# Topical Management Decisions in 2020

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IAS–USA

## Learning Objectives

After attending this presentation, learners will be able to:

- Describe treatment of women of childbearing potential
- Describe treatment strategies and how they are impacted by co-morbid conditions
- Identify how to safely optimize therapy in those virologically suppressed

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- 32 year old AA woman newly diagnosed with HIV
- No past medical history, but states multiple male partners with infrequent condom use in last year
- Laboratory studies:
  - CD4 150 cells/mL, VL 734,000 copies/mL, HIV Genotype is wild type, CBC and Metabolic panel negative, hepatitis studies negative, HLA-B5701 negative, pregnancy test negative
- Upon evaluation she appears to be healthy young women, normal vital signs, BMI 30 with otherwise completely normal examination
- She is ready to start therapy and is hoping for something simple
- Planning to do everything possible to avoid getting pregnant

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## ARS Question 1: What do you recommend?

1. Dolutegravir/abacavir/lamivudine
2. Dolutegravir plus emtricitabine/tenofovir
3. Dolutegravir/lamivudine
4. Bictegravir/emtricitabine/tenofovir alafenamide
5. Raltegravir plus emtricitabine/tenofovir
6. Doravirine plus 2 NRTIs
7. Something else

- 32yo AA women with multiple male partners, HIV-1 positive
- Exam normal except for BMI 30
- CD4 150 cells/uL, VL 734,000 c/mL, HLA-B5701 neg, genotype wild type, hepatitis studies, CBC, metabolic panel unremarkable

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## Current ART Regimens

| DHHS[1] | IAS-USA[2] |
|---|---|
| *Recommended initial regimens for most people with HIV:*<br>▪ BIC/TAF/FTC<br>▪ DTG/ABC/3TC, if HLA-B*5701 negative<br>▪ DTG + (TAF or TDF)/(FTC or 3TC)<br>▪ RAL + (TAF or TDF)/(FTC or 3TC)<br>▪ DTG/3TC, except for individuals with HIV-1 RNA > 500,000 c/mL, with HBV, or for whom results of HIV genotypic resistance testing or HBV testing are not yet available | *Generally recommended initial regimens:*<br>▪ BIC/TAF/FTC<br>▪ DTG/ABC/3TC, if HLA-B*5701 negative<br>▪ DTG + TAF/FTC |

1. DHHS Guidelines. December 2019. 2. Saag. JAMA. 2018;320:379.

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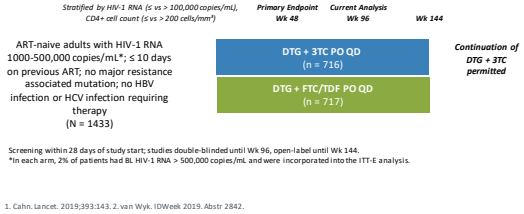
## GEMINI 1 and 2




Screening within 28 days of study start; studies double-blinded until Wk 96, open-label until Wk 144.
*In each arm, 2% of patients had BL HIV-1 RNA > 500,000 copies/mL and were incorporated into the ITT-E analysis.

1. Cahn. Lancet. 2019;393:143. 2. van Wyk. IDWeek 2019. Abstr 2842.

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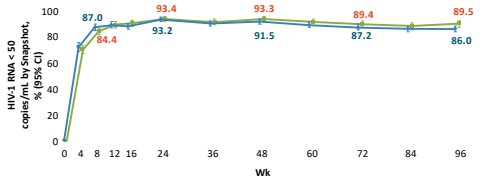
## GEMINI 1 and 2 (Week 96)

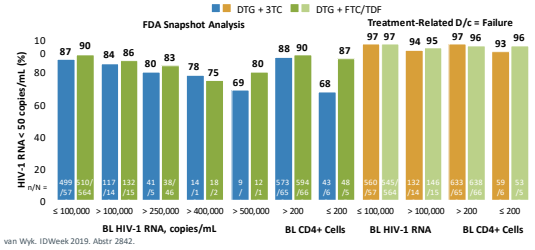



*Adjusted for baseline HIV-1 RNA, baseline CD4+ cell count, and study.
†Accounts for CVW, withdrawal for lack of efficacy or treatment-related AE, and participants meeting protocol-defined stopping criteria.

Cahn. IAS 2019. Abstr WEAB0404LB.



## GEMINI 1 and 2 by baseline VL and CD4




van Wyk. IDWeek 2019. Abstr 2842.



## ARS Question 2: What if she was planning to get pregnant?

1. Dolutegravir/abacavir/lamivudine
2. Dolutegravir plus emtricitabine/tenofovir
3. Dolutegravir/lamivudine
4. Bictegravir/emtricitabine/tenofovir alafenamide
5. Raltegravir plus emtricitabine/tenofovir
6. Doravirine plus 2 NRTIs
7. Something else

- 32yo AA women with multiple male partners, HIV-1 positive
- Exam normal except for BMI 30
- CD4 150 cells/uL, VL 734,000 c/mL, HLA-B5701 neg, genotype wild type, hepatitis studies, CBC, metabolic panel unremarkable

## ARS Question 3: If considering tenofovir-based regimen, which?

1. Dolutegravir plus emtricitabine/tenofovir disoproxil fumarate
2. Dolutegravir plus emtricitabine/tenofovir alafenamide
3. Bictegravir/emtricitabine/tenofovir alafenamide
4. Raltegravir plus emtricitabine/tenofovir DF
5. Raltegravir plus emtricitabine/TAF
6. Something else

- 32yo AA women with multiple male partners, HIV-1 positive
- Exam normal except for BMI 30
- CD4 150 cells/uL, VL 734,000 c/mL, HLA-B5701 neg, genotype wild type, hepatitis studies, CBC, metabolic panel unremarkable

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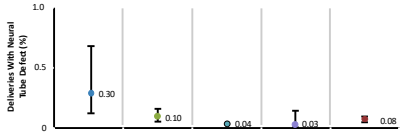
## Tsepamo: Prevalence of NTDs by ARV Use




| | At Conception | | | DTG During Pregnancy | HIV Negative |
|---|---|---|---|---|---|
| | DTG | Non-DTG | EFV | | |
| Total NTDs per exposures, n/N | 5/1683 | 15/14,792 | 3/7959 | 1/3840 | 70/89,372 |
| NTDs per exposures since May 2018, n/N | 1/1257 | 1/3492 | 0/2172 | 1/1028 | 9/23,315 |

Zash. NEJM. 2019;381:827.

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## Raltegravir Adverse Events in Pregnancy

- RAL manufacturer Adverse Event Review and Reporting System: 961 prospective, 520 retrospective reports through May 27, 2019
  - No evidence of increased rate of spontaneous abortion, stillbirth, or congenital anomalies in pregnant women exposed to RAL general population
  - No NTDs in prospective reports of RAL exposure at conception/during first trimester as of 9/6/2019; 1 case of anencephaly following second trimester RAL initiation
- No NTDs reported among 222 periconception exposures to RAL in UK National Study of HIV in Pregnancy and Childhood
- No NTDs reported among 218 periconception exposures to RAL in ANRS-French Perinatal Cohort

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Shamsuddin. IDWeek 2019. Abstr 886.

## Guidelines for DTG in Pregnancy

**WHO Guidance[1]**

- DTG **can be prescribed** for women/girls of childbearing potential who wish/or are not avoiding pregnancy **if they have been fully informed of the potential increase in the risk of neural tube defects** (at conception and until the end of the first trimester)

**DHHS Guidance[2]**

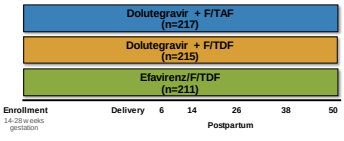
DTG a "**preferred**" ARV for pregnant women, irrespective of trimester
Based on higher rate of virologic suppression, faster rate of HIV-1 RNA decline, and higher genetic barrier of DTG vs other ARVs
DTG an "**alternative**" ARV for women who may conceive
Rationale: more time to reach virologic suppression using DTG-sparing ART in these cases

Slide 14 of 44 1. WHO ARV Policy Update. July 2019. 2. DHHS Perinatal Guidelines. April 2020.

## IMPAACT 2010 Study: DTG in Pregnancy

Phase 3 (22 sites, 9 countries)

Open-label
Pregnant women with HIV and 14 to 28 weeks gestation
Treatment-naïve
Up to 14 days of ART in current pregnancy allowed




Primary outcomes:
HIV RNA <200 copies/mL at delivery (non-inferiority margin: -10%)
Adverse pregnancy outcomes, maternal and infant grade 3 adverse events, infant neonatal death.
Baseline characteristics:
Age: 27 years.
Enrolled in Africa: 88%.
CD4: 466 cells/mm³.
HIV RNA: 903 copies/mL.
ART in pregnancy prior to entry: 83%.

Slide 15 of 44 Chinula L, et al. CROI 2020. Boston, MA. Abstract 130LB.

## IMPAACT 2010 Study: DTG in Pregnancy

- DTG-based ART was non-inferior and superior to efavirenz/F/TDF for HIV RNA <50 c/mL at delivery 98% versus 91% (*P*=0.005)
- DTG + F/TAF had fewer adverse pregnancy outcomes and fewer neonatal deaths than efavirenz/F/TDF

**Adverse Pregnancy Outcomes and Maternal/Infant Grade ≥3 Adverse Events**

| | Dolutegravir + F/TAF (n=217) | Dolutegravir + F/TDF (n=215) | Efavirenz / F/TDF (n=211) |
|---|---|---|---|
| Adverse pregnancy outcomes | | | |
| Any | 24* | 33 | 33 |
| Preterm delivery | 6† | 9 | 12 |
| Small for gestational age | 16 | 23 | 21 |
| Stillbirth | 4 | 5 | 2 |
| Grade ≥3 adverse events | | | |
| Maternal | 21 | 26 | 22 |
| Infant | 14 | 16 | 21 |
| Neonatal death | 1† | 1.5 | 5 |

Slide 16 of 44 Chinula L, et al. CROI 2020. Boston, MA. Abstract 130LB.

## ARS Question 4:

Started DTG plus FTC/TAF with good tolerance and viral suppression but progressive weight gain over next 18 months (BMI increased to 35) despite counseling about diet and exercise. What would you recommend?

1. Just keep working on diet and exercise
2. Switch to DTG/ABC/3TC
3. Switch to BIC/FTC/TAF
4. Switch to DTG/3TC
5. Switch to DTG/RPV
6. Switch to RAL-containing regimen
7. Switch to INSTI-sparing regimen, e.g. PI or NNRTI
8. Something else

- 32 yo HIV+ AA women with multiple male partners
- Started DTG + FTC/TAF 18 months ago with VL <50 c/mL but BMI increased from 30-35

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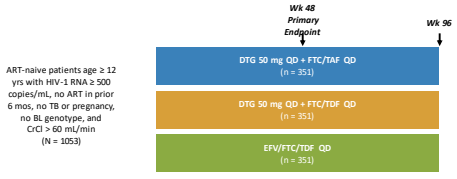
## ADVANCE: Phase III in South Africa




1. Venter. IAS 2019. Abstr WEAB0405LB. 2. Venter. NEJM. 2019;[Epub].

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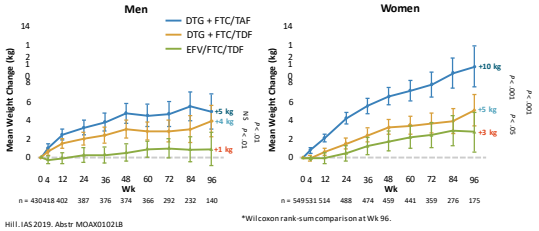
## ADVANCE: Phase III in South Africa




*Wilcoxon rank-sum comparison at Wk 96.

Hill. IAS 2019. Abstr MOAX0102LB

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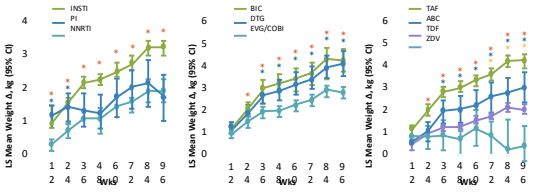
## Multiple Naïve Treatment Trials




*Color-coded to match respective comparators, denoting *P* ≤ .05 vs NNRTI (first panel), EVG/COBI (second panel), or ZDV (last panel).

Sax. Clin Infect Dis. 2019:[Epub].

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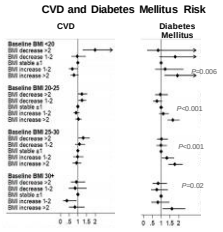
## D:A:D Study: Changes in BMI and CVD in PLWH

- Event rates (/1000 years) from 1999-2016 (n=43,011)
  - CVD: 5.8 (95% CI 5.5-6)
    - Rate males >females (6.9 vs 2.7)
  - DM: 4.5 (95% CI 4.2-4.7)
    - Rate males>females (4.8 vs 3.4)
- Increases in BMI across all baseline levels
  - Not associated with increased risk of CVD
  - Was associated with increased risk of DM
- Study limitations
  - Did not access impact of specific ARVs (no INSTI data), no behavioral data, and low event rates




Petoumenos K, et al. CROI 2020. Boston, MA. Abstract 83.

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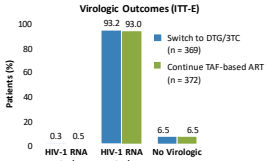
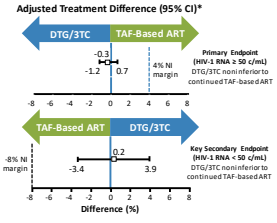
## Tango Study: Week 48 Virologic Response




Ait-Khaled. EACS 2019. Abstr PS7/2. van Wyk. IAS 2019. Abstr WEAB0403LB.

*Adjusted for baseline third agent class.

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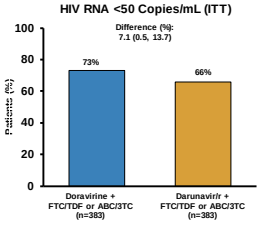
## DRIVE-FORWARD Study: DOR + 2 NRTIs (wk 96)

- Doravirine + 2 NRTIs demonstrated greater efficacy at week 96 than darunavir/r + 2 NRTIs
  - Similar results regardless of baseline subgroups (ie, HIV RNA level, CD4 count, NRTI combination, demographic characteristics)
- Resistance with virologic failure in the doravirine arm (n=2)
  - V106I, H221Y, F227C plus M184V
  - V106A, P225Y/H plus V118I, M184V
- Safety of the doravirine arm
  - Discontinuations due to adverse events (2%)
  - Favorable lipid profile




Molina J-M, et al. J Int AIDS Soc. 2018;21(suppl 6). Abstract LBPEC017.

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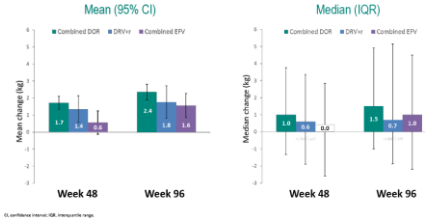
## DRIVE-FORWARD Change in Body Weight







CI, confidence interval; IQR, interquartile range.

Slide 24 of 44 Orkin C, et al. 17th EACS 2019. Abst. PS3/2

- DHHS guidelines recognize weight gain as a common and/or severe AE associated with ART

> ***"Weight gain has been associated with initiation of ART and subsequent viral suppression. The increase appears to be greater with INSTIs than with other drug classes. Greater weight increase has also been reported with TAF than with TDF and greater with DOR than EFV."***

- Further clarification on distribution of weight gain, if it is associated with cardiometabolic risk, and if it is reversible upon discontinuation of the offending agent is needed

Slide 25 of 44 DHHS Guidelines. December 2019.

## Optimizing therapy in suppressed patient

- 46 year old women diagnosed with HIV 10 years ago when diagnosed in Dallas with PJP with CD4 34 cells/uL, VL 430,000 c/mL
- Responded to PJP treatment and started on TDF/FTC/EFV with good response for several years
- Was on and off therapy several years ago with occasional elevations in viral load
- Stopped and then restarted therapy 18 months ago with DRV plus RTV-based regimen and now on DRV/COBI/FTC/TAF with stable suppression for last 12 months BUT with gastrointestinal complaints she relates to ARVs
- Moved to LA, no records available, on stable regimen but complains of mild gastrointestinal symptoms with CD4= 290 cells/uL, VL <20 copies/mL
- She is interested in a new regimen that is simple to take but that might not cause GI symptoms

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## ARS Question 5: Would you recommend proviral DNA genotype?

1. Yes
2. No
3. Maybe

- 46 yo woman, h/o PJP and possible failure in past on EFV/FTC/TDF
- CD4 290 cells/uL, VL <20 c/mL on DRV/COBI/FTC/TAF with GI symptoms
- Interested in change to eliminate GI symptoms

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## Role of proviral DNA genotype

- Potential role for assessing underlying resistance in those currently virologically suppressed
- Correlates with plasma HIV RNA results in those not suppressed
- Guidelines:
  - If switching in suppressed patient at risk for prior resistance, proviral DNA genotypic resistance testing can be considered
  - For those with no prior virologic failures and on first or second regimen, or have results from prior virologic failures, the use of the proviral DNA genotypic testing is unlikely to provide additional information
  - Always interpret with caution, as may not detect previously selected drug resistance and may identify those that are inconsistent with patient's response to treatment, making the clinical relevance questionable

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## ARS Question 6: Proviral genotype not available, what to do?

1. Continue current regimen and treat symptomatically
2. Switch to DTG + 2 NRTIs
3. Switch to BIC/FTC/TAF
4. Switch to RAL + 2 NRTIs
5. Switch to DTG/3TC
6. Switch to DTG/RPV
7. Switch to LA CAB/LA RPV when available
8. Something else

- 46 yo woman, h/o PJP and possible failure in past on EFV/FTC/TDF
- CD4 290 cells/uL, VL <20 c/mL on DRV/COBI/FTC/TAF with GI symptoms
- Interested in change to eliminate GI symptoms

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## ARS Question 7: What if documented M184V and K103N mutations?

1. Continue current regimen and treat symptomatically
2. Switch to DTG + 2 NRTIs
3. Switch to BIC/FTC/TAF
4. Switch to RAL + 2 NRTIs
5. Switch to DTG/3TC
6. Switch to DTG/RPV
7. Switch to LA CAB/LA RPV when available
8. Something else

- 46 yo woman, h/o PJP and possible failure in past on EFV/FTC/TDF **(DOCUMENTED M184V AND K103N)**
- CD4 290 cells/uL, VL <20 c/mL on DRV/COBI/FTC/TAF with GI symptoms
- Interested in change to eliminate GI symptoms

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## The why and how to switch

**Why**

- Simplify regimen (pill number and frequency)
- Tolerability
- Comorbidity
- Drug–drug and drug–food interactions
- Pregnancy
- Cost

**How**

- Maintain viral suppression to avoid resistance
- Need to consider
- Previous ART
- Previous resistance
- Likelihood of adherence
- Drug–drug or drug–food interactions
- Comorbid conditions

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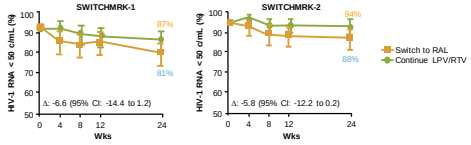
## SWITCHMRK: A cautionary tale

- Randomized, double-blind, active-controlled trials in which virologically suppressed pts continued LPV/RTV-based regimen or switched to RAL-based regimen (N = 702)




Prespecified noninferiority margin: -12%.

- **Underlying resistance matters**: percent with HIV-1 RNA < 50 c/mL for RAL vs LPV/RTV by investigator report of previous virologic failure: No, 89% vs 90%; Yes, 77% vs 92%

Eron JJ, et al. Lancet. 2010;375:396-407.

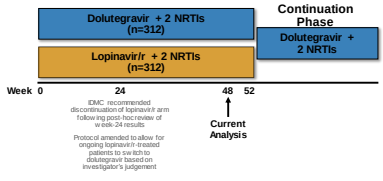


## Switching to DTG with underlying resistance

### Extrapolate from DAWNING

**Phase 3b (ongoing)**

**Open-label, non-inferiority**
**Virologic failure of NNRTI + 2 NRTIs (HIV RNA ≥400 copies/mL for >6 months)**
**No primary resistance to PIs or INSTIs**
**Investigator-selected NRTIs (≥1 fully active)**

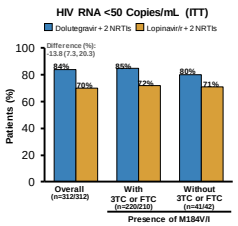



Brown D, et al. 26th CROI. Seattle, 2019. Abstract 144.
Aboud M, et al. *Lancet Infect Dis*. 2019;19:253-264.



## DAWNING

- HIV RNA <50 copies/mL at week 48
  - DTG superior to lopinavir/r (*P*<0.001)
- Post-hoc analysis found similar response rates in the DTG + 2 NRTIs arm regardless of
  - Pre-existing resistance to 1 of the NRTIs in the background
  - Use of either lamivudine or emtricitabine in the presence of M184V
  - Baseline NRTI resistance patterns
  - Use of second-line background NRTI
- Developed emergent dolutegravir resistance (n=2)




Brown D, et al. 26th CROI. Seattle, 2019. Abstract 144.
Aboud M, et al. *Lancet Infect Dis*. 2019;19:253-264.

## Switching to BIC/FTC/TAF with underlying resist

### GS 380-4030

*Stratified by known/suspected NRTI resistance at BL (K65R or ≥ 3 TAMS vs other NRTI RAMs vs none)*

***Wk 48***

Adults receiving DTG + FTC/(TAF or TDF) with HIV-1 RNA < 50 copies/mL for ≥ 3-6 mos,* no known INSTI resistance,† and no previous VF on INSTI (N = 565)

- BIC/FTC/TAF QD (n = 284)
- DTG + FTC/TAF QD (n = 281)

*3 mos if no known NRTI resistance mutations, 6 mos with known/suspected resistance.
†Documented or suspected NRTI, NNRTI, or PI resistance permitted.

Baseline characteristics:
- High NRTI resistance (K65R or ≥3 TAMs): 5%.
- Low/other NRTI resistance: M184V/I: 19%.
- No NRTI resistance: 26%.
- Any NNRTI and PI resistance: 21% and 7%.

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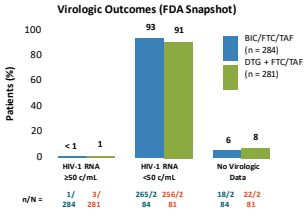
## GS 380-4030 outcomes




Sax. IAS 2019. Abstr MOAB0105

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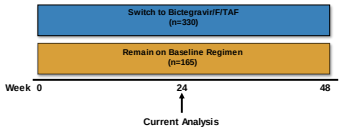
## BRAAVE: Switch to BIC/FTC/TAF in Black Adults

**Phase 3 study**

**Open-label**
**Black**
**On stable ART (2 NRTIs + 3rd agent)**
**HIV RNA <50 copies/mL**
**eGFR: ≥50 mL/min**

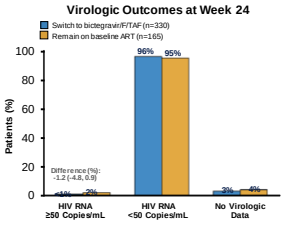



Primary outcome: HIV RNA ≥50 copies/mL at week 24.
NRTI backbone: F/TAF (67%), F/TDF (19%), ABC/3TC (14%).
3rd agent: INSTI (59%), NNRTI (29%), bPI (6%), other (6%).
**Resistance:**
**NRTI (14%), NNRTI (20%), PI (12%).**

Slide 37 of 44 Hagins D, et al. CROI 2020. Boston, MA. Abstract 36.

## BRAAVE Study

- BIC/F/TAF was non-inferior to remaining on baseline ART
  - Baseline resistance had no impact on maintaining virologic suppression
- No treatment-emergent resistance
- Switching to BIC/F/TAF was safe/well tolerated
  - Discontinuations due to AE: 2%
  - Small reductions in TC, Tg

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Hagins D, et al. CROI 2020. Boston, MA. Abstract 36.

## ARS Question 8: LA is available and patient wants it: what to do?

1. Discourage because of underlying resistance
2. Discourage because of other concerns with regimen
3. Counsel about risk but agree to trial with f/u

- 46 yo woman, h/o PJP and possible failure in past on EFV/FTC/TDF **(DOCUMENTED M184V AND K103N)**
- CD4 290 cells/uL, VL <20 c/mL on DRV/COBI/FTC/TAF with GI symptoms
- Interested in change to eliminate GI symptoms

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## ARS Question 9: You decide patient can try LA regimen: Q4 or Q8?

1. Only recommend Q4 weeks
2. Offer Q4 or Q8 weeks if available

- 46 yo woman, h/o PJP and possible failure in past on EFV/FTC/TDF **(DOCUMENTED M184V AND K103N)**
- CD4 290 cells/uL, VL <20 c/mL on DRV/COBI/FTC/TAF with GI symptoms
- Interested in change to eliminate GI symptoms

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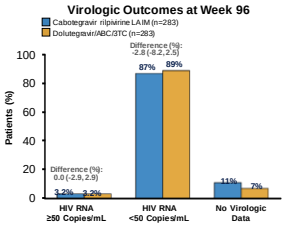
## FLAIR: Naïve patients with LA CAB/RPV qMonth




Orkin C, et al. CROI 2020. Boston, MA. Abstract 482LB.

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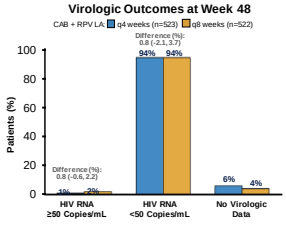
## ATLAS 2M: LA CAB/RPV Q4 vs. Q8 weeks

- CAB-LA + RVP-LA q4 and 8 weeks non-inferior
- Confirmed virologic failure rate
  - q4 versus q8 weeks: <1% versus 2%
  - All confirmed virologic failures (n=10) retained phenotypic sensitivity to DTG




Overton ET, et al. CROI 2020. Boston, MA. Abstract 34.

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## Managing roll out of Long Acting regimen

- Pharmacokinetic tail of distinct pharmacokinetics
- Missed visits
- Patient unable to access injectable medications
- Women of childbearing potential
- Other?

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## Question-and-Answer Session