION	DTG STARTED DURING PREGNANCY	HIV-NEG
NTDs/ Exposures	4/426	14/11,300	3/5,787	0/2,812	61/66,057
% with NTD (95% CI)	0.94% (0.37%, 2.4%)	0.12% (0.07%, 0.21%)	0.05% (0.02%, 0.15%)	0.00% (0.00%, 0.13%)	0.09% (0.07%, 0.12%)
Prevalence Difference (95%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

Slide 38 of 70

Update since 1 May 2018

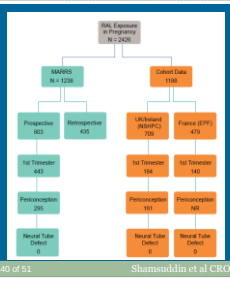
- From 1 May-15 July, there were **2 more NTDs;** 1 in an infant exposed to **DTG *started during pregnancy*** (8 weeks GA) and 1 birth to an **HIV-uninfected** woman
  - NTDs in DTG started in pregnancy: 1/3104 (0.03%, 95% CI 0.01%, 0.18%)

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



Slide 39 of 70

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 40 of 51

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

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

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

Slide 41 of 70

Question

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

Slide 42 of 70

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

Slide 43 of 70

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

A. TDF / 3TC / low dose (400mg) EFV (fdc; generic)
B. DTG / 3TC (fdc)
C. ABC/ 3TC / DTG (fdc)
D. TAF/ FTC (fdc) + DTG
E. TAF / FTC/ ELV / cobi (fdc)
F. TAF/ FTC / BIC (fdc)
G. TAF / FTC (fdc) + RAL (once daily)
H. TAF / FTC / RPV (fdc)
I. TAF/ FTC (fdc) + DRV/r (or cobi / fdc)
J. Some other option (e.g., DRV/r + DTG or …)

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 alon	26% (21/81)	95% (20/21)[a]
M184V/I + ≥ substitutio		(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] The protocol 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**

Slide 47 of 70

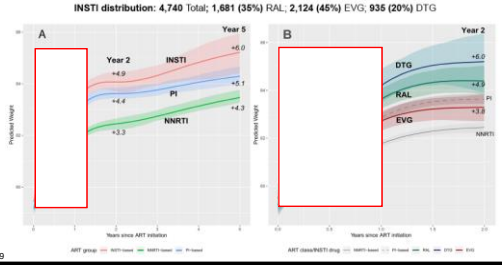
ARS 10: At this point you would…

A. Keep her on her current Rx (TAF/FTC/BIC)
B. Switch her to TDF/ FTC (fdc) / DRV/r
C. Switch her to TAF/ FTC / DRV/c (fdc)
D. Switch her to TDF / FTC / RPV (fdc)
E. Switch her to DTG / RLP (fdc)
F. Switch her to TAF / FTC / ATV/c
G. Some other option

Slide 48 of 70

Change in Weight Overtime – NA-ACCORD

Bourgi et al CROI 2019

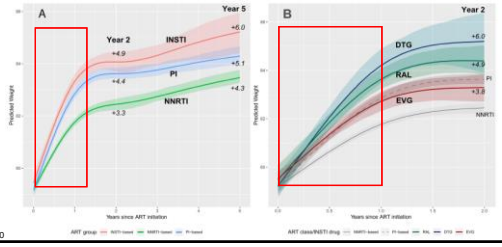


Slide 49

Change in Weight Overtime – NA-ACCORD

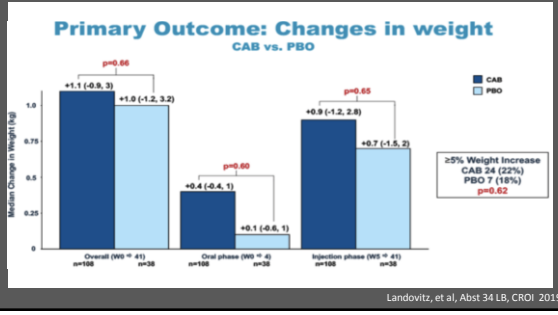
Bourgi et al CROI 2019

INSTI distribution: 4,740 Total; **1,681 (35%)** RAL; **2,124 (45%)** EVG; **935 (20%)** DTG



Slide 50

Cabotegravir vs Placebo for PrEP

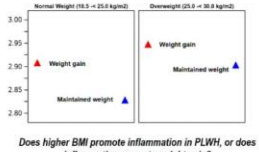


Landovitz, et al, Abst 34 LB, CROI 2019

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?

Baros, SH, et al. CROI 2019; Poster 673

Question

What should I use for PrEP Rx?

Slide 53 of 70

Case 8

- 45 yo Male makes an appointment to request PrEP
- He is single and has 1 – 4 different partners per month
- No significant PMHx
- No medications
- Labs are normal

Slide 54 of 70

ARS 11: At this point you would prescribe:

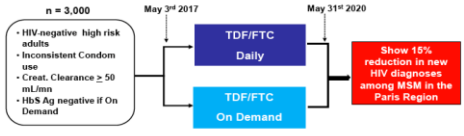
A. TDF / FTC (fdc) daily
B. TDF / 3TC (fdc; generic) daily
C. 2:1:1 (TDF/ FTC) PrEP (2 doses 12 hours prior to anticipated sexual activity…Then one dose daily for 2 days)
D. Not prescribe PrEP

Slide 55 of 70

Study Design

http://prevenir.anrs.fr/

Open-Label Prospective Cohort Study in the Paris Region



- **Participants opted for either Daily or On Demand PrEP and could switch regimens**
- Follow-up every 3 months with 4th Gen ELISA HIV test and plasma creatinine
- STI screening at physicians' discretion (Guidelines recommend every 3 months in MSM)
- Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

Slide 56 of 70

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

HIV Incidence (mITT Analysis)

Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)
TDF/FTC (Daily)	443	0 (0-0.8)
TDF/FTC (On Demand)	506	0 (0-0.7)

Mean Follow-up in this Open-Label Cohort: 7 months (SD: 4)

Incidence of study discontinuation:
3.3/100 PY including 1.5/100 PY who discontinued PrEP

85 HIV-infections averted*

* assuming an incidence of 9.17/100 PY as observed in the ANRS Ipergay study in Paris

Slide 57 of 70

Considerations of 2-1-1 vs Daily PrEP

	2-1-1 PrEP	Daily PrEP
Who can use it?	Only studied in MSM	Anyone
Chronic HBV	Can trigger a flair	Can be safety used
Planning	Need to plan sex at least 2hrs in advance	No planning needed
"Forgiveness"	Not forgiving of missed doses	Forgiving of missed doses during the week

Slide 58 of 70

Question

Should I simplify an "older" complex regimen?

Slide 59 of 70

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)

Slide 60 of 70

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

A. Continue current therapy (7 pills)
B. Switch to TAF / FTC/ ELV / c (fdc) /DRV (2 pills)
C. Switch to ABC/ 3TC / DTG (fdc) / DRV/c (2 pills)
D. Switch to TAF / FTC / RAL / DRV/c (4 pills)
E. Switch to TAF / FTC / DTG / DRV/c (3 pills)
F. Switch to TAF/FTC/BIC (1 Pill)
G. Switch to TAF / FTC / DTG (2 pills)
H. Some other regimen

Slide 61 of 70

Question

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

Slide 62 of 70

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

Slide 63 of 70

ARS 13: What ARV therapy should you use now?

A. Same regimen as originally on
B. Start an InSTI-based regimen
C. Start a PI-based regimen
D. Wait for repeat resistance test, then choose regimen based on results
E. Some other answer

Slide 64 of 70

Question

Should I stop abacavir in older patients?

Slide 65 of 70

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

Slide 66 of 70

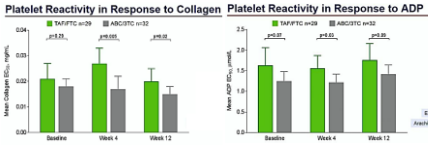
ARS 14: Besides asking him to quit smoking, what would you do?

A. Continue his current ARV Rx
B. Change his ABC/3TC to TAF / FTC containing Rx
C. Change his ABC/3TC to DRV/rit (continue DTG)
D. Some other option

Slide 67 of 70

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)

Mallon #677LB

Slide 68 of 70

Trial funded by Gilead Sciences, Inc

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
- Standard PrEP is daily TDF/FTC, though newer approaches are being developed, including 2:1:1 episodic treatment

Slide 69 of 70

Question-and-Answer

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