IAS Update 2019

JOHN E. MCKINNON, MD, MSC
SENIOR STAFF
HENRY FORD HOSPITAL

Disclosure

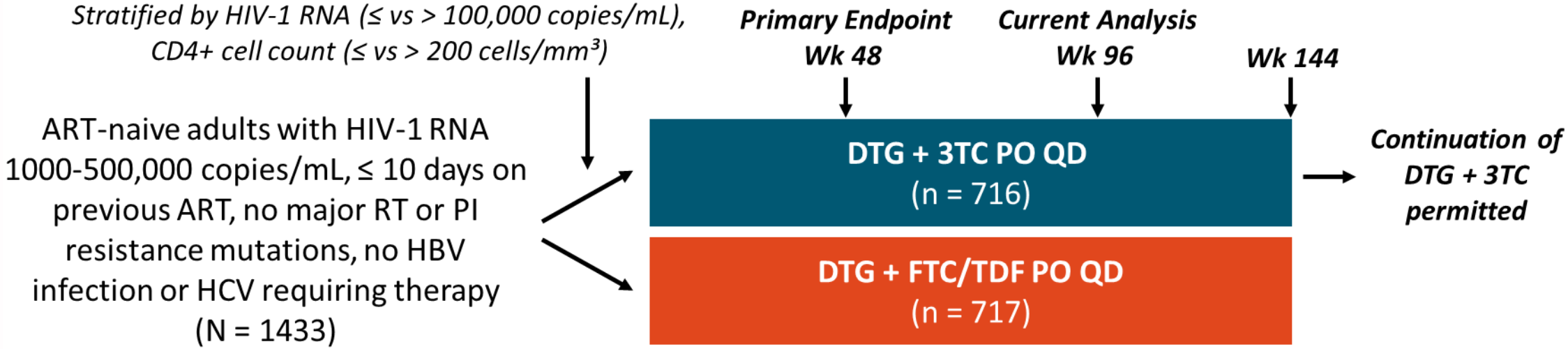
- I have participated in clinical studies, PI grants, research panels, advisory boards and have speaker for:
  - Abbott Molecular
  - Gilead Sciences
  - Viiv Healthcare
  - Merck & Co
- Data and slides were obtained and made for this presentation. Sources included from:
  - IAS 2019 abstracts, posters and presentations
  - Slides shared by investigators, companies
  - ClinicalOptions.com
  - NEJM

Outline

- **Integrase Studies**
- Integrase and Neural Tube Defects
- Weight gain
- Data from new ART and other agents
- Take home points

GEMINI-1 and -2: Study Design

- Parallel, international, randomized, double-blind phase III noninferiority studies



Screening within 28 days of study start; studies double-blinded until Wk 96, open-label until Wk 144.

- Secondary endpoints at Wk 96: HIV-1 RNA < 50 copies/mL (FDA Snapshot and TRDF analyses); AEs; resistance; changes from BL in bone, renal, and lipid parameters

Cahn. IAS 2019. Abstr WEAB0404LB. NCT02831673. NCT02831764.

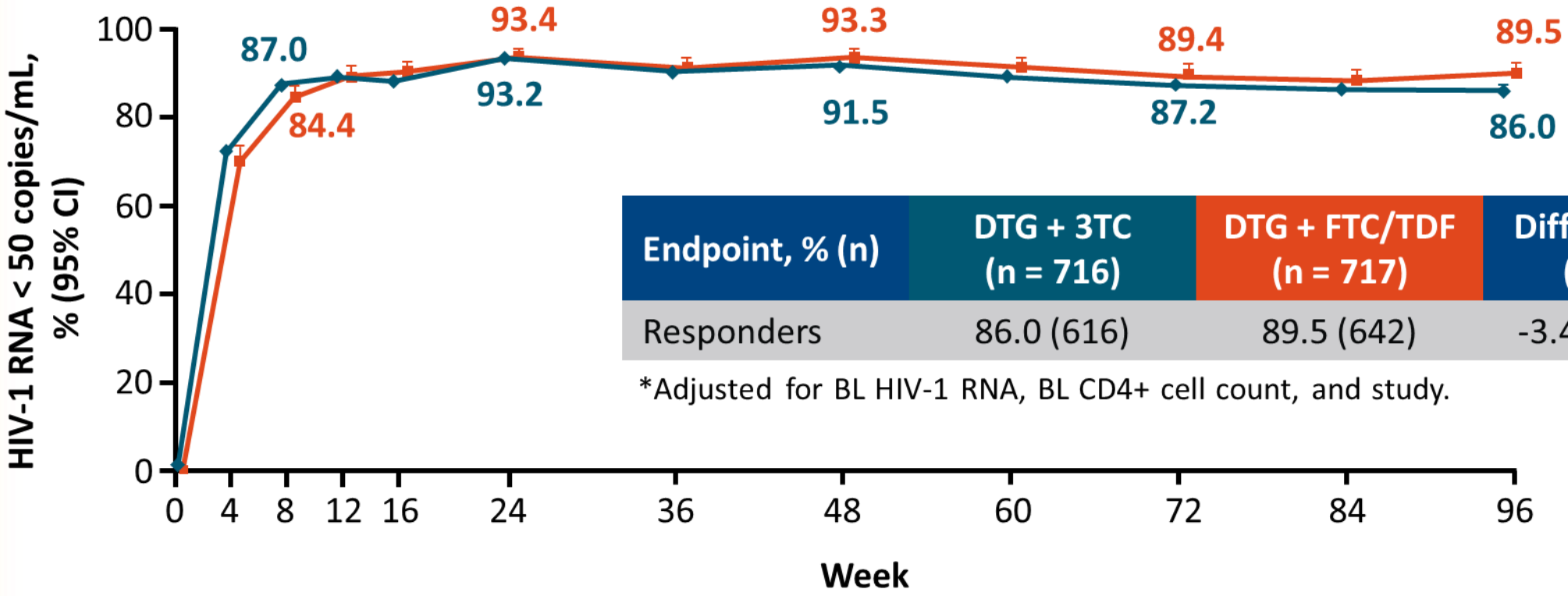
GEMINI-1 and -2: Baseline Characteristics

Characteristic	DTG + 3TC (n = 716)	DTG + FTC/TDF (n = 717)
Median age, yrs (range)	32.0 (18-72)	33.0 (18-70)
▪ ≥ 50 yrs of age, n (%)	65 (9)	80 (11)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
▪ Black/African heritage	97 (14)	76 (11)
▪ Asian	71 (10)	72 (10)
▪ White	480 (67)	497 (69)
▪ Other	68 (9)	72 (10)
Hispanic/Latino, n (%)	215 (30)	232 (32)
Median HIV-1 RNA, $\log_{10}$ copies/mL (range)	4.43 (1.59-6.27)	4.46 (2.11-6.37)
▪ ≤ 100,000 copies/mL, n (%)	576 (80)	564 (79)
Median CD4+ cell count, cells/mm^3 (range)	427.0 (19-1399)	438.0 (19-1497)
▪ > 200 cells/mm^3, n (%)	653 (91)	662 (92)

Cahn. IAS 2019. Abstr WEAB0404LB.

GEMINI-1 and -2: Virologic Response at Wk 96

- DTG + 3TC met criteria for noninferiority vs DTG + FTC/TDF in GEMINI-1, -2, and pooled analysis



Endpoint, % (n)	DTG + 3TC (n = 716)	DTG + FTC/TDF (n = 717)	Difference,* % (95% CI)
Responders	86.0 (616)	89.5 (642)	-3.4 (-6.7 to 0)

*Adjusted for BL HIV-1 RNA, BL CD4+ cell count, and study.

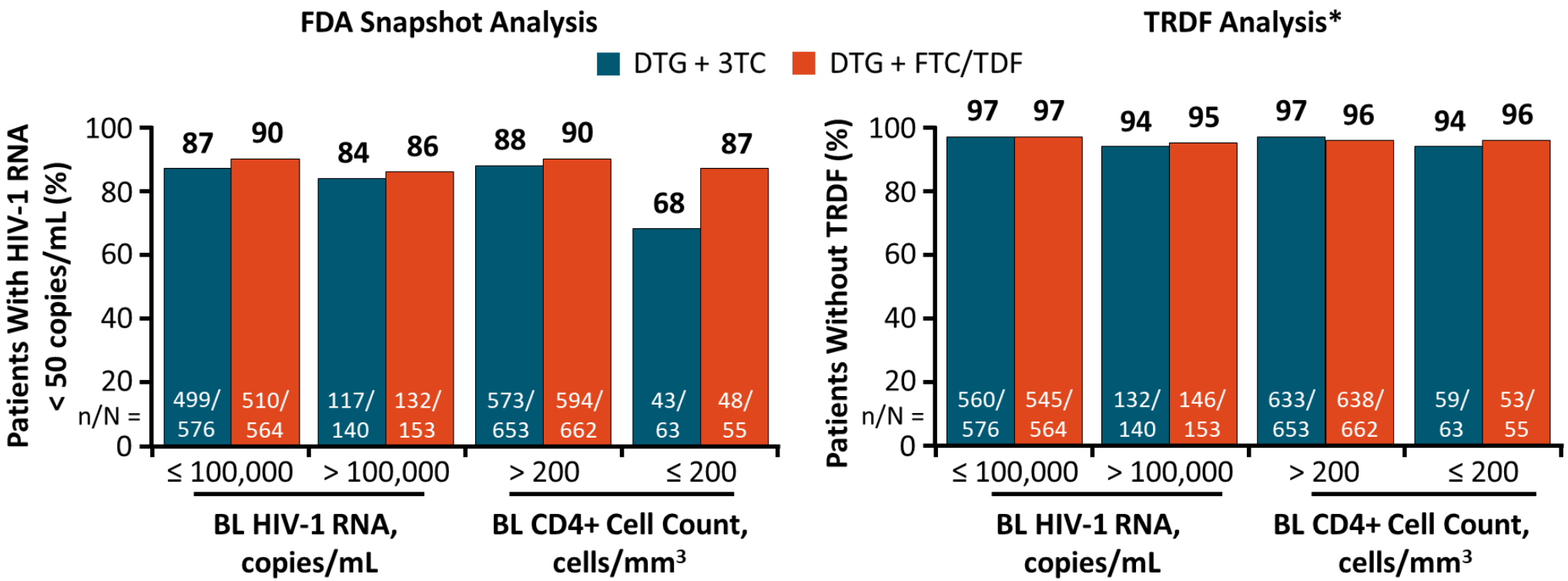
Cahn. IAS 2019. Abstr WEAB0404LB. Reproduced with permission.

GEMINI-1 and -2: Reasons for Nonresponse at Wk 96

Snapshot Outcome, % (n)	Wk 48		Wk 96	
	DTG + 3TC (n = 716)	DTG + FTC/TDF (n = 717)	DTG + 3TC (n = 716)	DTG + FTC/TDF (n = 717)
HIV-1 RNA ≥ 50 copies/mL	2.8 (20)	1.8 (13)	3.1 (22)	2.0 (14)
No virologic data	5.7 (41)	4.9 (35)	10.9 (78)	8.5 (61)
▪ Discontinuation for AE or death	1 (10)	2 (13)	3 (22)	3 (21)
▪ Discontinuation for other reasons*	4 (29)	3 (22)	8 (56)	5 (38)
▪ On study but data missing in window	< 1 (2)	0	0	< 1 (2)

*Includes protocol deviation, LTFU, physician decision, withdrawal by participant, and lack of efficacy (n = 1).

GEMINI-1 and -2: Virologic Response at Wk 96 by Baseline HIV-1 RNA and CD4+ Cell Count



*Accounts for CVW, withdrawal for lack of efficacy or treatment-related AEs, and participants meeting protocol-defined stopping criteria.

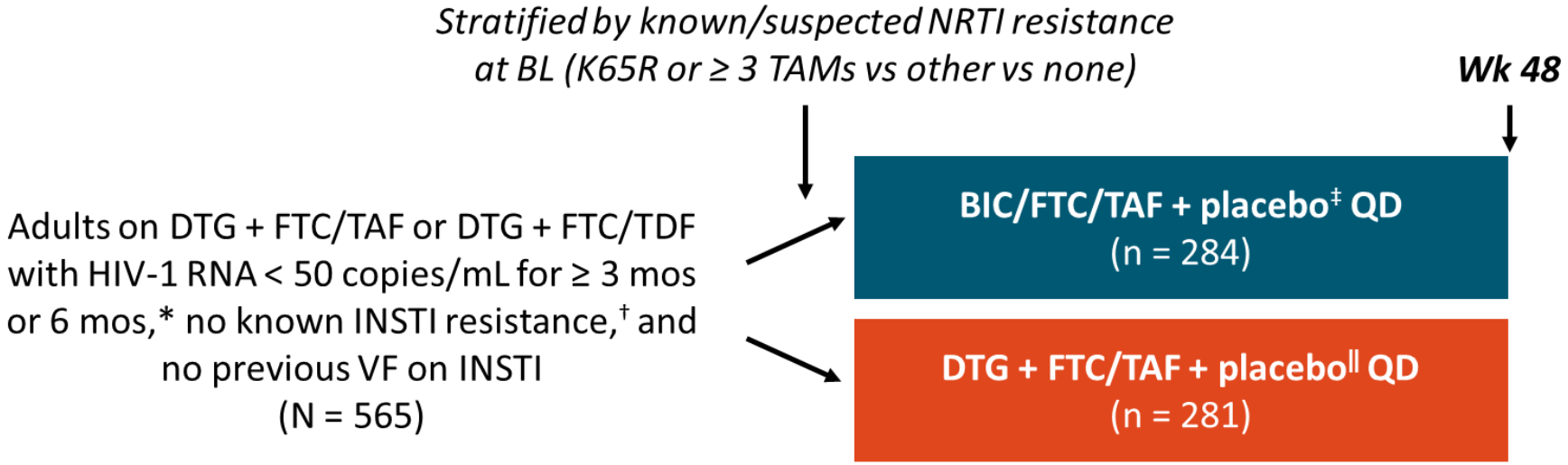
GEMINI-1 and -2: Conclusions

- Virologic efficacy of DTG + 3TC noninferior to DTG + FTC/TDF at Wk 96 by FDA Snapshot analysis in treatment-naive patients
  - HIV-1 RNA < 50 copies/mL in 86.0% vs 89.5% of patients, respectively
    - Adjusted difference: -3.4% (95% CI: -6.7% to 0%)
- Low rates of confirmed virologic withdrawal (ie, virologic failure) through Wk 96 (≤ 1.5% of patients per arm)
  - No treatment-emergent INSTI or NRTI mutations in any patient with CVW
- Safety and tolerability similar between arms through Wk 96
  - DTG + 3TC use associated with significant reduction in drug-related AEs, more favorable changes in renal and bone biomarkers
- Weight gain reported as an AE in 1.8% of patients receiving DTG + 3TC, 1.4% receiving DTG + FTC/TDF
  - Mean change from BL: 3.1 vs 2.1 kg, respectively

Cahn. IAS 2019. Abstr WEAB0404LB.

Study 380-4030: Study Design

- Randomized, double-blind, active-controlled phase III noninferiority trial



*3 mos if no known NRTI resistance mutations, 6 mos with known/suspected resistance. †Documented/suspected NRTI, NNRTI, or PI resistance permitted. ‡DTG + FTC/TAF placebo. ‖BIC/FTC/TAF placebo

- Primary endpoint: HIV-1 RNA ≥ 50 copies/mL at Wk 48 by FDA Snapshot algorithm
  - Noninferiority margin: 4%

Sax. IAS 2019. Abstr MOAB0105.

Study 380-4030

Characteristic	BIC/FTC/TAF (n = 284)	DTG + FTC/TAF (n = 281)
Median age, yrs (range)	51 (22-79)	50 (20-79)
Male, %	86	85
Race/ethnicity, %		
▪ White	71	72
▪ Black	24	22
▪ Hispanic/Latino	22	18
Median CD4+ cell count, cells/mm^3 (IQR)	659 (486-885)	642 (462-791)
Median $eGFR_{GC}$, mL/min (IQR)	97 (79-114)	100 (83-124)
NRTIs at BL: FTC/TAF, %	68	69

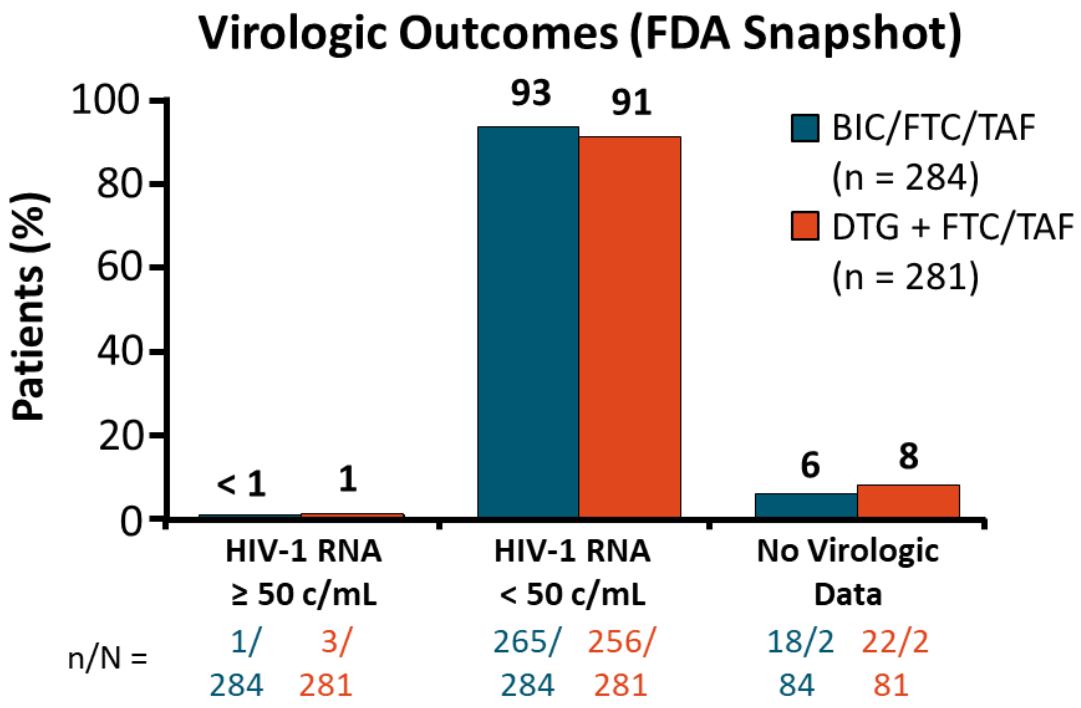
Resistance:

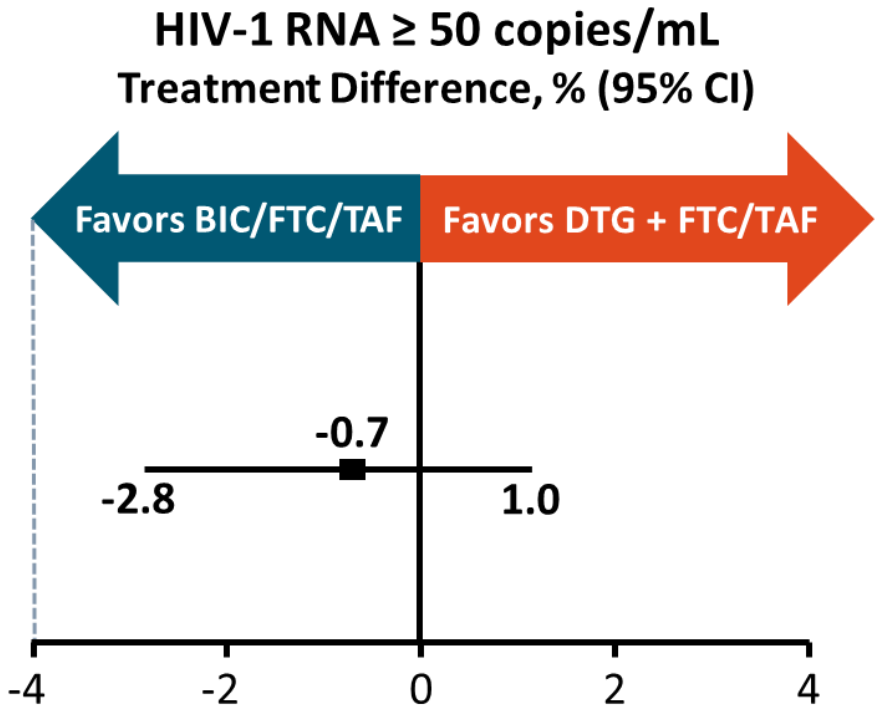
- Investigator assessed
- Hx genotype (50%)
- Proviral DNA (69%)
- Available in 83% of patients

NRTI Mutation, n (%)	Stratification* (n = 565)	Final Analysis† (n = 565)	BIC/FTC/TAF (n = 284)	DTG + FTC/TAF (n = 281)
Stratification categories				
▪ K65R/E/N or ≥ 3 TAMs‡	15 (3)	30 (5)	16 (6)	14 (5)
▪ Any other pattern‖	63 (11)	108 (19)	55 (19)	53 (19)
▪ No NRTI mutation	487 (86)	427 (76)	213 (75)	214 (76)
M184V/I¶ ± other mutations	29 (5)	81 (14)	47 (17)	34 (12)
M184V/I¶ only	12 (2)	21 (4)	15 (5)	6 (2)

Study 380-4030: Virologic Outcome at Wk 48

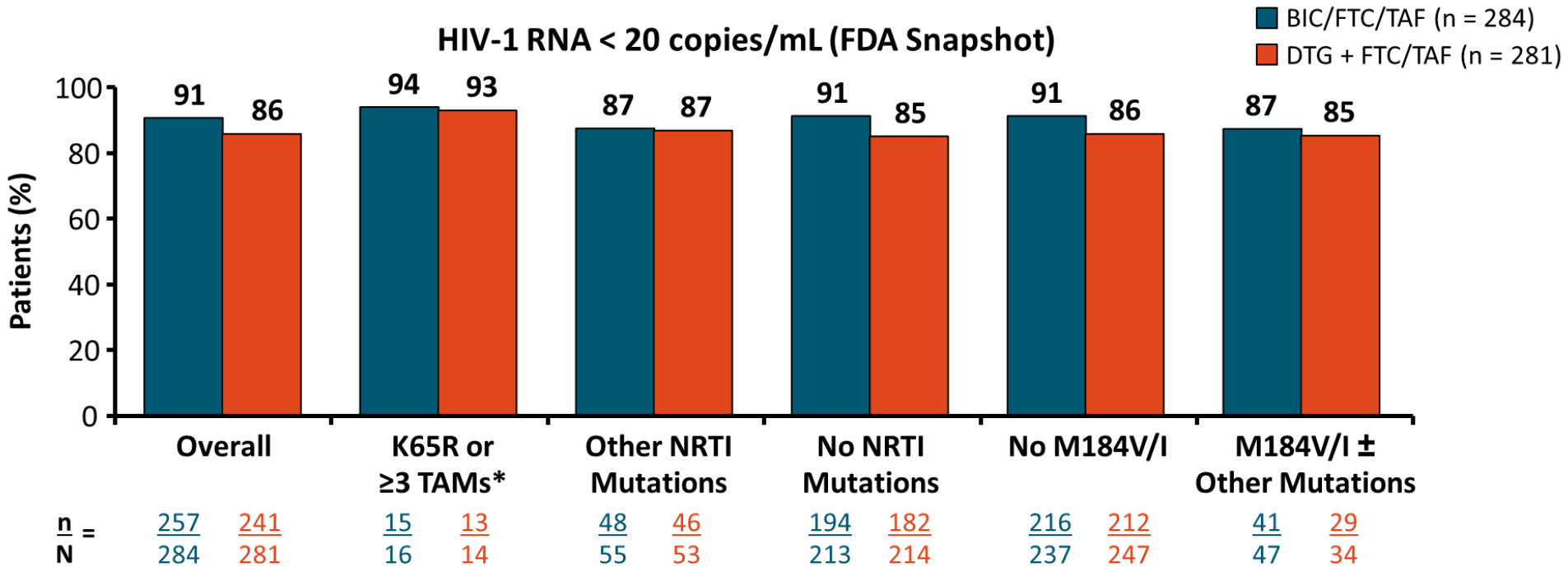
- BIC/FTC/TAF noninferior to remaining on DTG + FTC/TAF
- HIV-1 RNA ≥ 50 copies/mL not observed in any pts with preexisting NRTI resistance





Sax. IAS 2019. Abstr MOAB0105.

Study 380-4030



* Includes K65R/E/N, or ≥3 TAMs that include M41L or L210W, or T69 insertion.

- 64.1% of patients on BIC/FTC/TAF and 60.5% of patients on DTG + FTC/TAF had undetectable HIV-1 RNA, consistent across resistance categories

Study 380-4030: Conclusions

- Switching to BIC/FTC/TAF from DTG + FTC/TAF or DTG + FTC/TDF was noninferior to continuing DTG + FTC/TAF in virologically suppressed patients, even though study population included patients with documented or suspected NRTI, NNRTI, or PI resistance
- Wk 48 HIV-1 RNA ≥ 50 copies/mL was not observed for any patient with preexisting NRTI resistance mutation
- Longer duration of ART, a prior PI-containing regimen, black race, and BL PI or NNRTI resistance were associated with NRTI resistance mutation at BL
- No treatment-emergent resistance through Wk 48 in either arm
- Adverse events, changes in fasting lipids, and changes in weight were similar between treatment groups

Paul Sax (presenting author comments)

- M184V alone likely to be able to be managed with a (TAF or TDF)/FTC regimen and either DTG or BIC
- Questions:
  - K65R + M184V management
  - Switching patients suppressed on a PI regimen but with NRTI resistance

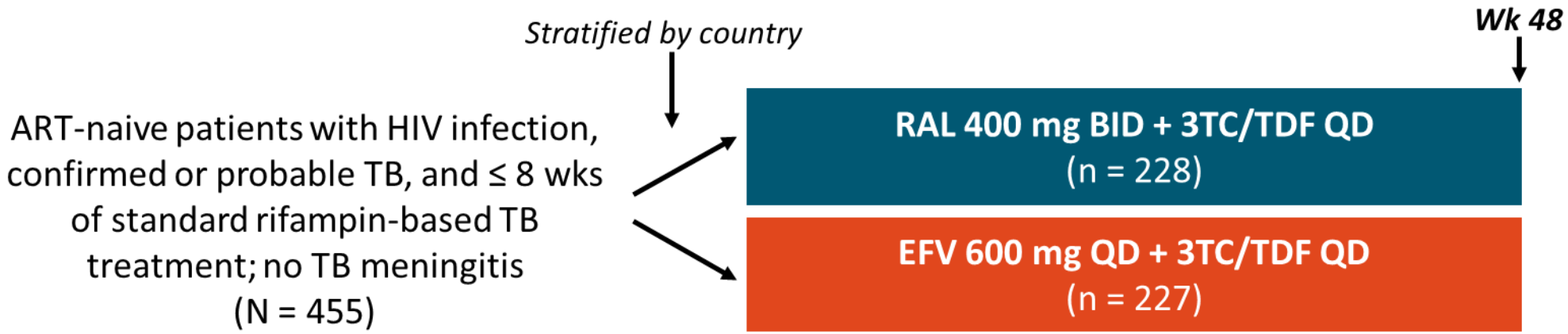
ANRS 12300 Reflate TB2: RAL + 3TC/TDF Does Not Achieve Noninferior Efficacy vs EFV + 3TC/TDF at Wk 48 in ART-Naive Adults With HIV and TB

- INSTI-based ART with DTG or RAL has been assessed as an alternative to EFV-based regimens for treatment of patients coinfected with HIV and TB[1,2]
  - PK analyses show that using a double dose of DTG or RAL compensates for their drug–drug interaction with rifampin[3,4]
- Phase II ANRS 12180 Reflate TB study demonstrated similar proportions of HIV/TB-coinfected patients achieving HIV-1 RNA < 50 copies/mL at Wk 48 with 3TC/TDF plus RAL 400 mg BID, RAL 800 mg BID, or EFV 600 mg QD[2]
  - RAL 400 mg BID better tolerated than RAL 800 mg BID
- Current phase III study evaluates noninferiority of RAL 400 mg BID vs EFV 600 mg QD, each with 3TC/TDF, in patients coinfected with HIV and TB[6]

1. Dooley. Clin Infect Dis. 2019;[Epub]. 2. Grinsztejn. Lancet Infect Dis. 2014;14:459.
3. Dooley. JAIDS. 2013;62:21. 4. Taburet. Clin Infect Dis. 2015;61:1328. 6. De Castro. IAS 2019. Abstr MOAB0101.

ANRS 12300 Reflate TB2: Study Design

- International, randomized, open-label phase III noninferiority trial

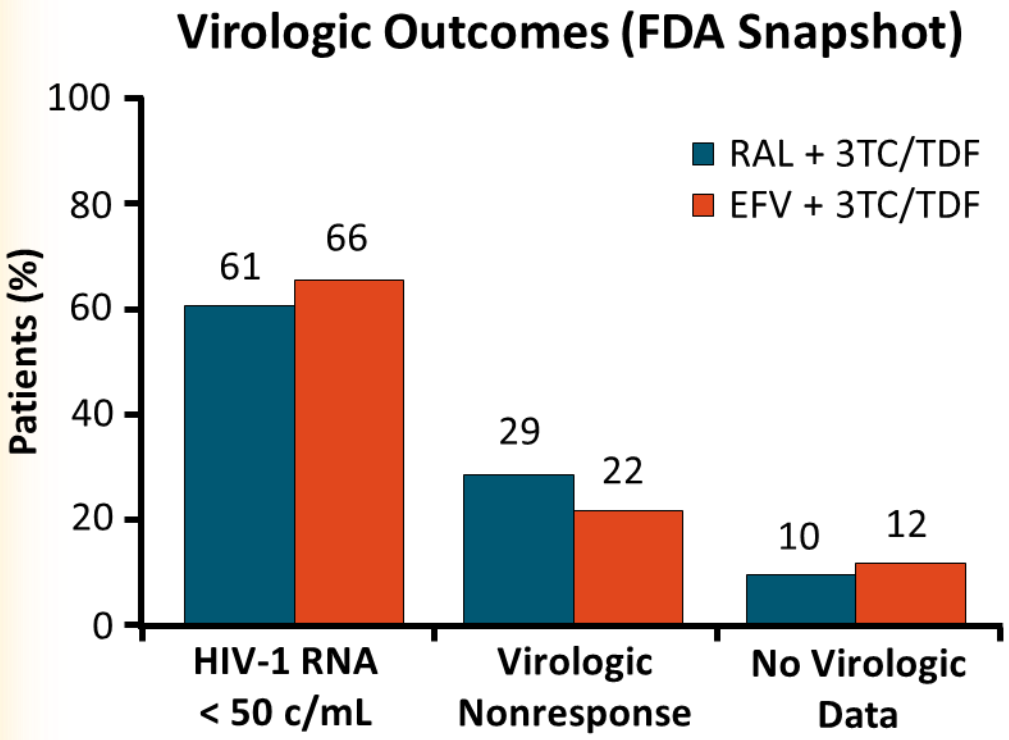


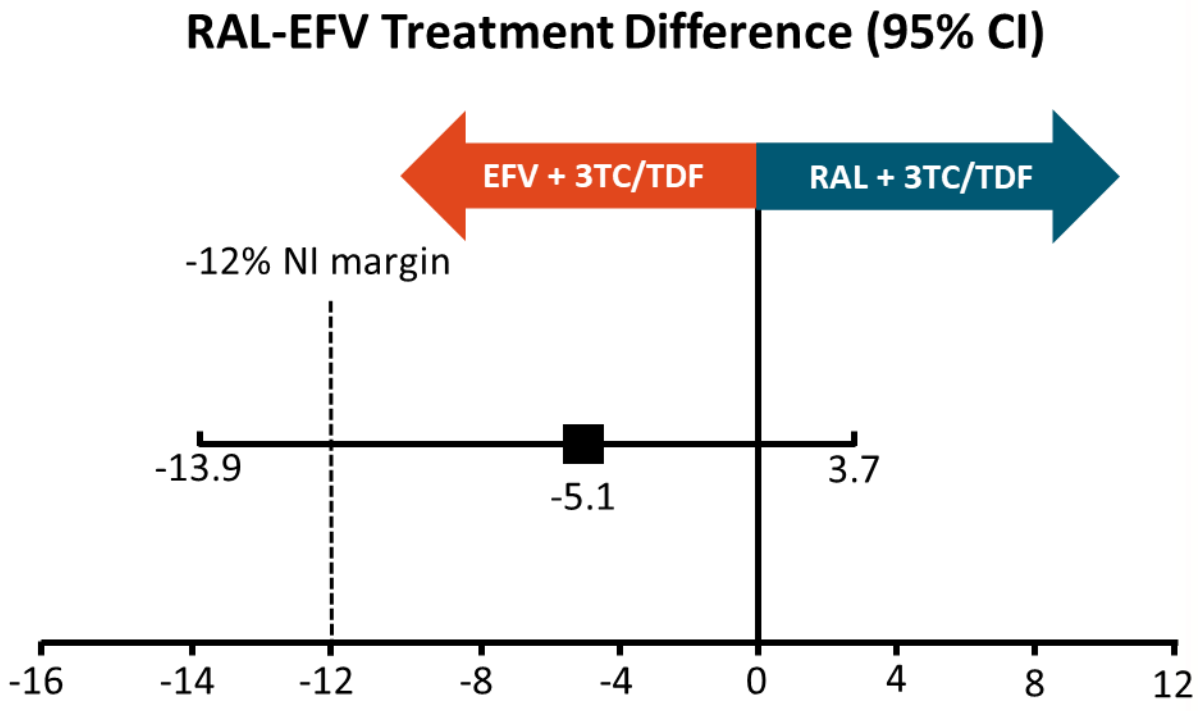
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48 by FDA Snapshot algorithm in ITT population
  - Noninferiority margin: -12%

De Castro. IAS 2019. Abstr MOAB0101.

ANRS 12300 Reflate TB2: Primary Endpoint at Wk 48

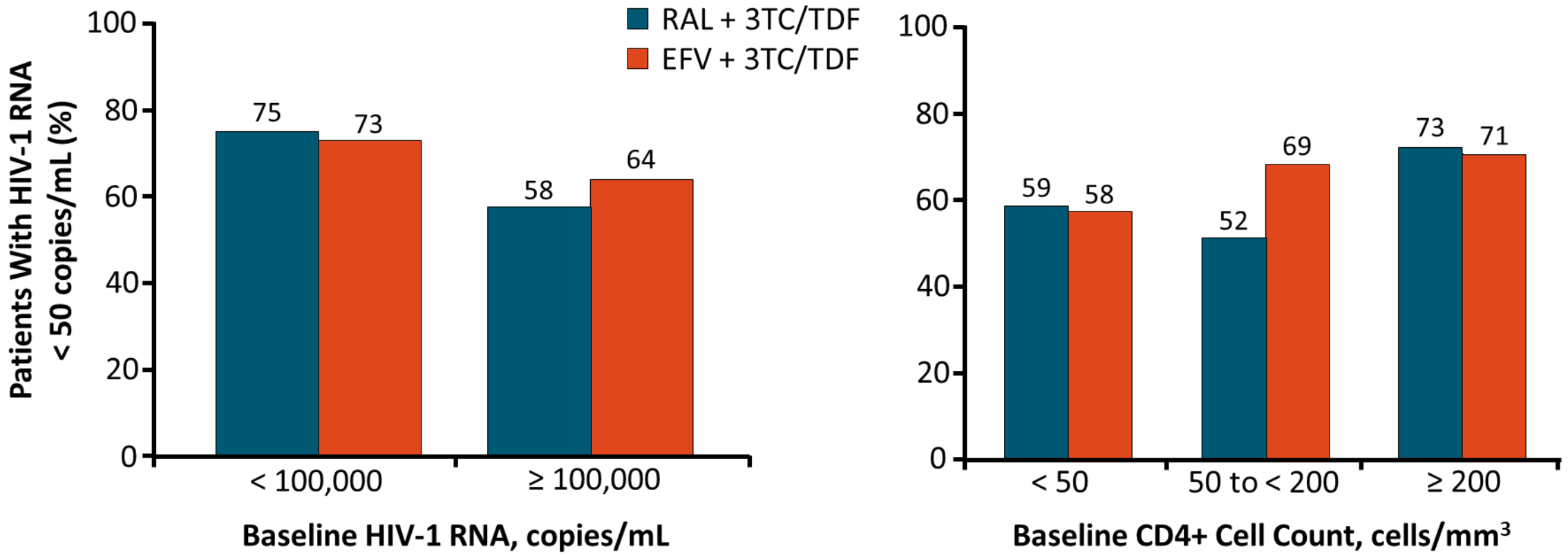
- RAL 400 mg BID + 3TC/TDF did not meet criteria for noninferior efficacy vs EFV 600 mg QD + 3TC/TDF





De Castro. IAS 2019. Abstr MOAB0101. Reproduced with permission.

ANRS 12300 Reflate TB2: Virologic Response at Wk 48 by Baseline HIV-1 RNA or CD4+ Cell Count



De Castro. IAS 2019. Abstr MOAB0101. Reproduced with permission.

ANRS 12300 Reflate TB2: Conclusions

- At Wk 48, RAL 400 mg BID + 3TC/TDF did not meet criteria for noninferior virologic efficacy vs EFV 600 mg QD + 3TC/TDF in patients coinfected with HIV and TB
  - HIV-1 RNA < 50 copies/mL in 61% vs 66%, respectively
    - Treatment difference: -5.1% (95% CI: -13.9% to 3.7%, exceeding noninferiority margin of -12.0%)
  - Analysis of risk factors for virologic failure is ongoing
- Based on these data, the study investigators concluded that EFV-based therapy remains the preferred first-line choice for this population
  - RAL 400 mg BID may be an appropriate alternative in select patients

De Castro. IAS 2019. Abstr MOAB0101.

Outline

- Integrase Studies
- **Integrase and Neural Tube Defects**
- Weight gain
- New ART agent data
- Take home points

Tsepamo: Background

- In May 2018, unplanned analysis of Tsepamo birth outcomes surveillance study found increase in NTD incidence among Botswanan women who conceived while receiving DTG[1]
  - DTG vs non-DTG ART: 0.94% (0.37% to 2.4%) vs 0.12% (0.07% to 0.21%)
- Warnings issued by WHO, EMA, FDA regarding use of DTG at time of conception[2-4] and some countries halted plans to use DTG-based ART as preferred first-line therapy
- In July 2018, WHO guidelines updated to recommend DTG + 3TC/TDF as preferred first-line regimen for women and adolescent girls using effective contraception or not of childbearing potential[5]
  - EFV 600 mg + (3TC or FTC)/TDF recommended for women and adolescent girls who want to become pregnant or not using effective contraception
- Current analysis reports updated Tsepamo birth outcomes as of March 2019[6]

1. Zash. NEJM. 2018; 379:979. 2. WHO Statement. May 2018. 3. EMA Statement. May 2018.
4. FDA. Sept 2018. 5. WHO ART. 2018. 6. Zash. IAS 2019. Abstr MOAX0105LB.

Tsepamo: Study Design

- Birth outcomes surveillance study among Botswanan women ± HIV infection; initiated August 2014
  - Original plan: assess NTD prevalence in live-born infants/stillbirths among women receiving EFV at conception
  - Comparative analysis expanded to include DTG in response to (1) 2016 update to Botswana adult first-line ART guidelines recommending DTG vs EFV (both plus FTC/TDF), and (2) 2018 WHO HIV guidelines committee request for preliminary data on pregnancy outcomes in women initiating DTG before pregnancy
- Data abstracted from obstetric cards of all in-hospital deliveries
  - Government midwives trained to assess congenital abnormalities performed infant surface exams; abnormalities photographed with maternal consent and reviewed by external medical geneticist (blinded to drug exposure history)
  - From July to September 2018, surveillance area expanded from 8 to 18 hospitals to capture ~ 72% of all births in Botswana
- Primary analysis: prevalence of NTDs with DTG vs non-DTG ART; secondary analyses: all major external structural malformations, other adverse birth outcomes

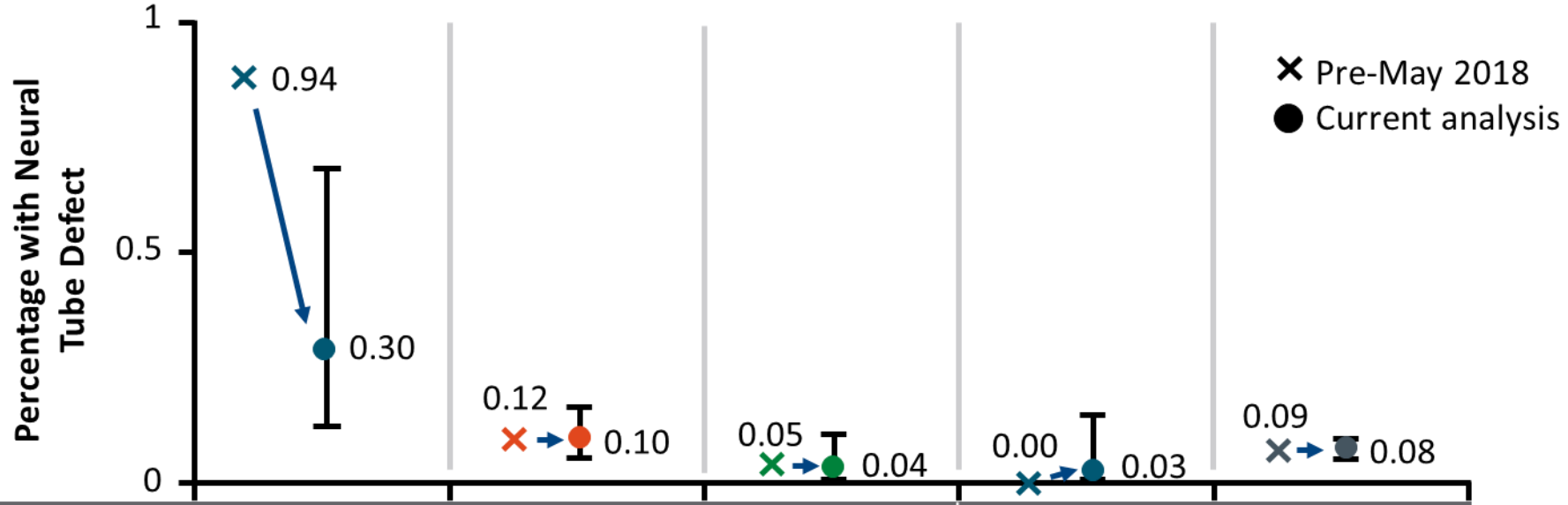
Zash. IAS 2019. Abstr MOAX0105LB. Zash. NEJM. 2019;[Epub].

Tsepamo: Baseline Characteristics

Characteristic	Conception			Pregnancy	HIV Negative (n = 89,372)
	DTG (n = 1683)	Non-DTG (n = 14,792)	EFV (n = 7959)	DTG (n = 3840)	
Potential NTD confounders					
▪ Median age, yrs (IQR)	29 (25-34)	33 (29-37)	32 (27-36)	28 (23-33)	25 (21-30)
▪ History of epilepsy/diabetes, n (%)	3 (0.2)	35 (0.2)	19 (0.2)	11 (0.3)	193 (0.2)
▪ High weight in pregnancy, %	218	1,717	904	506	11,669
▪ Conception exposure to TMP/SMX, n (%)	1 (0.1)	0 (0)	0 (0)	0 (0)	0 (0)
▪ Folate prescribed prior to conception, n (%)	1 (0.1)	28 (0.4)	13 (0.3)	4 (0.2)	132 (0.3)
▪ Folate prescribed during pregnancy, n (%)	1,110 (66)	7,416 (50)	4,032 (51)	2,087 (54)	42,637 (48)
Median ART duration prior to conception, wks (range)	45 (20-69)	240 (131-392)	156 (93-242)	N/A	N/A
Median CD4+ cell count during pregnancy, cells/mm^3 (range)	566 (410-713)	532 (408-686)	525 (399-679)	426 (291-588)	N/A

Zash. IAS 2019. Abstr MOAX0105LB.

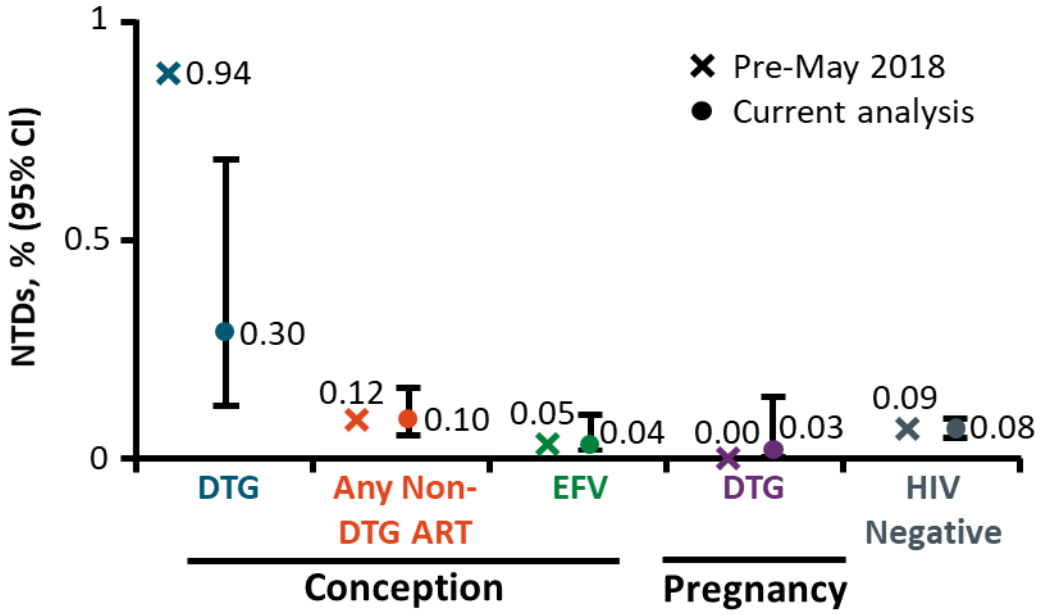
Tsepamo: Prevalence of NTDs by ARV Exposure



	Conception			Pregnancy	HIV Negative
	DTG (n = 1683)	Non-DTG (n = 14,792)	EFV (n = 7959)	DTG (n = 3840)	(n = 89,372)
Total NTDs per exposures, n/N	5/1683	15/14792	3/7959	1/3840	70/89372
▪ Prevalence difference, % (95% CI)	Ref	0.20 (0.01-0.59)	0.26 (0.07-0.66)	0.27 (0.06-0.67)	0.22 (0.05-0.62)
NTDs per exposures since May 2018, n/N	1/1275	1/3492	0/2172	1/1028	9/23,315

Zash. IAS 2019. Abstr MOAX0105LB.

Tsepamo: Major Structural Malformations



Outcome	At Conception			DTG in Pregnancy (n = 3840)	HIV Negative (n = 89,372)
	DTG (n = 1683)	Non-DTG (n = 14,792)	EFV (n = 7959)		
NTDs per exposures, n/N	5/1683	15/14792	3/7959	1/3840	70/89372
▪ Prevalence difference, % (95% CI)	Reference	0.20 (0.01-0.59)	0.26 (0.07-0.66)	0.27 (0.06-0.67)	0.22 (0.05-0.62)
NTDs per exposures since May 2018, n/N	1/1275	1/3492	0/2172	1/1028	9/23,315

Zash. IAS 2019. Abstr MOAX0105LB.

Tsepamo: Additional Adverse Birth Outcomes With Dolutegravir vs Efavirenz

- No difference between DTG and EFV for any single adverse birth outcome, including preterm/very preterm birth (< 37/< 32 wks), small gestational age, stillbirth, in-hospital neonatal death
- Analysis included single births since October 2016

Outcome	DTG at Conception (n = 1271)	EFV at Conception (n = 4430)	Adjusted RR (95% CI)*
Any adverse birth outcome, n (%)	422 (33.2)	1550 (35.0)	0.94 (0.86-1.02)
Any severe birth outcome (SB, NND, vPTB , vSGA), n (%)	151 (11.9)	568 (12.8)	0.89 (0.74-1.05)

Zash. IAS 2019. Abstr MOAX0105LB.

Tsepamo: Conclusions

- In current analysis, NTD prevalence among women who received DTG at conception lower than initially signaled, but still slightly higher than other exposure groups[1]
  - Data as of March 2019: 0.3% DTG vs 0.1% non-DTG ART; estimated difference: 0.20% to 0.27%
- Investigators suggest clinical and policy recommendations should consider the small but significant increased risk of NTD with DTG in context of other factors, including considerable benefits of DTG, lack of comparable data for other ARVs, unknown risk factors of ART exposure in utero
- Based on current findings and additional surveillance reports,[2,3] WHO released updated recommendations reconfirming use of DTG-based ART as preferred first-line and second-line therapy[4]
  - Committee emphasized need for continued monitoring of NTD prevalence and patient counseling/shared decision-making

1. Zash. IAS 2019. Abstr MOAX0105LB. 2. Raesima. IAS 2019. Abstr MOAX0106LB.
3. Pereira. IAS 2019. Abstr MOAX0104LB. 4. WHO ARV Policy Brief. 2019.

Additional NTD Data From Botswana and Brazil

- Prospective birth outcomes surveillance study among Botswanan women commissioned by Botswana Ministry of Health and Wellness in response to May 2018 Tsepamo findings[1]
  - Surveillance area included 22 facilities not covered by Tsepamo (October 2018 to March 2019); potential NTDs evaluated by trained midwives prior to discharge with suspected NTDs reviewed by blinded geneticist
- Retrospective cohort of Brazilian women with HIV found no NTDs among births to women with possible exposure to DTG at conception from 2017-2018 (n = 384)[2]

Outcome	HIV Positive			HIV Negative (n = 2328)
	DTG (n = 152)	Any Non-DTG ART (n = 381)	EFV (n = 261)	
NTDs, n (%) [95% CI]	1 (0.66) [0.02 to 3.69]	0 (0) [0 to 0.79]	0 (0) [0 to 1.15]	2 (0.09) [0.01 to 0.31]
Prevalence difference, % (95% CI)	Reference	0.66 (-0.73 to 4.16)	0.66 (-1.25 to 4.16)	0.58 (-0.10 to 4.10)

1. Raesima. IAS 2019. Abstr MOAX0106LB. 2. Pereira. IAS 2019. Abstr MOAX0104LB.

Outline

- Integrase Studies
- Integrase and Neural Tube Defects
- **Weight gain**
- Data from new ART and other agents
- Take home points

Weight gain and HIV disease

Old studies looked at several strategies for weight gain in HIV/AIDS patients (some example reviews below)

- Pre-ART era
  - Dronabinol (Plasse TF, 1991)
  - Megestrol (Farrar DJ, 1999)
- Early ART era
  - Evaluation of Resting Energy Expenditure in the HAART era (Shevitz AH, 2000)
  - Exercise to avoid involuntary weight loss (Arey BD, 2002)
  - Lipodystrophy in HIV with recommendation for diet and exercise to avoid fat deposition (Chen D, 2002)
- Post 2005 Era
  - Insulin resistance, glucose intolerance and DM in HIV-infected patients. Known weight gains with ART. (Florescu D, 2007)
  - Cyproheptadine for HIV patients for weight gain and increasing appetite. (Dabaghzadeh F, 2012)
  - Cannabis (dronabinol) (Schoonees A, 2013; Whiting PF, 2015; Badowski ME, 2016)
  - Progesterone (Taylor JK, 2016)
  - ART had a positive effect in children weight gains and growth curves (Golucci A, 2019)

Dolutegravir plus Two Different Prodrugs of Tenofovir to Treat HIV

- Rationale
  - Use of newer regimens with higher barrier to resistance, lower toxicity, good potency
- The data presented comes from the ADVANCE trial
- The study expanded the work on weight gain with integrase inhibitors.

Venter WDF, et al, NEJM 2019

Methods

- Design
  - Open label, non-inferiority, 96 week phase 3 trial comparing 3 first line regimens in HIV-1 infection starting ART
- Primary endpoint: 48 week viral suppression
  - Secondary endpoints: multiple, including safety
- Johannesburg from February 2017 to May 2018
- Population
  - 12 yo and older, creatinine clearance >60
  - No prior ART more than 30 days, pregnancy, active TB treatment
  - No baseline ART drug resistance genotype testing

Methods

- Regimens
  - TAF/FTC plus DTG
  - TDF/FTC plus DTG
  - TDF/FTC/EFV(generic)
- Randomization (Yes) 1:1:1
  - Patients 12-19 yo were randomized separately
  - 351 patients were included in each of the three arms

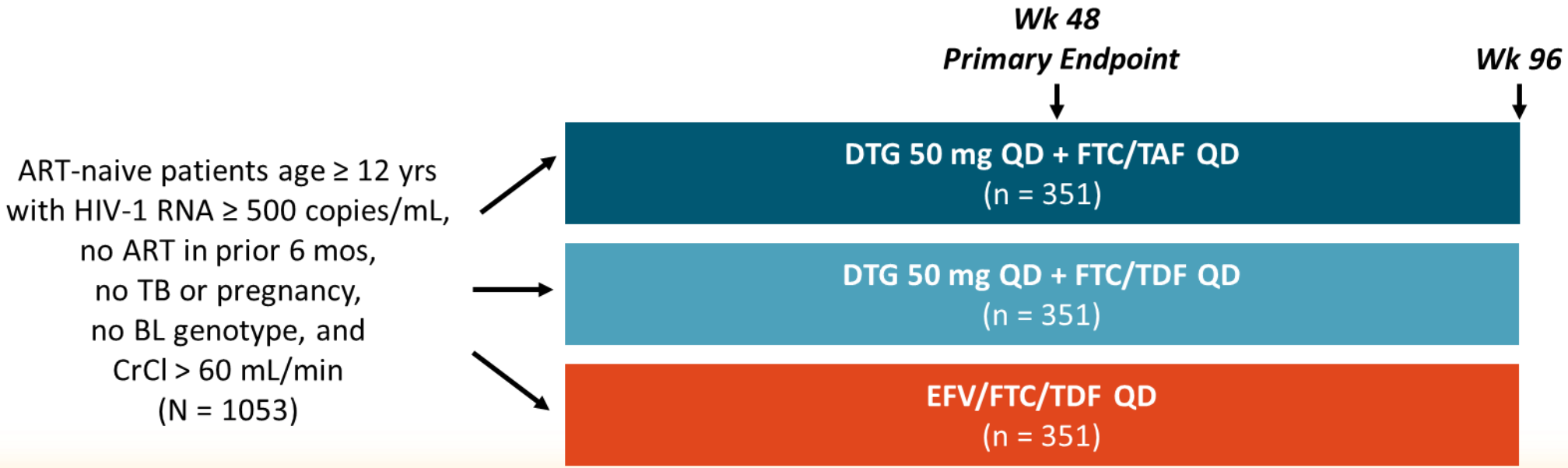
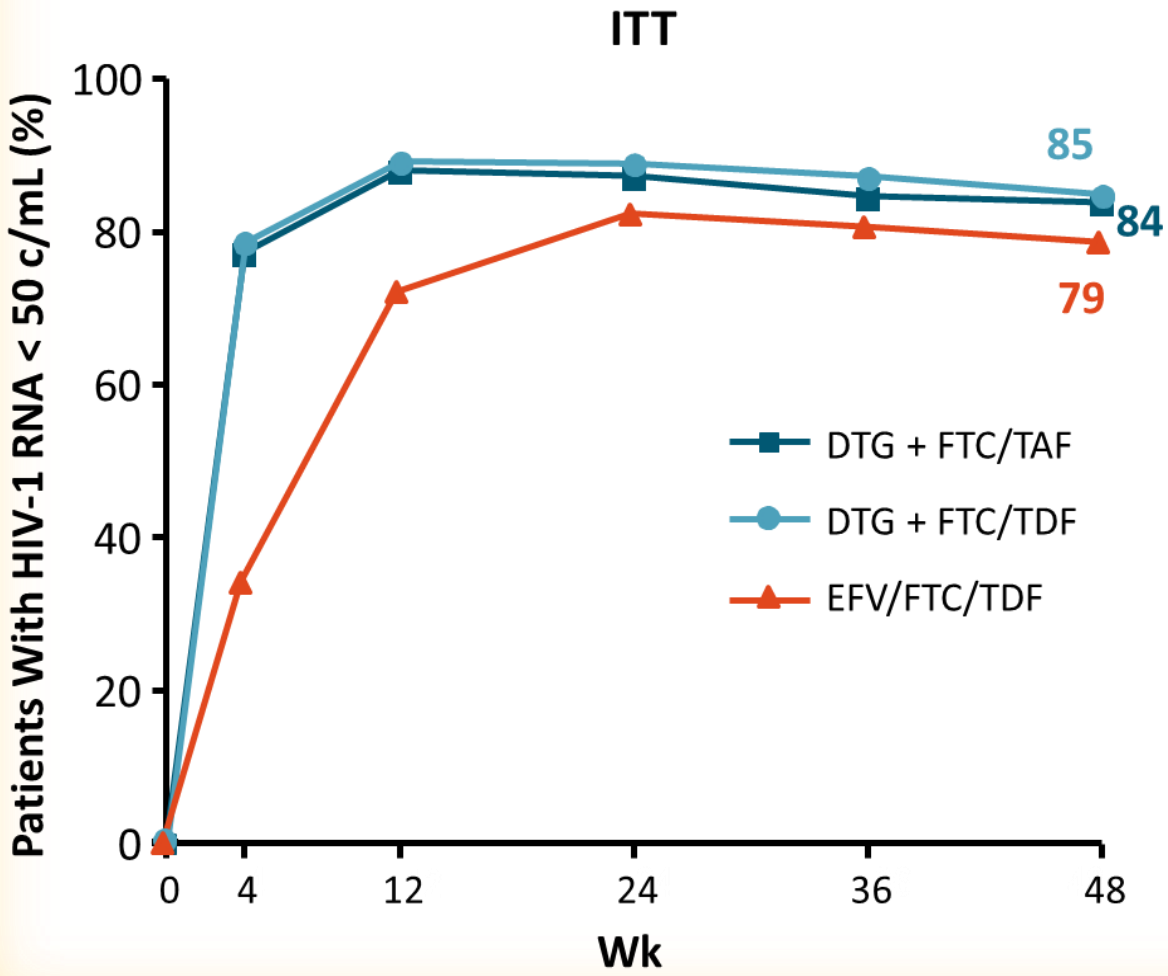
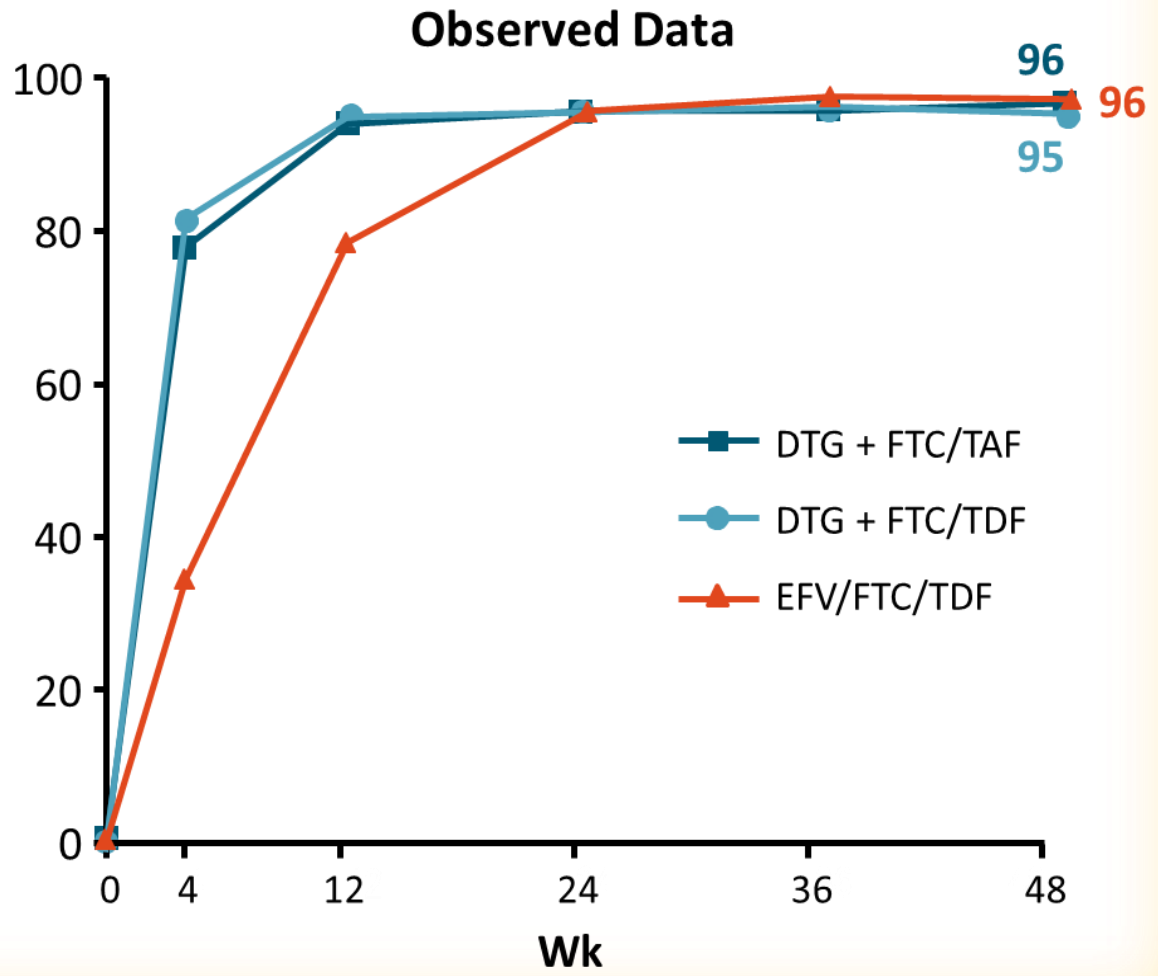


Table 1. Baseline Characteristics of the Patients.*

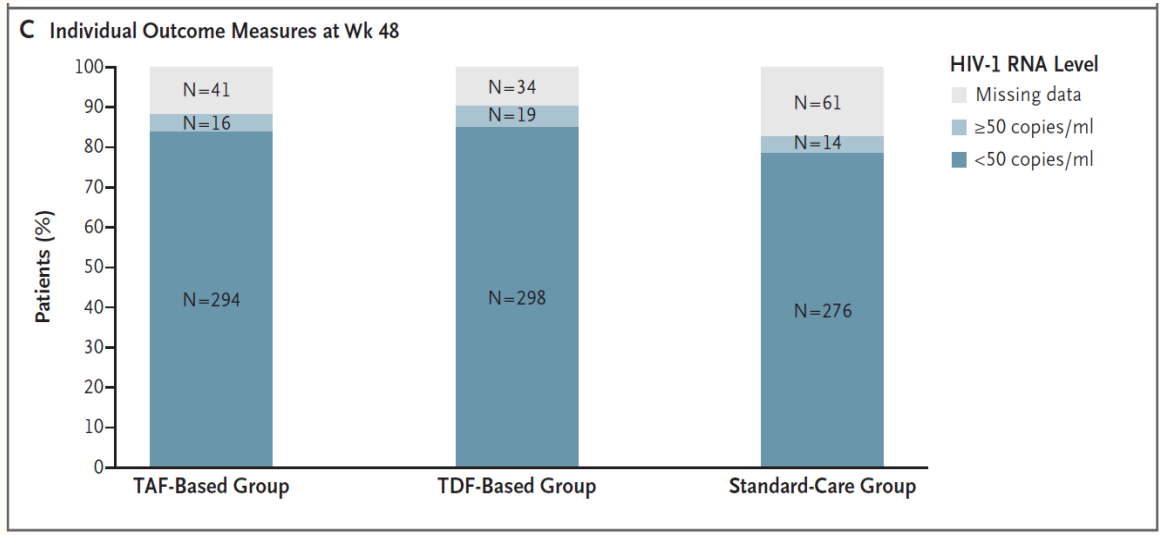
Characteristic	TAF-Based Group (N=351)	TDF-Based Group (N=351)	Standard-Care Group (N=351)
Female sex — no. (%)	214 (61)	208 (59)	201 (57)
Age — yr	33±7.8	32±8.1	32±7.4
Race — no. (%)†			
Black	349 (99)	351 (100)	351 (100)
Mixed race	2 (1)	0	0
Country of origin — no. (%)			
South Africa	213 (61)	223 (64)	219 (62)
Zimbabwe	116 (33)	108 (31)	115 (33)
Other	22 (6)	20 (6)	17 (5)
Body weight — kg			
Male patients	67.9±10.9	67.1±11.2	67.3±11.9
Female patients	68.8±14.8	69.5±16.2	70.2±16.5
Body-mass index			
Male patients	21.7±3.7	21.6±3.3	21.8±3.6
Female patients	25.6±5.0	26.1±6.1	26.1±6.2
Categories of body-mass index — no./total no. (%)			
<18.5: underweight	42/350 (12)	35/351 (10)	37/351 (11)
18.5 to <25: normal	177/350 (51)	190/351 (54)	193/351 (55)
25 to <30: overweight	96/350 (27)	78/351 (22)	77/351 (22)

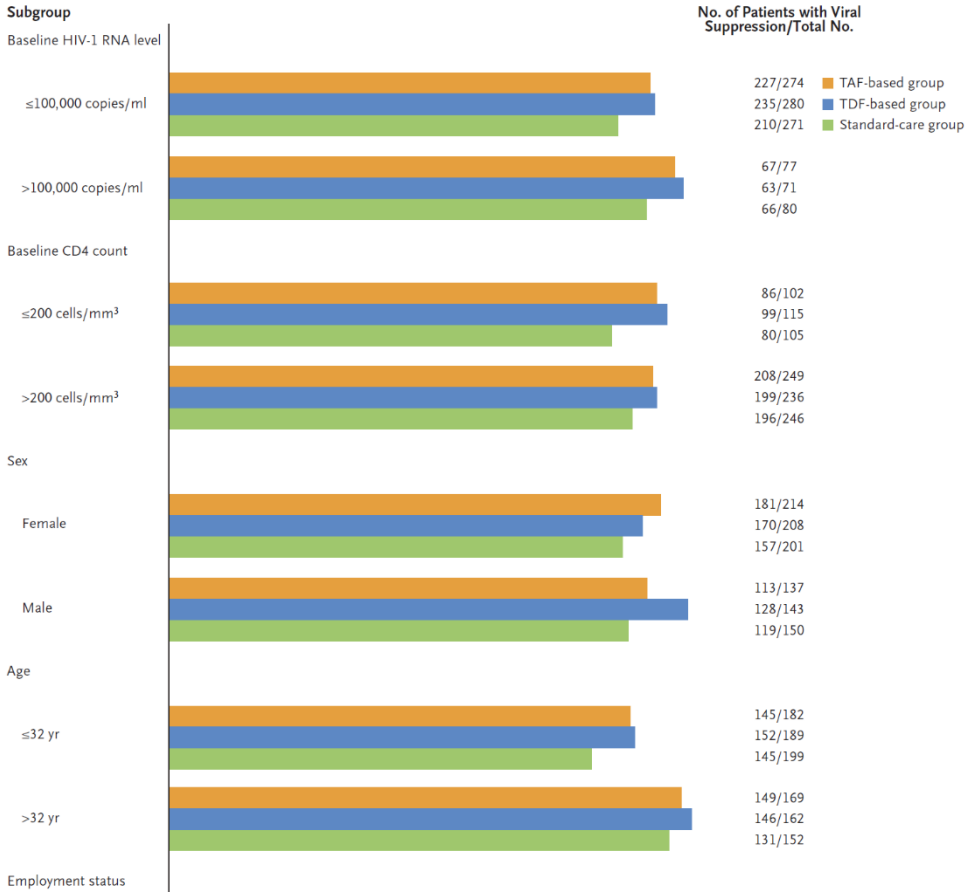
Treatment Response





Treatment Response

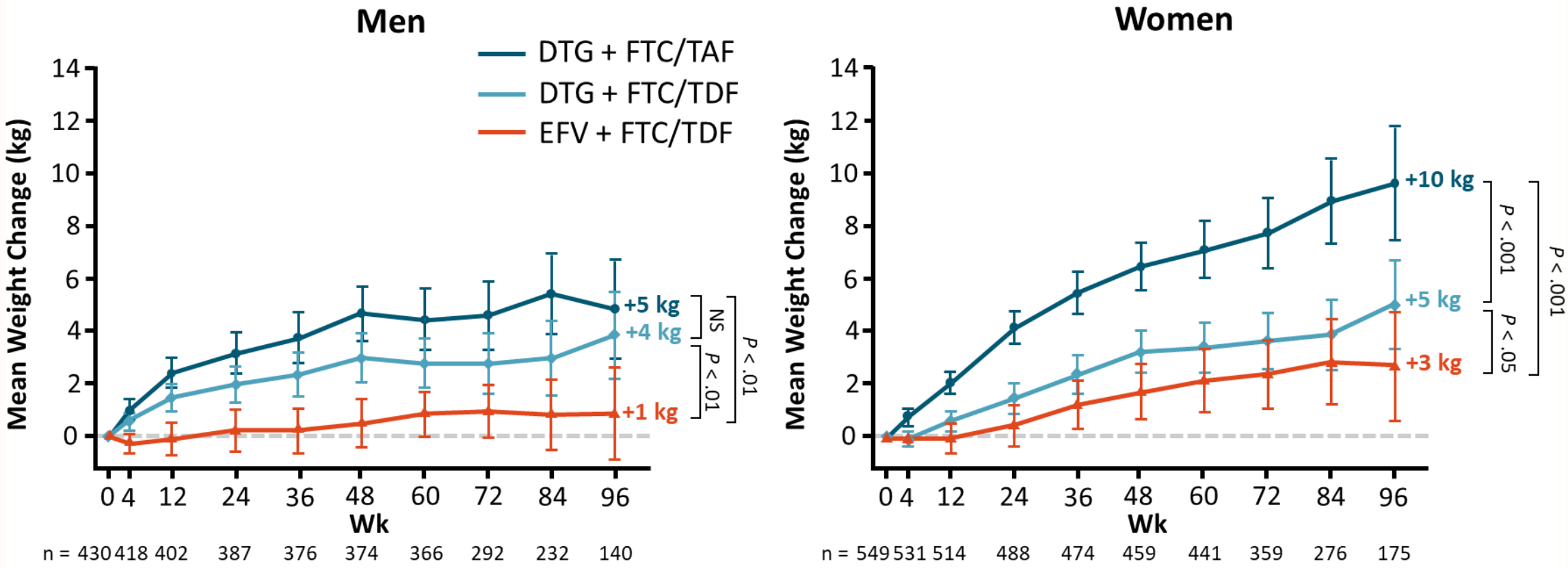




Weight Gain

Adverse Event	TAF-Based Group (N=351)	TDF-Based Group (N=351)	Standard-Care Group (N=351)
DXA of body composition — kg¶			
Mean change in truncal fat			
Male patients	0.6	0.1	–0.4
Female patients	1.7	0.7	0.1
Mean change in truncal lean mass			
Male patients	1.8	1.2	0.7
Female patients	1.1	1.0	0.6
Mean change in limb fat			
Male patients	0.5	0.1	–0.4
Female patients	1.9	0.6	0.2
Mean change in limb lean mass			
Male patients	2.2	1.5	0.7
Female patients	1.8	1.2	0.7
New obesity — no./total no. (%)‖			
Male patients	8/113 (7)	4/127 (3)	4/116 (3)
Female patients	26/133 (20)	13/123 (11)	9/104 (9)

Weight Gain


Men
DTG + FTC/TAF
DTG + FTC/TDF
EFV + FTC/TDF
Mean Weight Change (kg)
14
12
10
8
6
4
2
0
+5 kg
+4 kg
+1 kg
NS
P < .01
P < .01
0 4 12 24 36 48 60 72 84 96
Wk
n = 430 418 402 387 376 374 366 292 232 140
Women
Mean Weight Change (kg)
+10 kg
+5 kg
+3 kg
P < .001
P < .05
P < .001
0 4 12 24 36 48 60 72 84 96
Wk
n = 549 531 514 488 474 459 441 359 276 175

Discussion by Authors for Virologic Endpoints

- DTG combined with either tenofovir pro-drug was non-inferior to the standard of care arm (EFV/FTC/TDF) for patients achieving VL suppression at week 48.
- The standard of care had higher treatment discontinuations and lost to follow up.
- Virologic efficacy was similar to larger trials, despite no baseline drug resistance testing.
  - WHO recommends to use DTG instead of EFV as first line in countries where EFV resistance is >10% (such as South Africa)

Discussion by Authors for Weight Gain

- DTG arms had significant more weight gain than SoC arm, especially with TAF in the regimen.
- Weight gain has emerged as major concern with respect to integrase inhibitor class and is now noted on the package inserts.
- Weight gain was less severe in TDF regimens (EFV or DTG)
- Patients who were female, lower CD_4 counts and higher viral loads at baseline had the most weight gains.
- The authors dismissed the notion that the weight gain was related to “return to health”
- Weight gain seen in this trial in Black male patients was similar to that seen in White male patients in the registration studies comparing DTG and Bictegravir.
- Truncal fat weight gains are concerning for associated CVD risk.
- The authors did not have a proposed mechanism on how TAF amplified the weight gain or it was lowered by TDF.

Take Home Points

- DTG regimens with ABC/3TC or FTC/tenofovir have demonstrated efficacy in multiple studies and have been compared to several regimens (EFV, DRV, BIC).
- Weight gain with integrase inhibitors is real, more for women and with more adipose tissue by DXA
- Issues remain about dosing of DTG and TAF in high endemic TB regions

NAMSAL and ADVANCE: Progressive Weight Gain and Clinical Obesity

Outcome	NAMSAL			ADVANCE			
	DTG + 3TC/TDF (n = 293)	EFV + 3TC/TDF (n = 278)	*P* Value	DTG + FTC/TAF	DTG + FTC/TDF	EFV/ FTC/TDF	*P* Value
Mean Δ in weight, kg							
▪ Wk 48	+5	+3	< .001	+6	+3	+1	< .001
▪ Wk 96	NA	NA		+8	+5	+2	
Mean Δ in BMI at Wk 48	+1.7	+1.2	< .001	NR	NR	NR	
Treatment-emergent overweight (BMI 25-29.9), %							
▪ Wk 48	16	17	NS	23	14	9	NS
▪ Wk 96	NA	NA		25	13	11	
Treatment-emergent obesity (BMI ≥ 30), %							
▪ Wk 48	12	5	< .01	14	7	6	< .01
▪ Wk 96	NA	NA		19	8	4	

Hill. IAS 2019. Abstr MOAX0102LB. NAMSAL trial done in Cameroon and ADVANCE trial done in South Africa.

Outline

- Integrase Studies
- Integrase and Neural Tube Defects
- Weight gain
- **Data from new ART and other agents**
- Take home points

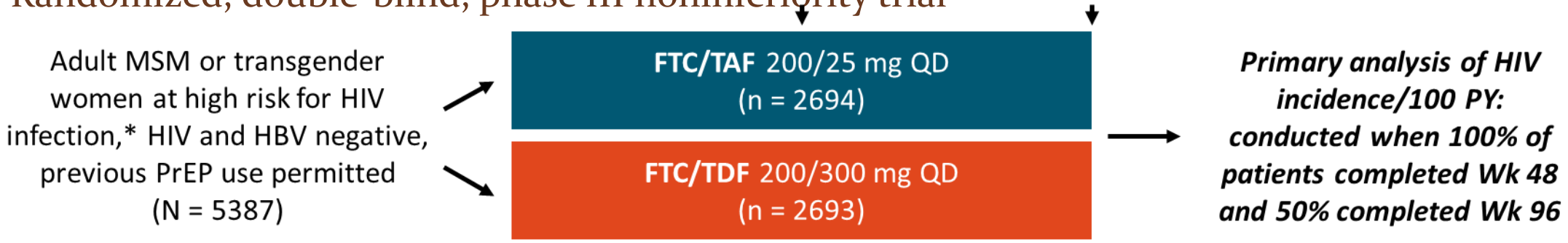
DISCOVER: Background

- Randomized phase III DISCOVER trial demonstrated noninferiority of FTC/TAF vs FTC/TDF as PrEP in cis-MSM and transgender women at high risk of HIV infection[1]
  - Rate of HIV incidence/100 PY (primary analysis): 0.16 with FTC/TAF, 0.34 with FTC/TDF
  - IRR: 0.47 (95% CI: 0.19-1.15); noninferiority established when upper bound of 95% CI of IRR < 1.62
- Unknown whether chance alone accounts for point estimate of HIV incidence rate being 53% lower with FTC/TAF vs FTC/TDF as PrEP in DISCOVER[2]
  - Probability of this finding being due to chance alone: 3 in 1000
  - Post hoc Bayesian analysis identified 96% probability with 95% credible interval that PrEP with FTC/TAF offers greater efficacy than FTC/TDF
- Current analysis of DISCOVER trial assessed whether adherence, PK, sexual behavior, and STI incidence could account for differences in HIV infection rates with FTC/TAF vs FTC/TDF as PrEP[2]

1. Hare. CROI 2019. Abstr 104LB. 2. Spinner. IAS 2019. Abstr TUAC0403LB.

DISCOVER: Study Design

- Randomized, double-blind, phase III noninferiority trial



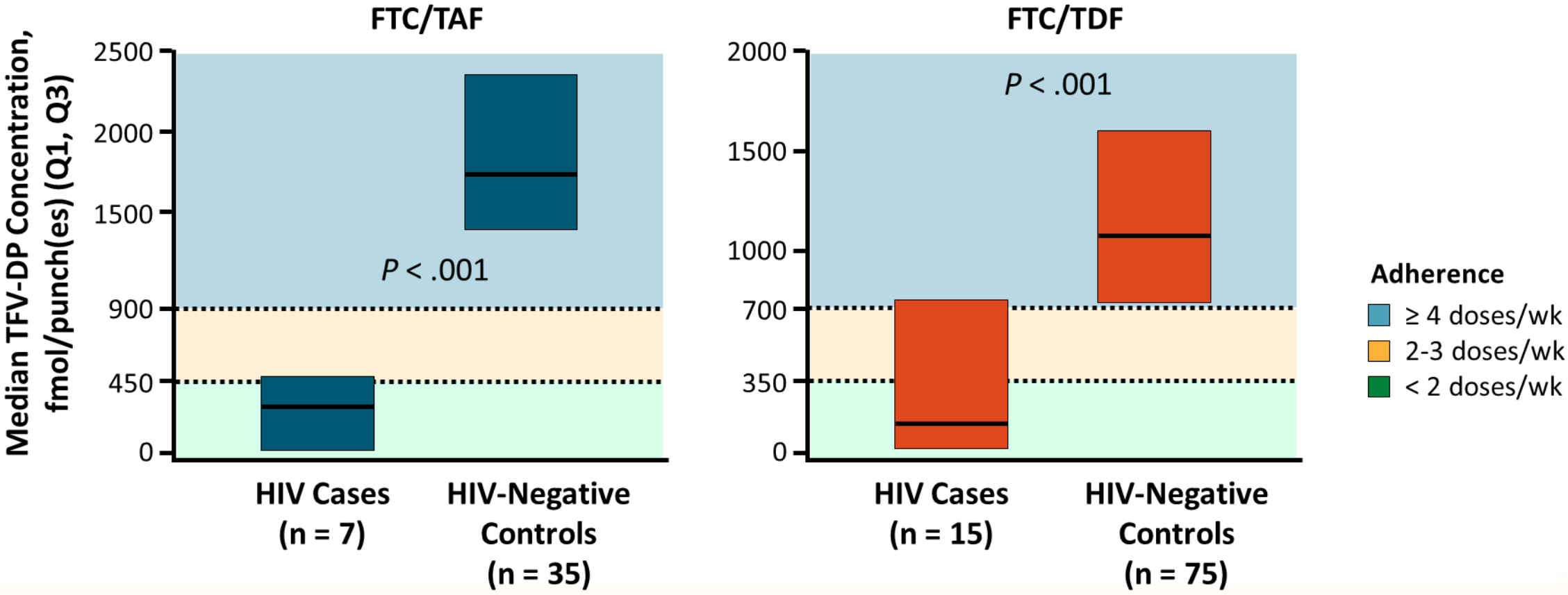
- Current analysis:
  - Self-reported HIV risk behavior
  - STI incidence: rectal, urine, oropharynx GC/CT testing via NAAT; syphilis testing; AEs
  - PK: TFV-DP in PBMCs at Wk 4 in randomized subset (n = 324); simulated duration above protective threshold for TAF and TDF
  - Adherence: pill count, self-report, DBS analysis
  - Adherence and efficacy: relationship assessed with nested case-control study, where 22 cases with incident HIV matched to 5 controls each on geography, timing of HIV diagnosis, and rectal STI status

*Diagnosed with rectal gonorrhea, chlamydia, or syphilis in 24 wks pre-enrollment; ≥ 2 episodes of condomless anal sex with ≥ 2 unique partners in 12 wks pre-enrollment.

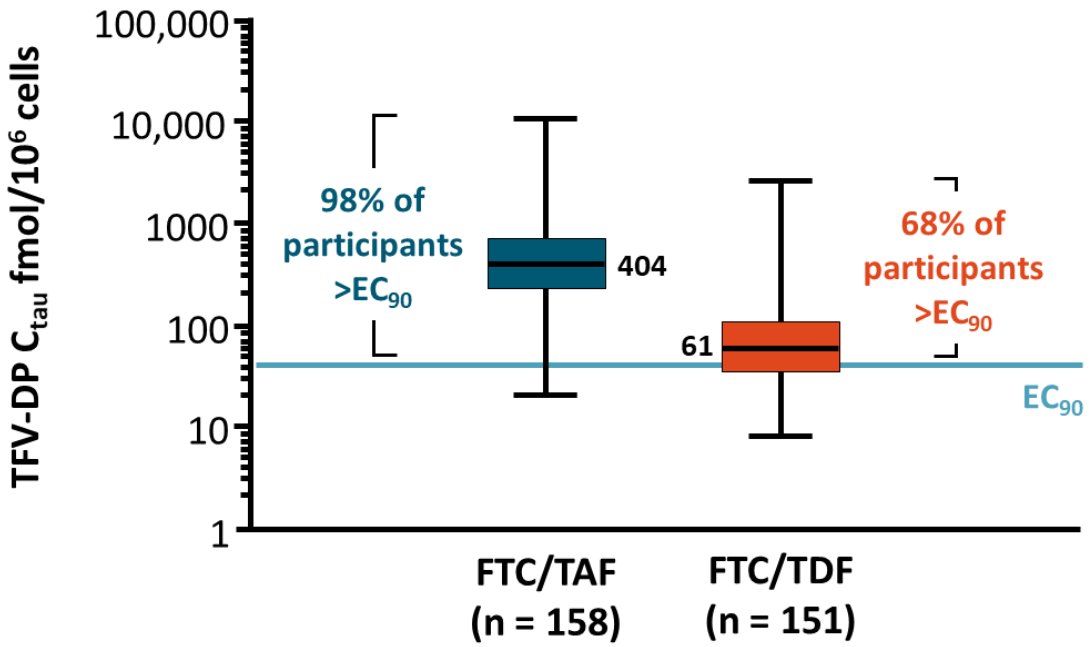
Spinner. IAS 2019. Abstr TUAC0403LB.

DISCOVER: Adherence by DBS at HIV Diagnosis Visit in Nested Case-Control Study

- Low adherence (< 2 doses/wk) associated with significantly increased risk of HIV infection in both arms (both $P < .001$)



DISCOVER: PBMC TFV-DP Levels at Wk 4

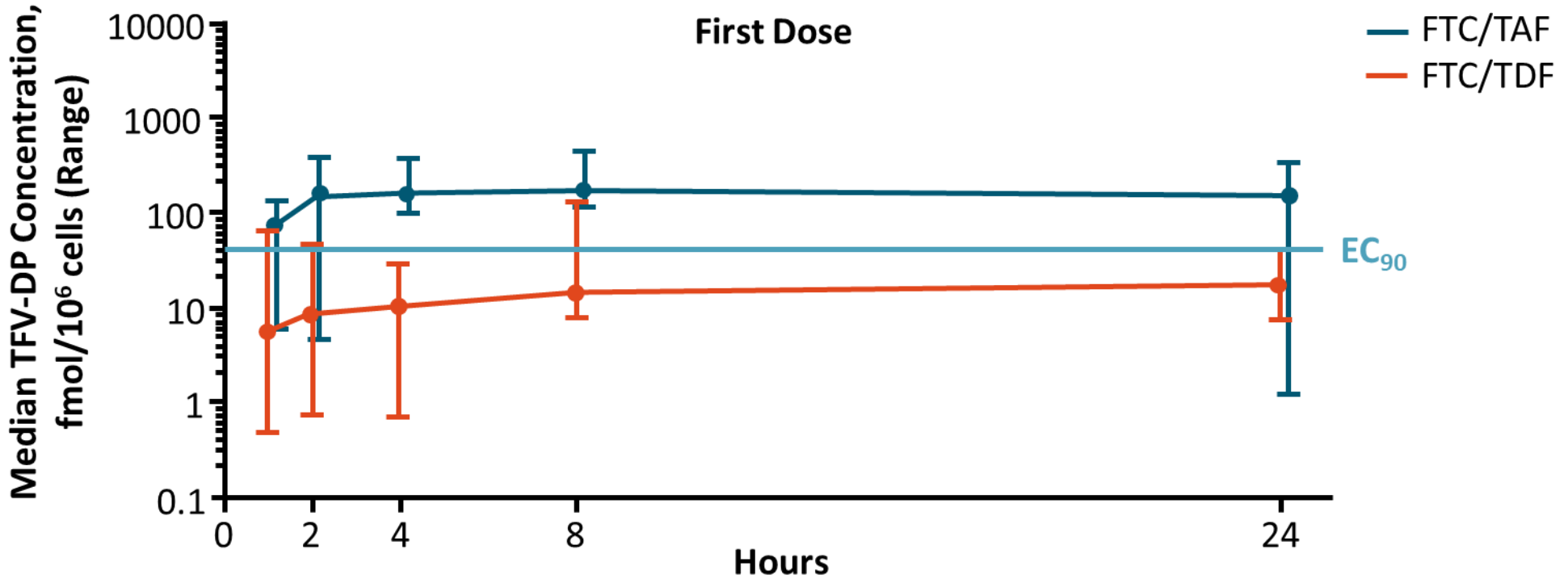


- Steady-state PBMC TFV-DP levels 6.3-fold higher with FTC/TAF vs FTC/TDF
- FTC/TAF associated with higher PBMC TFV-DP levels and greater proportion of patients with TFV-DP > EC_{90}

*EC_{90} for PBMC TFV-DP levels: 40 fmol/10^6 cells associated with 90% HIV risk reduction.

DISCOVER: Rapidity in Achieving EC_{90}

- In a phase I study in healthy volunteers, median PBMC TFV-DP concentration > EC_{90} within 1-2 hrs (all within 4 hrs) of dosing with FTC/TAF; with FTC/TDF, EC_{90} reached only after 3 daily doses



DISCOVER: Conclusions

- In analysis of DISCOVER trial assessing possible factors behind trend towards lower HIV infection rate with FTC/TAF vs FTC/TDF as PrEP, only PK parameters differed between arms
  - Adherence, sexual risk behavior, and STI incidence comparable with FTC/TAF vs FTC/TDF
  - PBMC TFV-DP levels were 6.3-fold higher with FTC/TAF vs FTC/TDF
  - PBMC TFV-DP EC_{90} achieved by 98% of patients with FTC/TAF vs 68% with FTC/TDF at Wk 4
  - EC_{90} reached within 1-2 hrs of first FTC/TAF dose vs after 3 daily doses of FTC/TDF
  - Simulation indicated that concentrations > EC_{90} would last for 16 days after final dose of FTC/TAF vs 10 days after FTC/TDF
- Investigators suggested that the trend toward greater prevention efficacy with FTC/TAF most likely due to more rapid achievement of protective levels and prolonged duration of protection

Spinner. IAS 2019. Abstr TUAC0403LB.

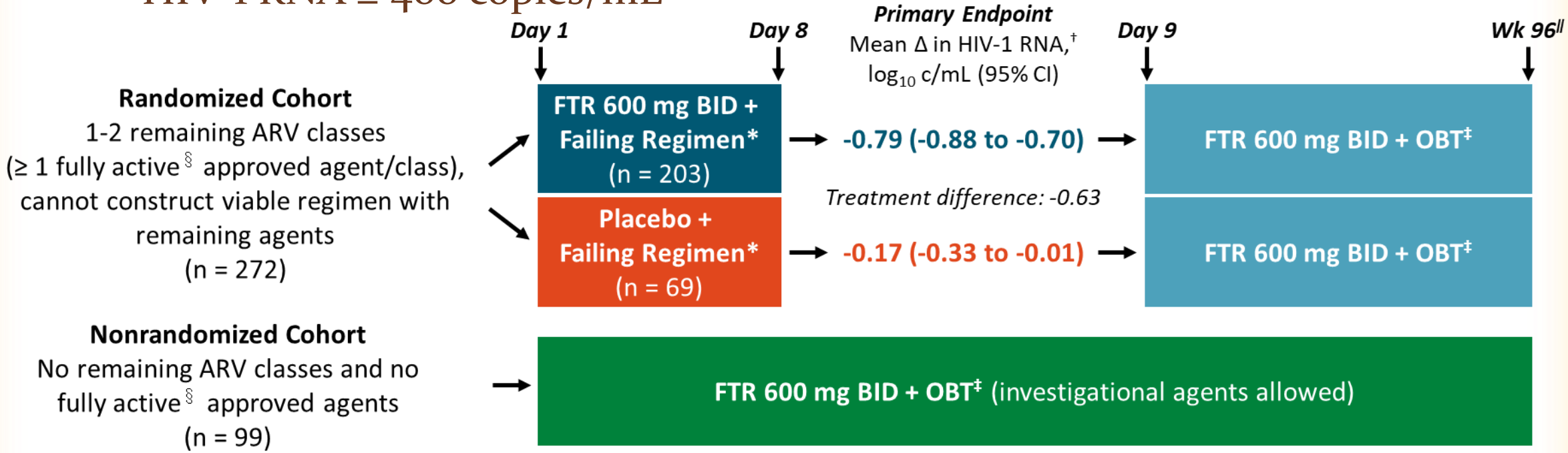
BRIGHTE: Wk 96 Results From Phase III Study of Fostemsavir + OBT in Heavily Treatment–Experienced Patients Failing Current ART

- Fostemsavir: prodrug of temsavir, a first-in-class attachment inhibitor that blocks viral entry into CD4+ T-cells via HIV gp120 binding and stabilization[1,2]
  - Not cross-resistant to other HIV entry inhibitors in vitro, with efficacy generally independent of HIV tropism[3,4]
- BRIGHTE: ongoing phase III study of fostemsavir in heavily treatment–experienced patients with multidrug-resistant HIV infection[5]
  - Primary analysis demonstrated superior efficacy of fostemsavir vs placebo after 8 days as functional monotherapy[6]
  - Following addition of OBT at Day 9, 54% of patients achieved HIV-1 RNA < 40 copies/mL at Wk 48[7]
- Current analysis of BRIGHTE reports efficacy, safety of fostemsavir + OBT through Wk 96[8]

1. Langley. Proteins. 2015;83:331. 2. Thompson. CROI 2019. Abstr 483. 3. Li. Antimicrob Agents Chemother. 2013;57:4172.
4. Nowicka-Sans. Antimicrob Agents Chemother. 2012;56:3498. 5. NCT02362503. 6. Kozal. EACS 2017. Abstr PS8/5.
7. Aberg. Glasgow 2018. Abstr O344A. 8. Lataillade. IAS 2019. Abstr MOAB0102.

BRIGHTE: Study Design

- Wk 96 analysis of randomized, double-blind phase III trial in heavily treatment–experienced adults failing current ART with confirmed HIV-1 RNA ≥ 400 copies/mL

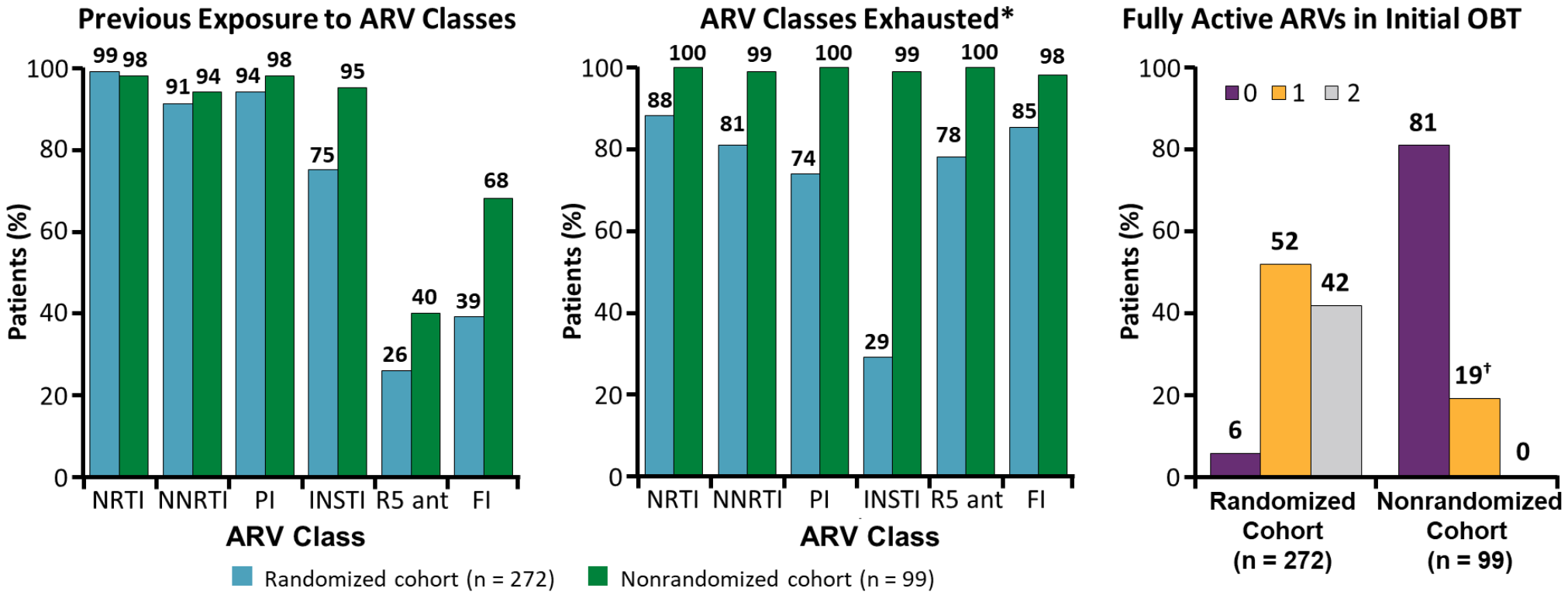


*Blinded. †Day 8 adjusted by Day 1. ‡Open label. § No evidence of resistance; patient eligible for, tolerant of, willing to receive the ARV. ‖Measured from start of open-label treatment. Study conducted until another option, rollover study, or approved ARV available.

BRIGHTE: Baseline Characteristics

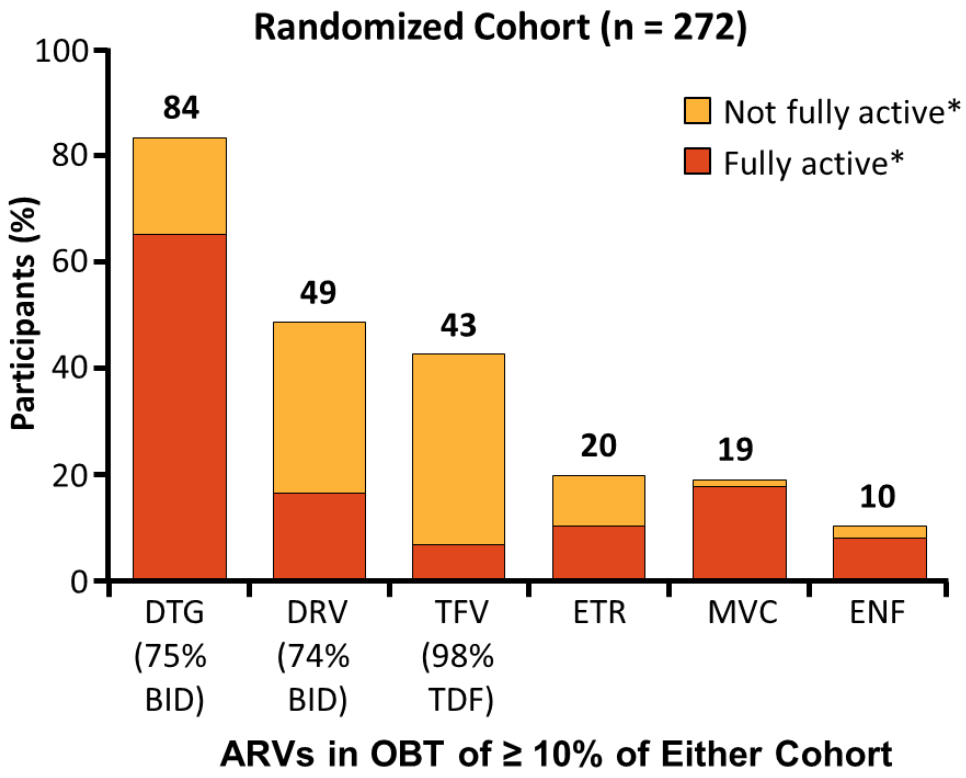
Characteristic	Randomized			Nonrandomized	All Treated Patients (N = 371)
	Placebo (n = 69)	FTR 600 mg BID (n = 203)	Total (n = 272)	FTR 600 mg BID (n = 99)	
Median age, yrs (range) ▪ < 50 yrs, n (%)	45 (19-66) 46 (67)	48 (18-73) 116 (57)	48 (18-73) 162 (60)	50 (17-72) 44 (44)	49 (17-73) 206 (56)
Female, n (%)	12 (17)	60 (30)	72 (26)	10 (10)	82 (22)
White, n (%)	48 (70)	137 (67)	185 (68)	74 (75)	259 (70)
Median HIV-1 RNA, $\log_{10}$ c/mL (IQR)	4.5 (3.6-5.2)	4.7 (4.0-5.1)	4.7 (3.9-5.1)	4.3 (3.6-4.8)	4.6 (3.9-5.0)
HIV-1 RNA, n (%) ▪ < 400 c/mL ▪ 400 to < 1000 c/mL ▪ 1000 to < 100,000 c/mL ▪ ≥ 100,000 c/mL	 7 (10) 3 (4) 35 (51) 24 (35)	 14 (7) 7 (3) 126 (62) 56 (28)	 21 (8) 10 (4) 161 (59) 80 (29)	 5 (5) 4 (4) 75 (76) 15 (15)	 26 (7) 14 (4) 236 (64) 95 (26)
Median CD4+ cell count, cells/mm^3 (IQR)	100 (23-244)	99 (15-203)	99 (15-203)	41 (6-161)	80 (11-202)
CD4+ cell count, n (%) ▪ < 20 cells/mm^3 ▪ 20 to < 50 cells/mm^3 ▪ 50 to < 200 cells/mm^3 ▪ 200 to < 500 cells/mm^3 ▪ ≥ 500 cells/mm^3	 17 (25) 6 (9) 26 (38) 16 (23) 4 (6)	 55 (27) 19 (9) 76 (37) 42 (21) 11 (5)	 72 (26) 25 (9) 102 (37) 58 (21) 15 (6)	 40 (40) 14 (14) 25 (25) 18 (18) 2 (2)	 112 (30) 39 (11) 127 (34) 76 (20) 17 (5)
AIDS diagnosis,* n (%)	61 (88)	170 (84)	231 (85)	89 (90)	320 (86)

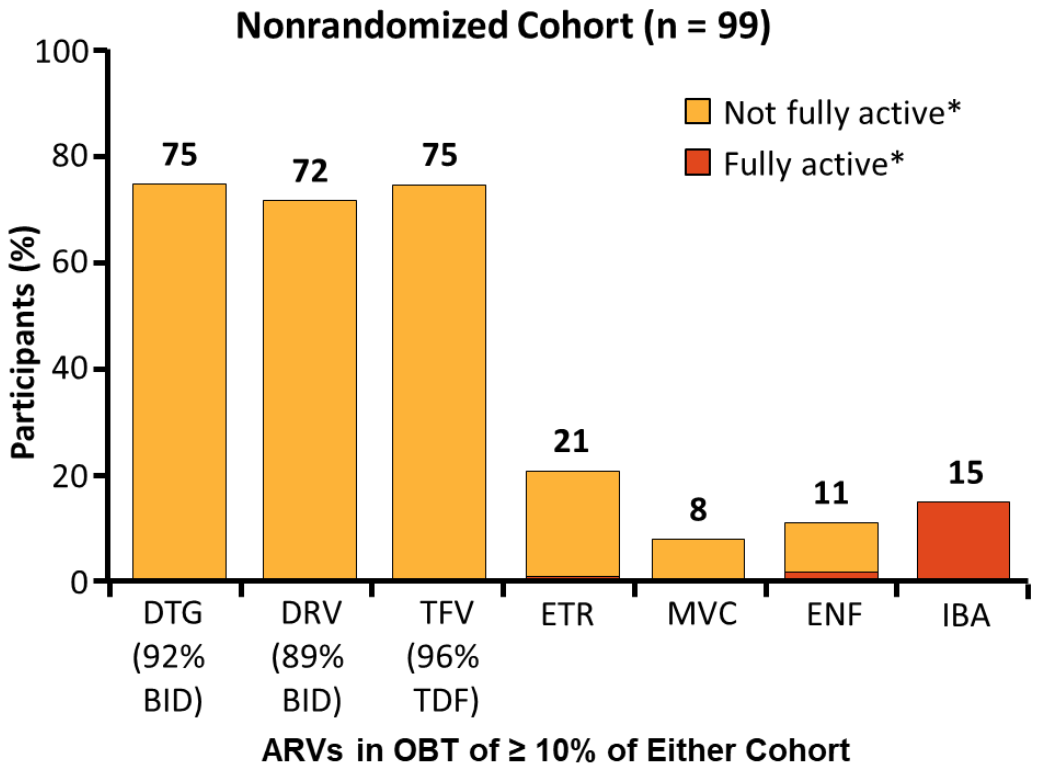
BRIGHTE: Baseline ARV Exposure and Resistance



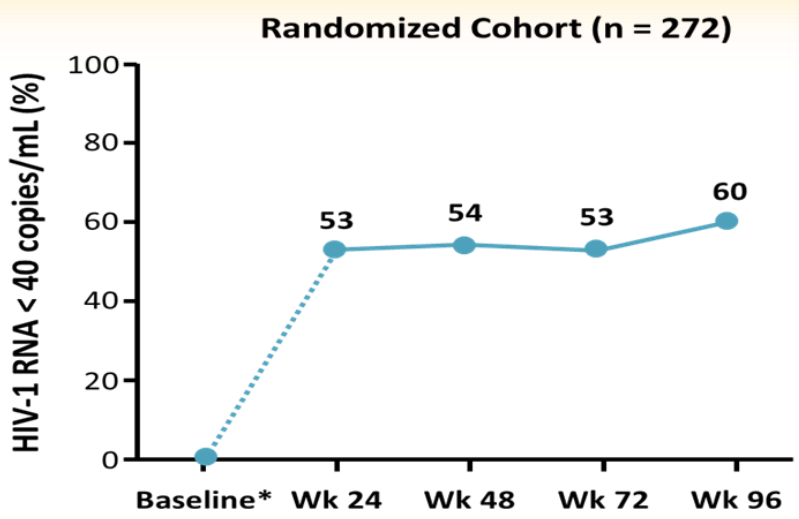
*Patients lacking any remaining FAAs within indicated ARV class, based on commercial phenotype assays, historical resistance, eligibility, and tolerability. †Of these 19 patients, 15 received investigational ibalizumab and 4 were incorrectly assigned to the nonrandomized cohort.

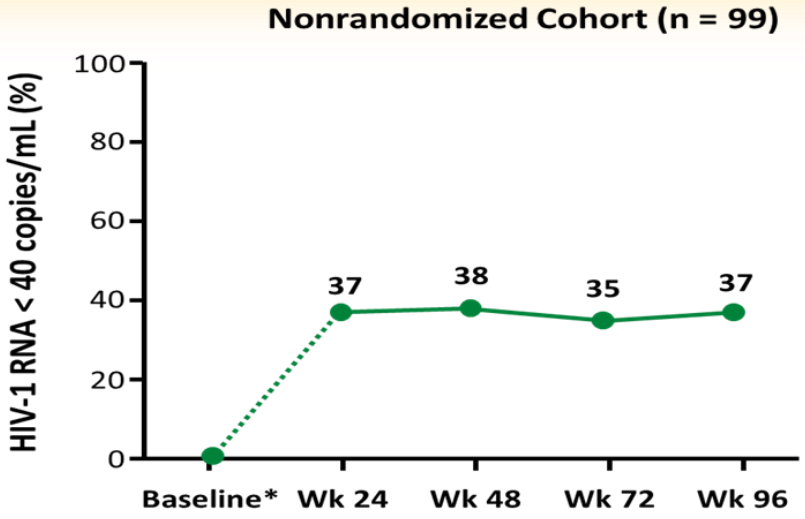
BRIGHTE: Most Common ARVs in Initial OBT



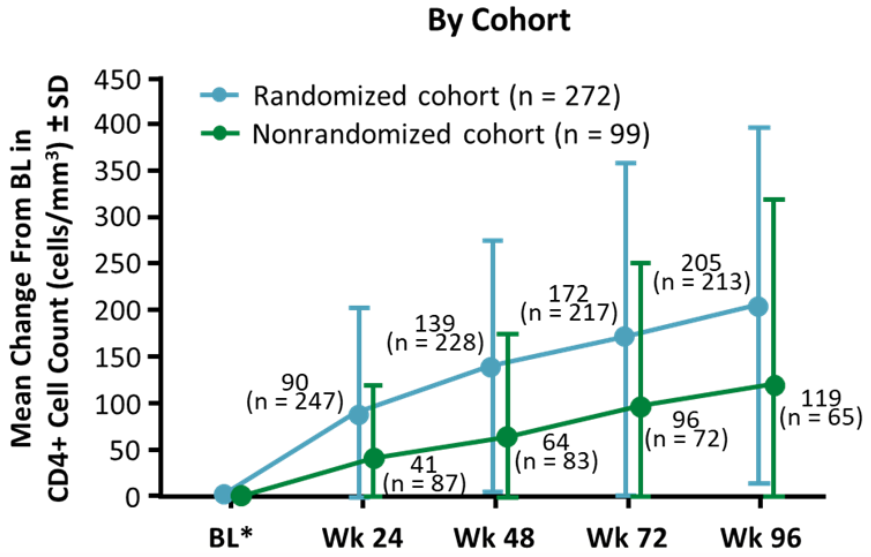


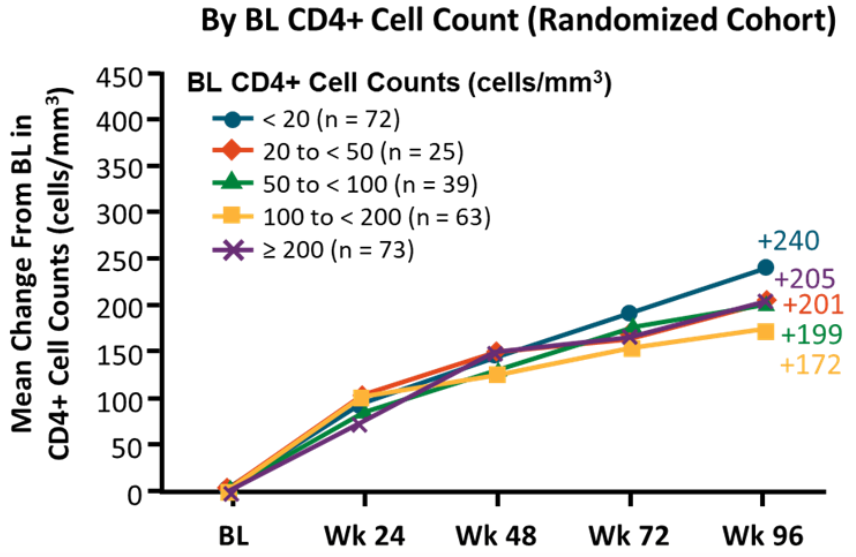
*Determined by commercial phenotype assays, historical resistance, eligibility, and tolerability.





*Snapshot analysis excluded baseline data. 1 patient had BL HIV-1 RNA < 40 copies/mL.





*BL mean CD4+ cell count, cells/mm^3: randomized cohort, 153; nonrandomized cohort, 99.

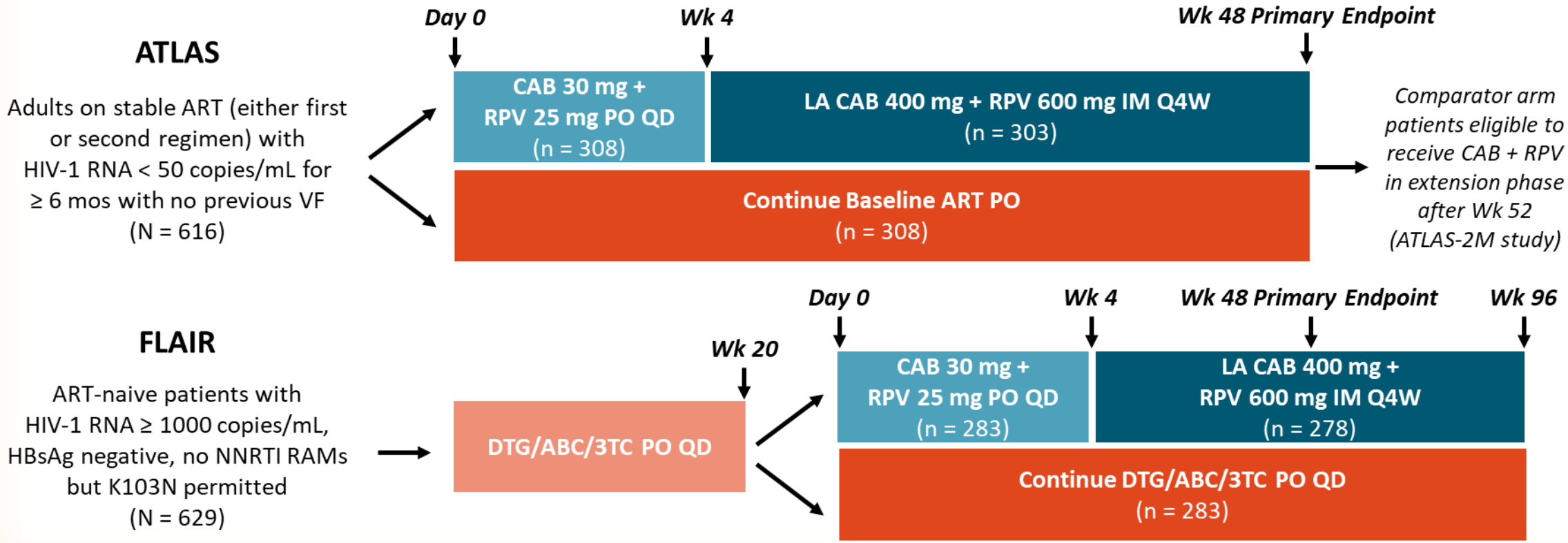
BRIGHTE: Conclusions

- In this Wk 96 analysis of the ongoing phase III BRIGHTE trial, virologic suppression rates and CD4+ cell counts continued to improve in heavily treatment–experienced patients receiving fostemsavir + OBT
  - Wk 96 HIV-1 RNA < 40 copies/mL (Snapshot analysis): 60% in randomized cohort, 37% in nonrandomized cohort
  - Improvements in both CD4+ cell count and CD4+/CD8+ ratio continued through Wk 96, including in subgroup with lowest CD4+ cell count at baseline
- Fostemsavir-containing ART generally well tolerated with no new safety signals through Wk 96
  - Low rate of AE-related discontinuation (7% of all treated patients)
- Study investigators concluded that BRIGHTE data support ongoing development of fostemsavir for heavily treatment–experienced patients with multidrug-resistant HIV

Lataillade. IAS 2019. Abstr MOAB0102.

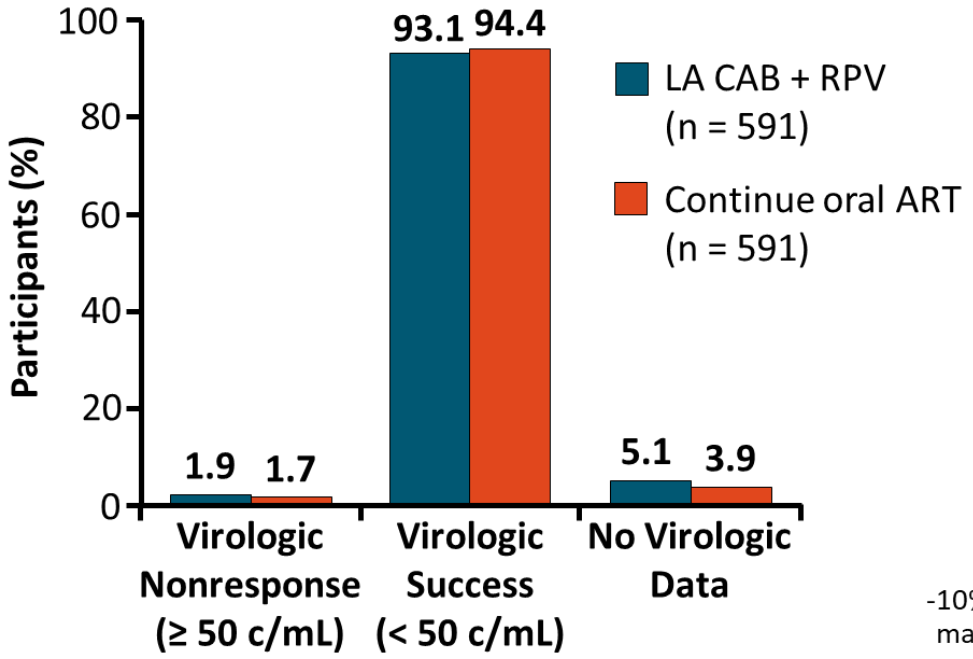
ATLAS and FLAIR Pooled Analysis: Long-Acting Injectable CAB + RPV vs Daily Oral Three-Drug ART

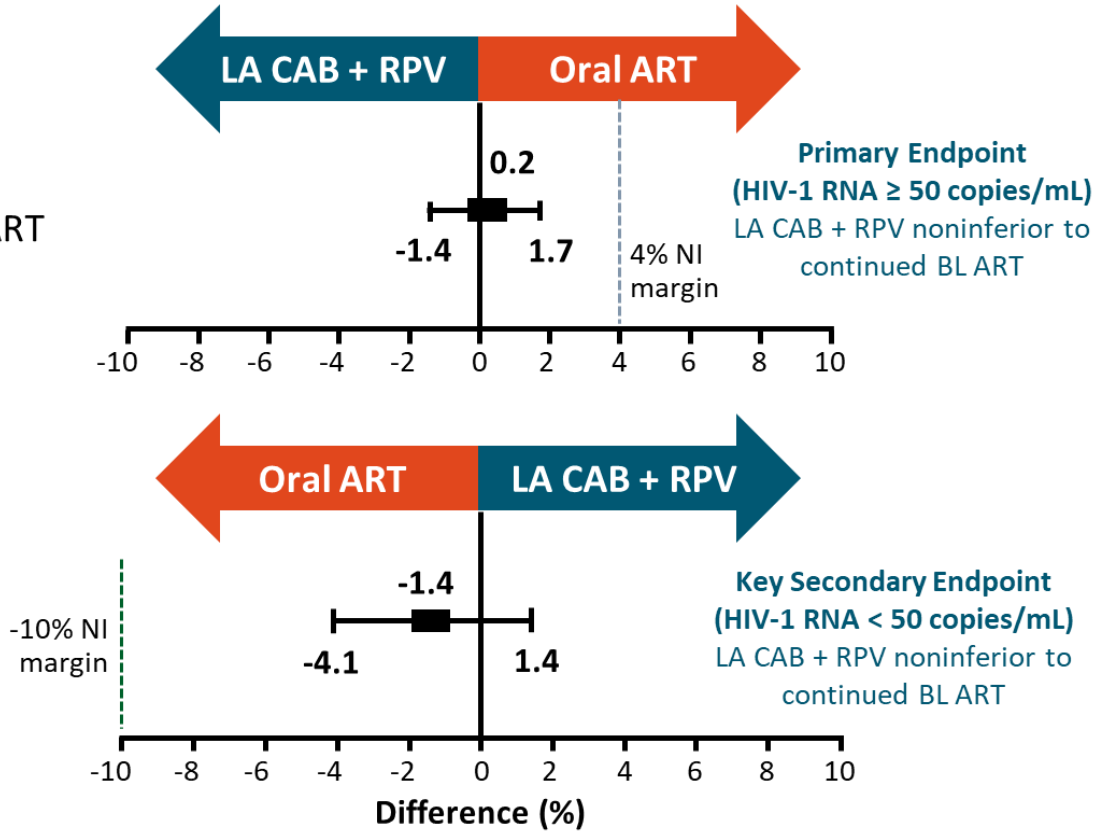
- Multicenter, randomized, open-label phase III non-inferiority trials
- Primary endpoint for both trials: HIV-1 RNA ≥ 50 copies/mL at Wk 48 by FDA Snapshot in ITT-E



Overton. IAS 2019. Abstr MOPEB257.

ATLAS & FLAIR Pooled 48 Week Analyses





Overton. IAS 2019. Abstr MOPEB257.

ATLAS: Patient Views on Long-Acting CAB + RPV

- 86% to 90% of LA CAB + RPV recipients scored **ISRs and pain** at Wk 48 as **totally or very acceptable** in PIN questionnaire

Acceptability, %		LA CAB + RPV	
		Wk 5 (n = 296)	Wk 48 (n = 303)
ISRs	▪ Totally	48	67
	▪ Very	26	23
	▪ Moderately	18	7
	▪ A little	5	3
	▪ Not at all	3	1
Pain	▪ Totally	29	55
	▪ Very	35	31
	▪ Moderately	20	9
	▪ A little	10	4
	▪ Not at all	6	1

P < .001 for Δ over time in "acceptability of ISRs" domain of PIN.

- **Greater improvement** in **treatment satisfaction** by HIVTSQ at Wks 24, 44 with LA CAB + RPV vs daily oral ART

Adjusted Mean Δ From BL in Tx Satisfaction*	LA CAB + RPV	BL Oral ART	Difference (95% CI)†
Wk 24	6.43	1.05	5.39 (4.17-6.60)
Wk 44	6.12	0.44	5.68 (4.37-6.98)

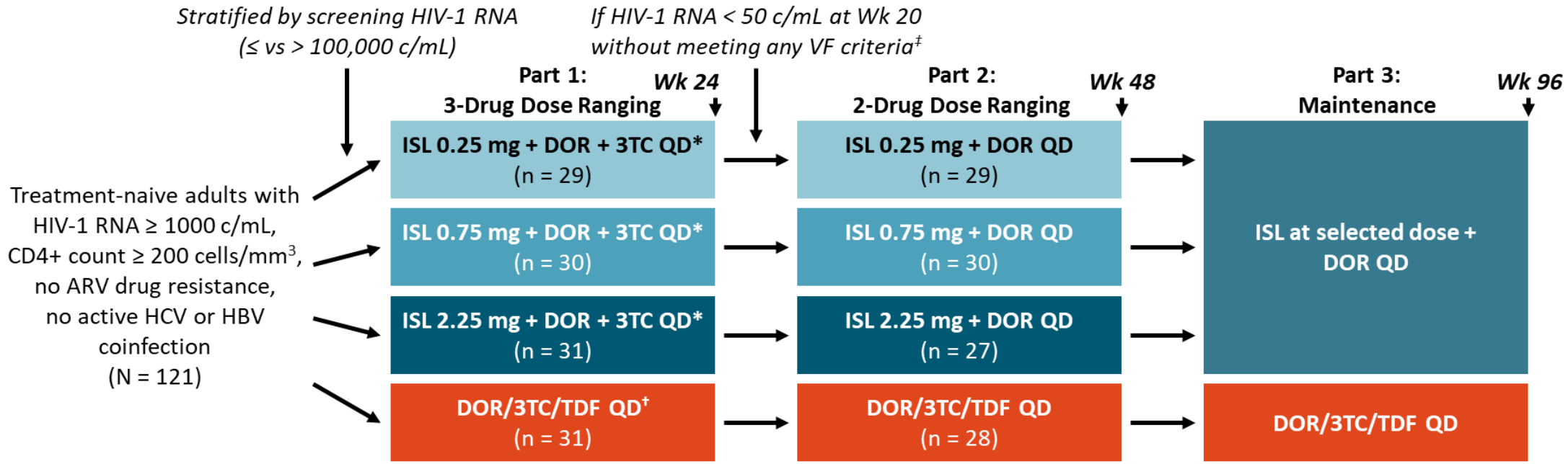
*Adjusted for BL score, sex, age, race, and BL third agent class.
†*P* < .001 for all listed differences.

Patient Preference for ART Delivery Method by Population, % (n/N)	Long-acting IM	Daily PO
ITT-E	86 (266/308)	2 (7/308)
Responding patients	97 (266/273)	3 (7/273)

Murray. IAS 2019. Abstr MOAB0103.

DRIVE2Simplify Part 2: Islatravir + Doravirine vs DOR/3TC/TDF in ART-Naive Adults

- Current analysis of Part 2 for international, randomized, double-blind phase IIb trial

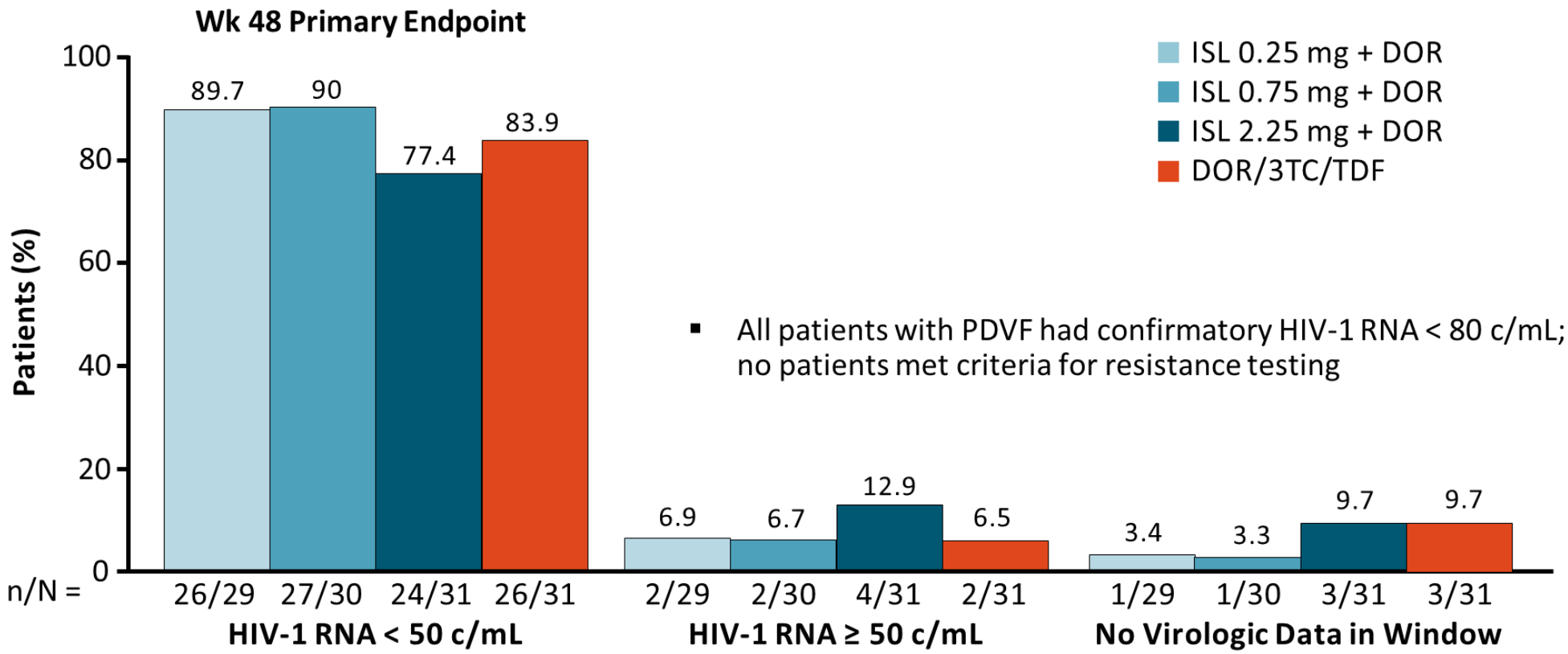


- Primary endpoints: rate of HIV-1 RNA < 50 c/mL at Wks 24 and 48 (FDA Snapshot), AEs, AE-related d/c

*Received placebo for DOR/3TC/TDF. †Received placebo for ISL + DOR + 3TC QD.
‡If HIV-1 RNA ≥ 50 c/mL at Wk 20, continued Part 1 until HIV-1 RNA < 50 c/mL and, if not meeting any VF criteria, transitioned to Part 2.

Molina. IAS 2019. Abstr WEAB0402LB.

DRIVE2 Simplify Part 2: Virologic Outcomes Wk 48 (FDA Snapshot)



- All patients with PDVF had confirmatory HIV-1 RNA < 80 c/mL; no patients met criteria for resistance testing

No deaths. No increase of Aes with ISL vs. DOR/3TC/TDF

Molina. IAS 2019. Abstr WEAB0402LB.

Thank you