

Efficacy and Safety of Bictegravir/Emtricitabine/Tenofovir Alafenamide vs Comparators in Women and Girls: an Analysis of 5 Clinical Trials

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Disclosures

Professor Orkin has received:

- ◆ Honoraria for lectures and advisory boards from Gilead Sciences, Janssen, MSD and ViiV
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- ◆ Research grants to my institution from Gilead Sciences, Janssen, MSD and ViiV

Introduction

- ◆ Globally, girls and women make up more than half of the people living with HIV (52%)¹
 - 19.1 million girls and women living with HIV



Introduction

- ◆ Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a once-daily, guidelines approved, single-tablet regimen with demonstrated efficacy and safety in clinical trials of treatment-naïve and virologically suppressed adults, adolescents and children living with HIV²⁻⁶
- ◆ Girls and women remain significantly under-represented in clinical trials
- ◆ B/F/TAF development program included a dedicated phase 3 study of women (n=470)²
 - Africa, Asia, Western Europe, North America, Russia, and the Caribbean

2. Kityo C, et al. CROI 2018. Boston, MA. Poster 500

3. Wohl D, et al. Lancet HIV 2019;6(6):e355-e363

4. Stellbrink, HJ, et al. Lancet HIV 2019; pii: S2352-3018(19)30080-3

5. Gaur A, et al. CROI 2019. Seattle, WA. Oral 46

6. Maggiolo F, et al. IAS 2019. Mexico City. Poster MOPEB238

Methods

- ◆ Efficacy and safety of B/F/TAF vs comparators were assessed in 679 women* and girls* across five phase 2 or 3 B/F/TAF clinical trials through 48 weeks

Women/girls (n)

B/F/TAF, Comparator

69, 70

Study 1489³

ART-naïve Adults

Study 1490⁴

ART-naïve Adults

234, 236

Study 1961²

HIV Suppressed Women

E/C/F/TAF, E/C/F/TDF, or ATV+RTV+F/TDF

59

Study 1474⁵

HIV Suppressed Ages 6-17

on 2 NRTIs + 3rd agent

11

Study 4449⁶

HIV Suppressed Ages 65+

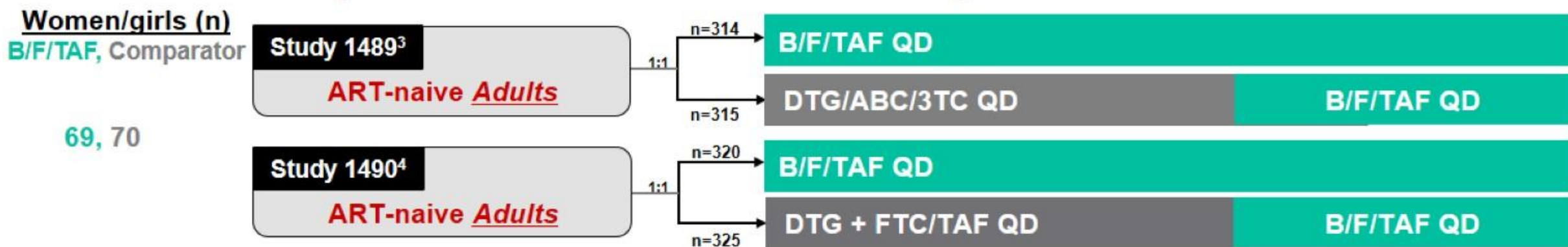
on 2 NRTIs + 3rd agent

373, 306

* Sex at birth

Methods

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234, 236

Study 1961²

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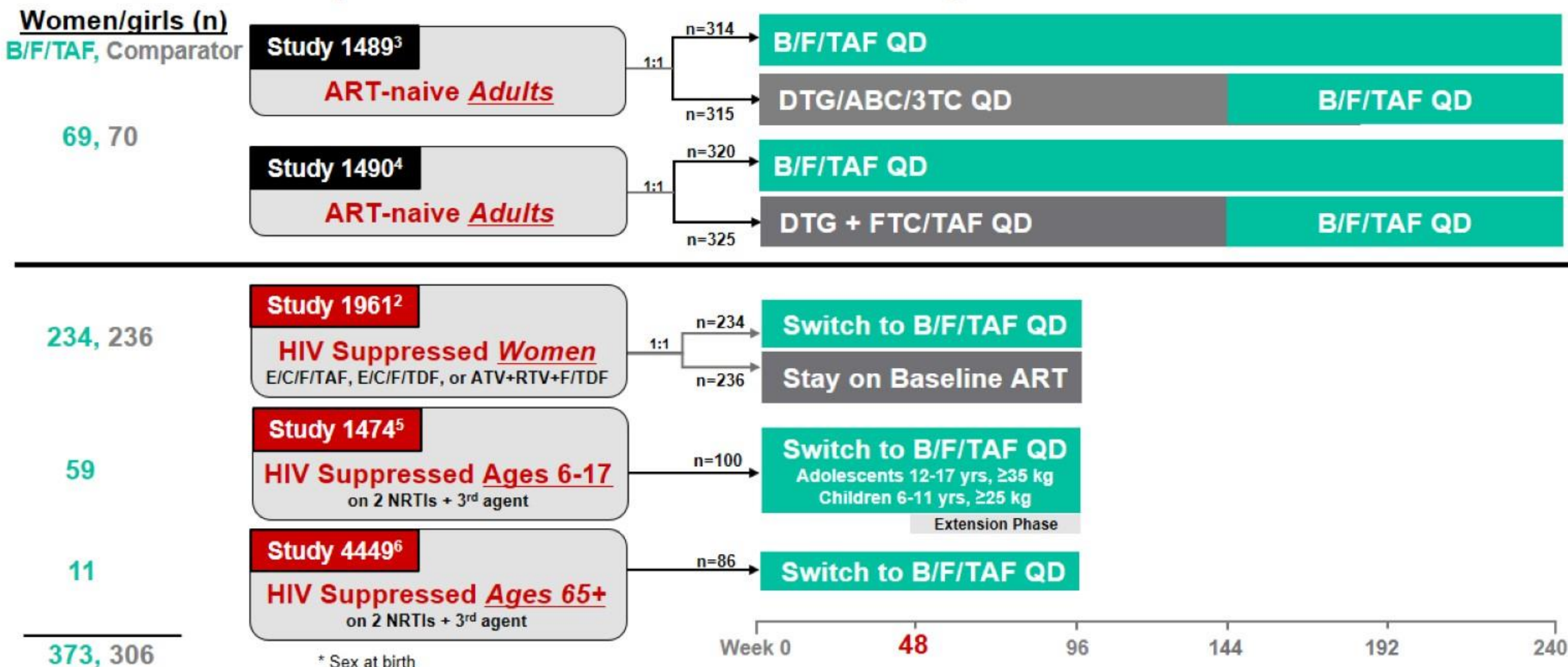
373, 306

* Sex at birth



Methods

- ♦ Efficacy and safety of B/F/TAF vs comparators were assessed in 679 women* and girls* across five phase 2 or 3 B/F/TAF clinical trials through 48 weeks



Assessments



Efficacy

- ◆ Virologic suppression (HIV-1 RNA < 50 copies/mL)
- ◆ Treatment-emergent resistance



Adverse events

- ◆ All Grades
- ◆ Grade 3-4
- ◆ Study drug-related
- ◆ Leading to discontinuation
- ◆ Fractures
- ◆ Weight



Laboratory parameters

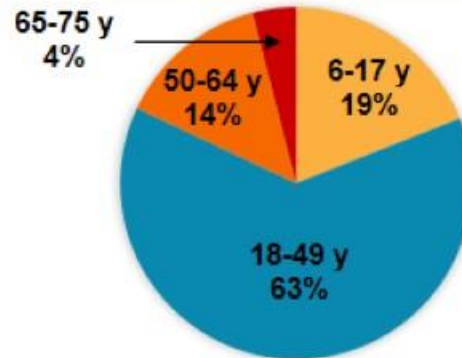
- ◆ Grade 3-4
- ◆ Renal function and biomarkers*
- ◆ Bone mineral density†

* Renal biomarkers were not assessed in Study 1474 (pediatrics)

† Bone mineral density was only assessed in Study 1489 (ART-naïve B/F/TAF vs DTG/ABC/3TC)

Demographics & Baseline Characteristics: B/F/TAF Participants

Virologically Suppressed



6 to 17
n=59

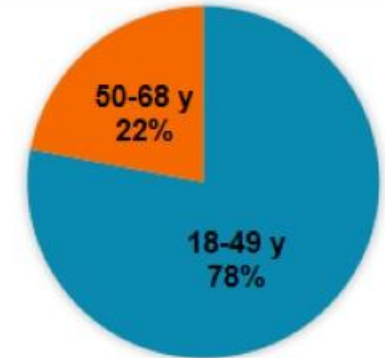
18 to 49
n=191

50 to 64
n=43

65 to 75
n=11

Age (years)

Treatment-Naive

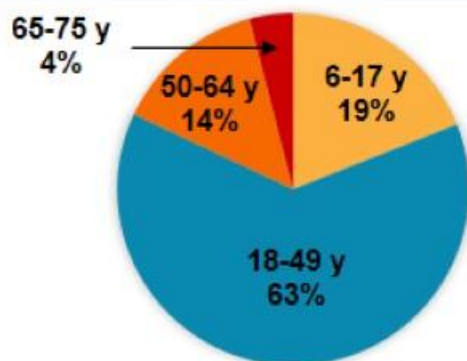


18 to 49
n=54

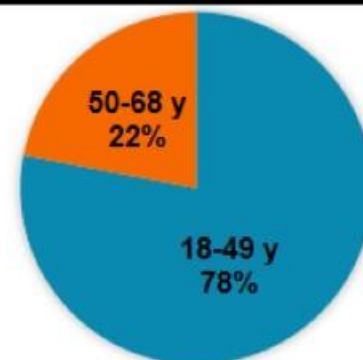
50 to 68
n=15

Demographics & Baseline Characteristics: B/F/TAF Participants

Virologically Suppressed



Treatment-Naïve



Age (years)

6 to 17
n=59

18 to 49
n=191

50 to 64
n=43

65 to 75
n=11

18 to 49
n=54

50 to 68
n=15

Race/ethnicity

Black

78%

38%

44%

9%

White

3%

29%

23%

91%

Asian

17%

23%

12%

0

Median HIV-1 RNA, log₁₀ c/mL

All <50 c/mL

Median CD4, cells/μL

848

666

682

726

Median eGFR, mL/min*

147

101

87

70

48%

47%

35%

40%

0

0

4.27

4.25

411

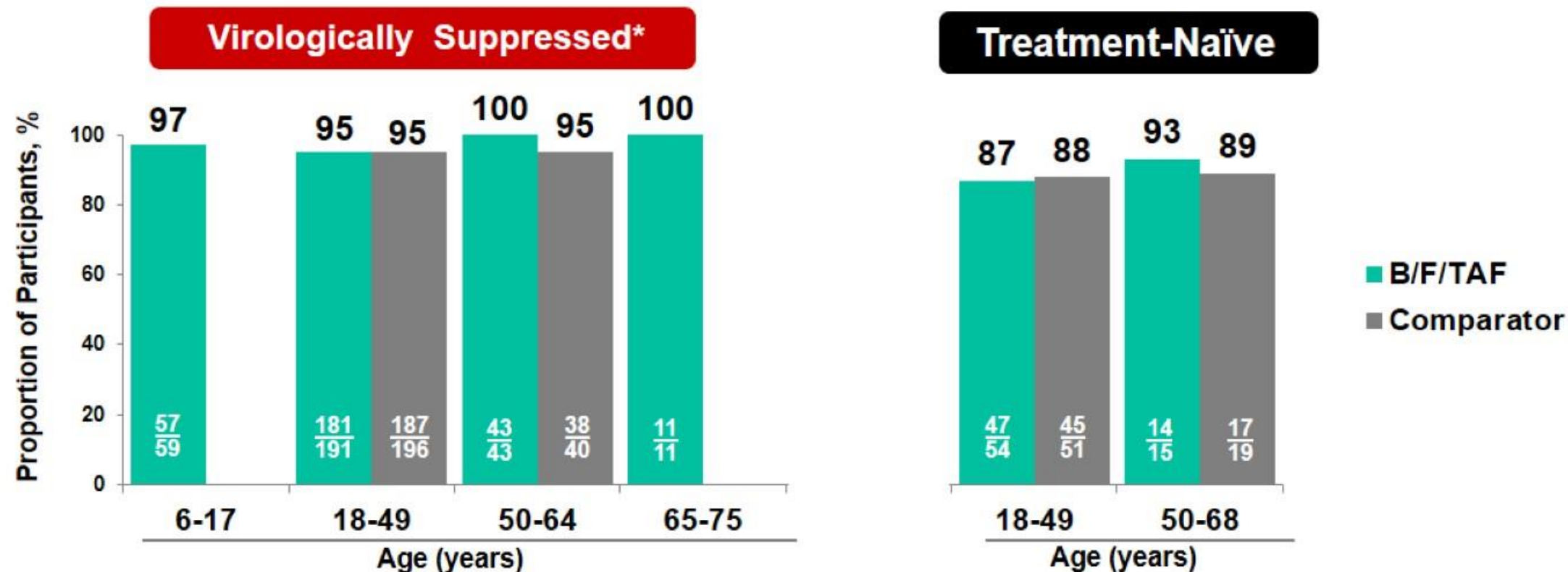
522

129

86

* Estimated glomerular filtration rate (eGFR) calculated using Schwartz formula for pediatrics (mL/min/1.72m²) and Cockcroft-Gault for adults

HIV-1 RNA <50 c/mL & Resistance at Weeks 48



- ◆ No treatment-emergent resistance was detected with B/F/TAF[†]
- ◆ B/F/TAF findings are consistent with overall analyses including both sexes[‡]

* HIV-1 RNA ≥ 50 c/mL: 2.1% vs 1.5% and 0 vs 2.5% for B/F/TAF vs comparators in 18-49 and 50-64 years of age, respectively

† 1 participant on comparator regimen developed M184M/I/V in E/C/F/TAF participant at Week 48 and the woman subsequently resuppressed HIV-1 RNA after switching to B/F/TAF

‡ HIV-1 RNA <50 c/mL (both sexes): 99% in 6-17 yrs (Study 1474), 87% in 65-75 yrs (Study 4449), 91% (B/F/TAF) vs 93% in comparators in 18-68 yrs (Pooled Studies 1489-1490)

Adverse Events (AEs)

Participants	Virologically Suppressed			ART-Naïve	
	6-17 yrs n=59	18-49 yrs n=191	50-75 yrs n=54	18-49 yrs n=54	50-68 yrs n=15
Any Grade AE	78%	63%	80%	85%	80%
Study Drug-Related AEs	14%	9%	6%	19%	7%
Discontinuation due to AE, n	1*	0	0	0	0

- ◆ Findings are consistent with overall analyses including both sexes
- ◆ Of 373 women and girls treated with B/F/TAF, only 1 (0.1%) discontinued study drug due to an AE*
 - No discontinuations due to bone, renal, or hepatic AEs
- ◆ Overall rates of Grade 3-4 AEs and serious AEs were low and similar to comparators (not shown)
- ◆ Two participants had fractures on B/F/TAF: 1) finger and 2) bilateral traumatic wrist fractures, both in >65 years†
- ◆ AEs of weight increase and weight decrease were reported in ≤ 1% of women
 - B/F/TAF (3/314 and 1/314) and comparators (1/306 and 1/306), respectively‡

* One girl with Grade 2 anxiety and insomnia

† Both fractures in virologically suppressed women were deemed not study drug related by the investigator (Study 4449)

‡ All weight increase AEs were reported in ART-naïve women age 18-49 years; weight decrease AEs were reported in 1 ART-naïve woman (18-49 years) on B/F/TAF and 1 virologically suppressed woman (≥ 50 years) on comparator

Grade 3-4 Laboratory Abnormalities*

Participants, %	Virologically Suppressed			ART-Naïve	
	6-17 yrs n=59	18-49 yrs n=191	50-75 yrs n=54	18-49 yrs n=54	50-68 yrs n=15
Grade 3-4	17%	19%	11%	17%	21%
Grade 3-4 Hematuria	19%	13%	2%	2%	0
Grade 3-4 Neutropenia	7%	1%	0	4%	7%
↑ LDL (>4.92 mmol/L) [†]	0	4%	2%	2%	7%
↑ Total Cholesterol (>7.77 mmol/L) [†]	0	<1%	0	0	0
↑ Triglycerides (>8.47 mmol/L) [†]	0	0	0	0	0

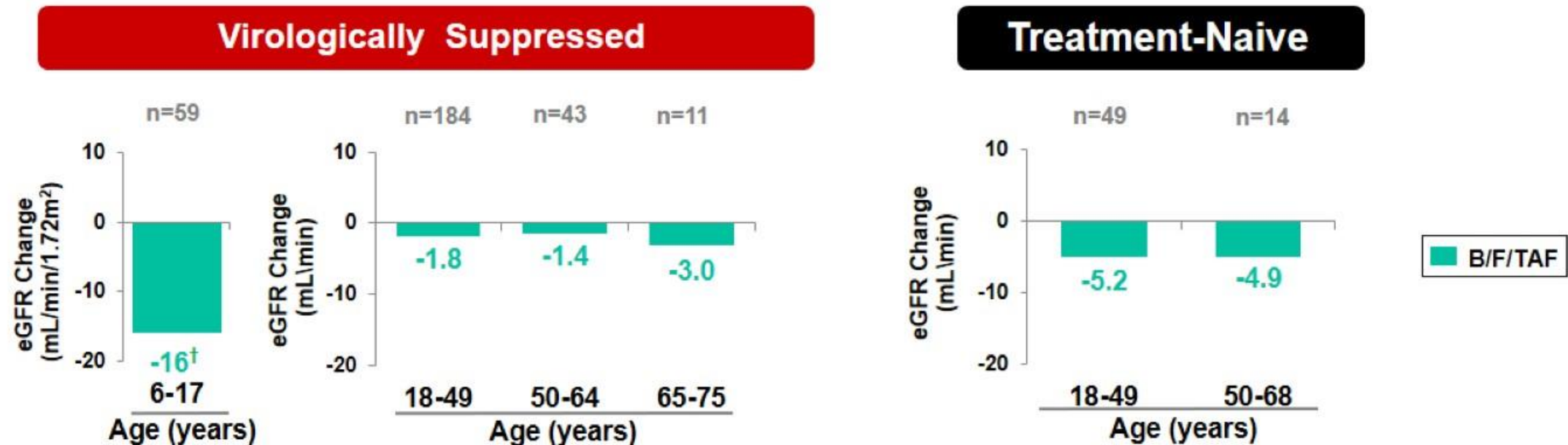
- ◆ Except for hematuria and neutropenia, no Grade 3-4 laboratory abnormality occurred in ≥5% and more than 1 participant
- ◆ Grade 3-4 LDL and total cholesterol elevations were infrequent in participants on B/F/TAF

LDL, low density lipoprotein

* Not all participants contributed samples at all time points

† LDL > 190 mg/dL, total cholesterol >300 mg/dL, and triglycerides > 750 mg/dL

eGFR: Median Change from Baseline to Week 48*



- ♦ Small eGFR changes were observed in B/F/TAF participants
 - Consistent with the known effect of bictegravir on OCT-2 and MATE-1, with no effect on actual GFR
 - Similar to comparators[‡]

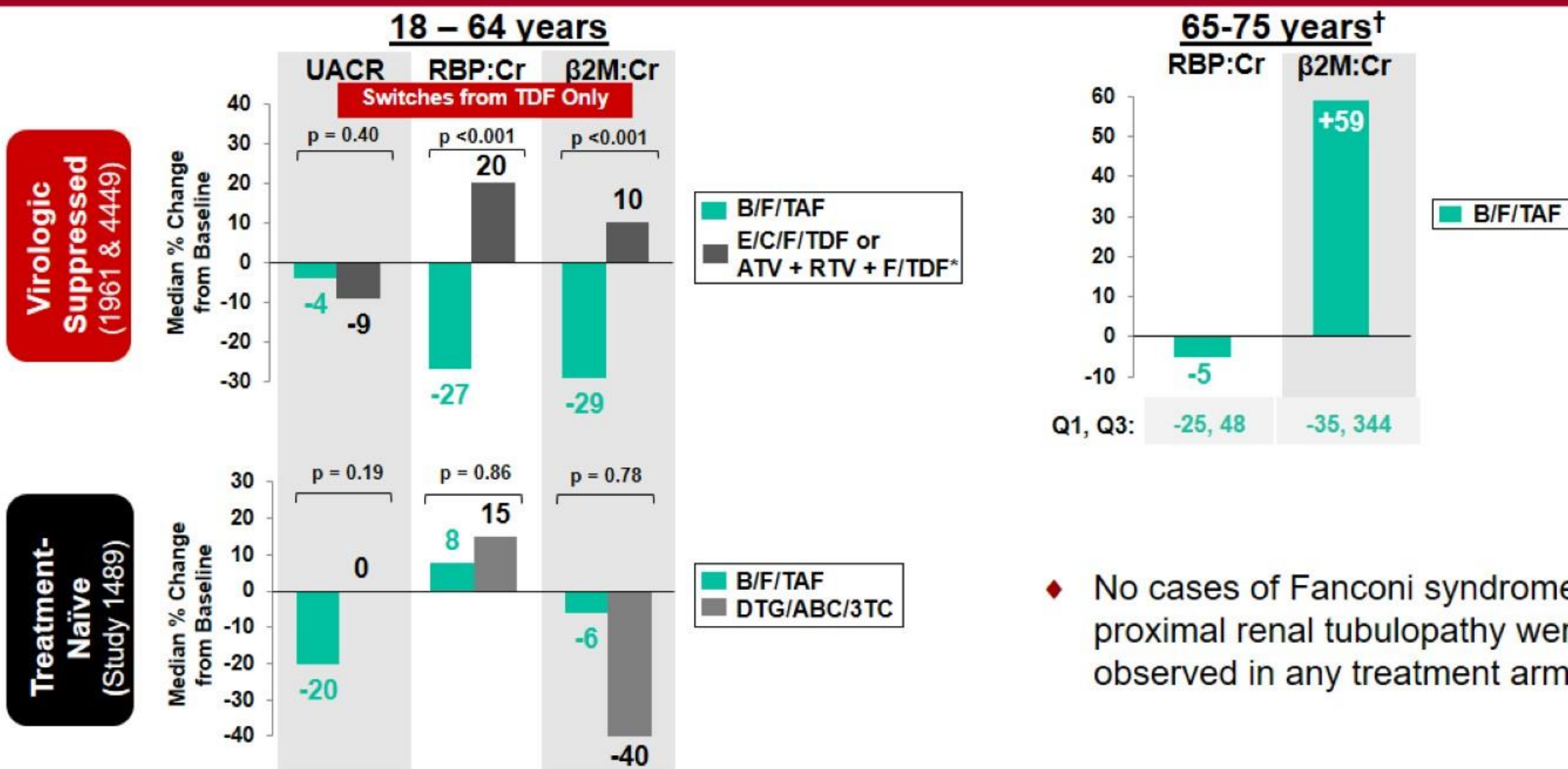
eGFR, estimated glomerular filtration rate. MATE-1, multidrug and toxin extrusion protein 1. OCT-2, organic cation transporter 2

* eGFR calculated using Schwartz formula for pediatrics and Cockcroft-Gault for adults

[†] Week 48 median eGFR was 133 mL/min/1.72m² in the pediatric population

[‡] Median eGFR changes in the comparator arms: in virologically suppressed 18-64 years of age -3 mL/min and in treatment-naïve -10 and +4 mL/min (DTG/ABC/3TC) and -11 and -5 mL/min (DTG+F/TAF), for <50 and ≥50 years of age, respectively

Renal Biomarkers: Median Change from Baseline to Week 48



◆ No cases of Fanconi syndrome or proximal renal tubulopathy were observed in any treatment arms

P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment groups

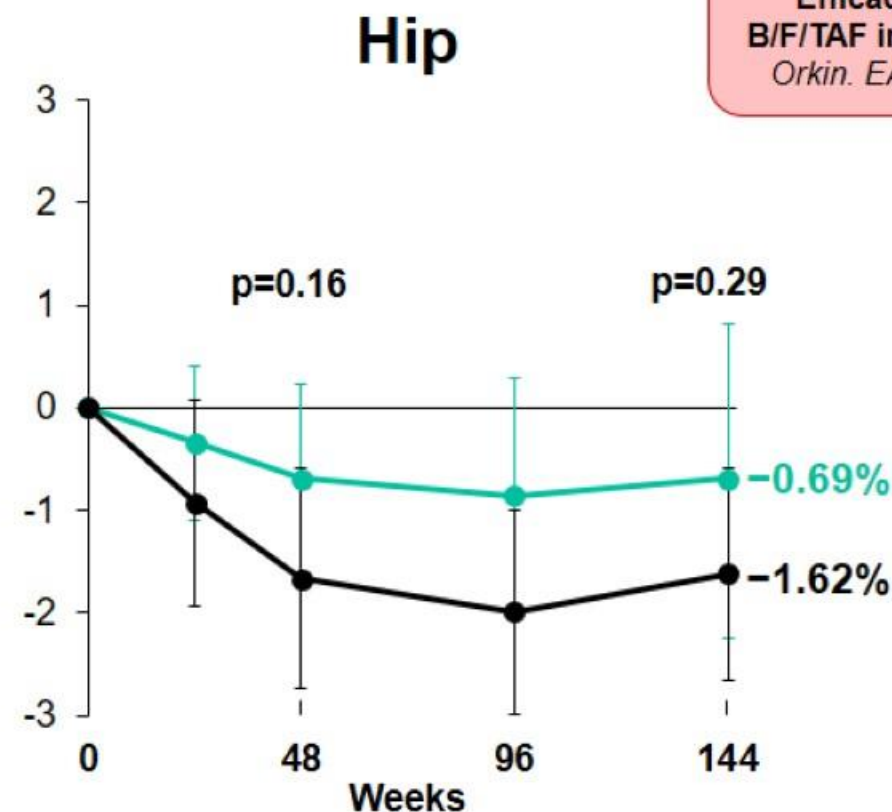
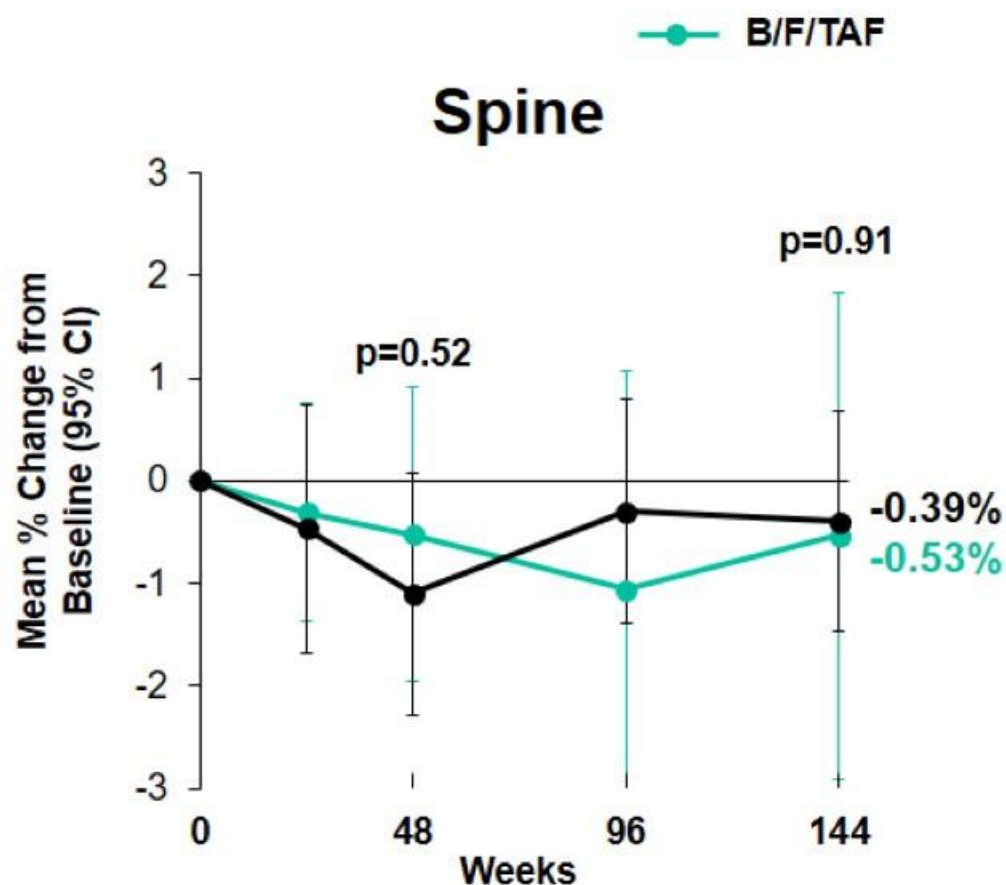
* 48% of the overall Study 1961 population had baseline TDF-based regimen: E/C/F/TDF (42%) and ATV+RTV+FTC/TDF (6%)

† In Study 4449 4/8 women with urinary protein to creatinine ratio (UACR) > 200 mg/g improved to <200 mg/g at W48

Treatment-Naïve: Study 1489

Bone Mineral Density: Mean Change from Baseline to Week 144

Long-term (Week 144)
Efficacy and Safety of
B/F/TAF in ART-naïve Adults
Orkin. EACS 2019. PE3/14



B/F/TAF	n=28	25	26	23	21
DTG/ABC/3TC	n=28	26	26	24	24

B/F/TAF	n=27	25	25	22	20
DTG/ABC/3TC	n=28	26	26	24	24

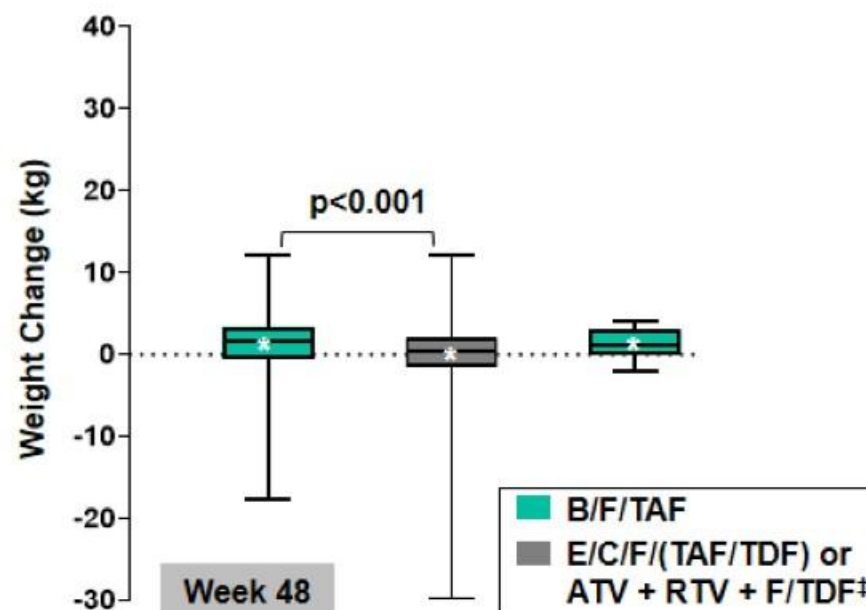
CI, confidence interval. BMD measured by dual-energy x-ray absorptiometry
P-values compare B/F/TAF vs DTG/ABC/3TC by analysis of variance model

Weight: Change from Baseline to Week 48*†

Virologically Suppressed

18-64 years

65-75 years

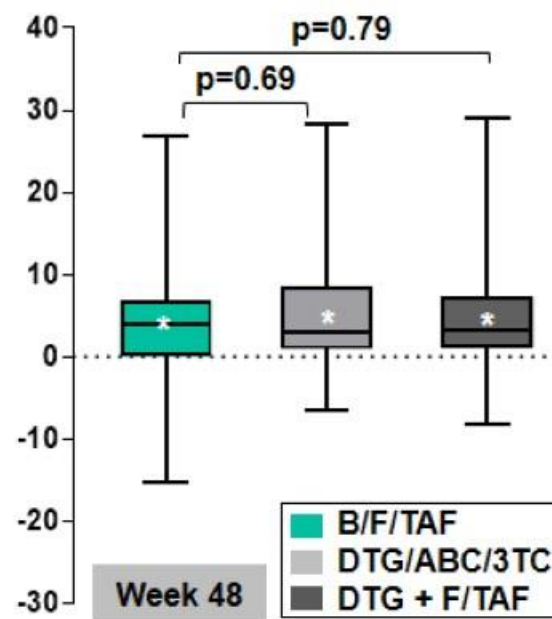


B/F/TAF Comparators B/F/TAF

Sample size (n):	229	230	11
Baseline median weight (kg):	67	68	62
Mean change (kg)	1.3	0.1	1.2
Median change (kg)	1.5	0.4	1.0

Treatment-Naïve

18-68 years



B/F/TAF Comparators

63	30	32
74	84	70
4.0	4.9	4.6
4.0	2.9	3.2

Q, quartile. P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment group

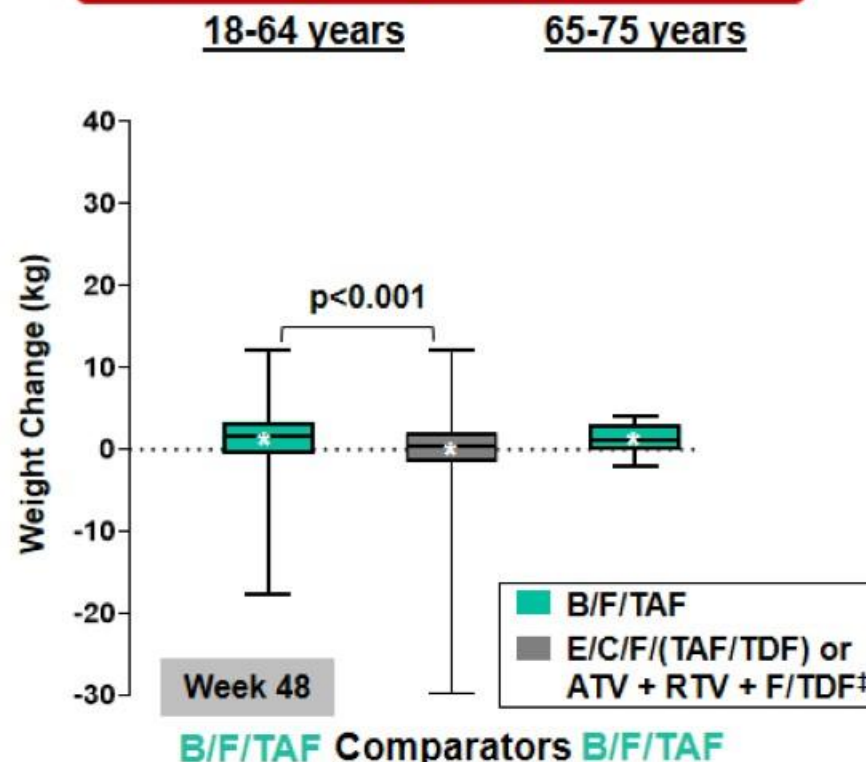
* Box plot represents min, Q1, median, Q3 and max values with asterisk representing mean values

† Small absolute difference in Week 48 weight changes between treatment arms for the mean, median, maximum, Q1 and Q3 values: < 1.5 kg for virologically suppressed and < 2.0 kg for ART-naïve

‡ Comparators: E/C/F/TAF (53%), E/C/F/TDF (42%), and ATV+RTV+FTC/TDF (6%)

Weight: Change from Baseline to Weeks 48 & 144*†

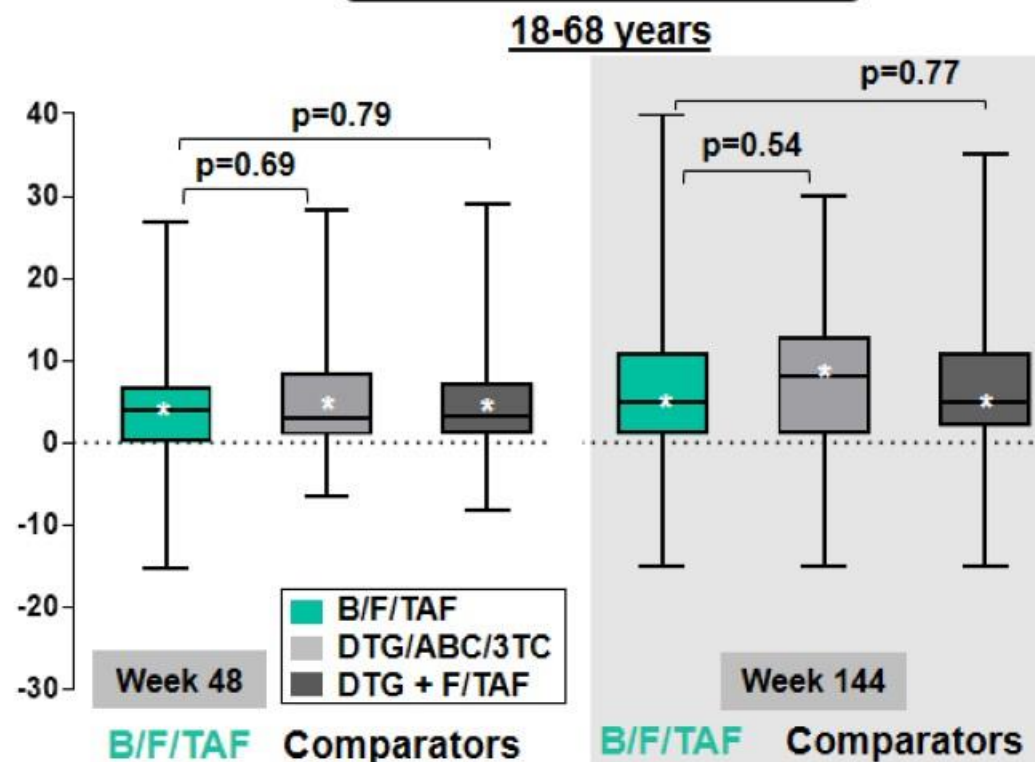
Virologically Suppressed



Sample size (n):
Baseline median weight (kg):
Mean change (kg)
Median change (kg)

Group	18-64 years	65-75 years
Sample size (n)	229	11
Baseline median weight (kg)	67	62
Mean change (kg)	1.3	1.2
Median change (kg)	1.5	1.0

Treatment-Naïve



Group	18-68 years
Sample size (n)	63
Baseline median weight (kg)	74
Mean change (kg)	4.0
Median change (kg)	4.0

Group	18-68 years
Sample size (n)	50
Baseline median weight (kg)	74
Mean change (kg)	6.7
Median change (kg)	5.0

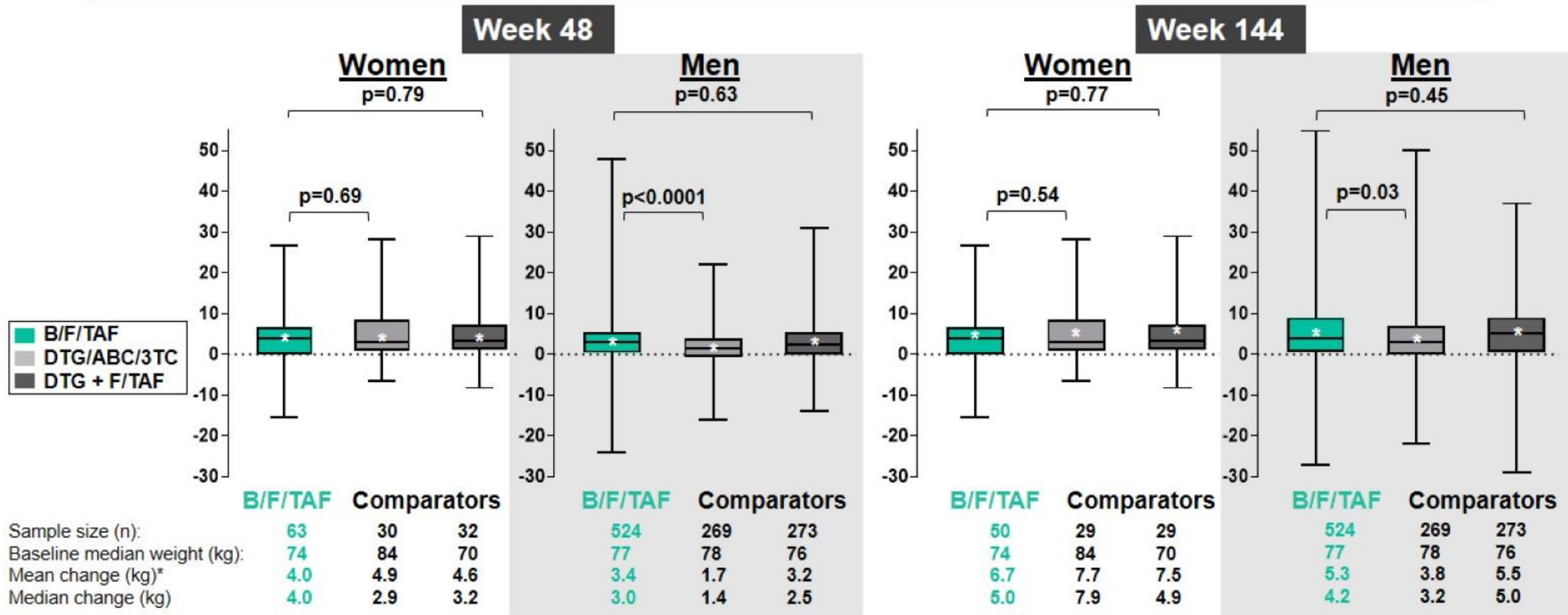
Q, quartile. P-values were from the 2-sided Wilcoxon rank sum test to compare the 2 treatment group

* Box plot represents min, Q1, median, Q3 and max values with asterisk representing mean values

† Small absolute difference in Week 48 weight changes between treatment arms for the mean, median, maximum, Q1 and Q3 values: < 1.5 kg for virologically suppressed and < 2.0 kg for ART-naïve

‡ Comparators: E/C/F/TAF (53%), E/C/F/TDF (42%), and ATV+RTV+FTC/TDF (6%)

Weight: Change from Baseline to Week 48 and 144



- Differences between treatment arms for weight changes from baseline to Weeks 48 & 144 were < 2 kg for mean, median, Q1 and Q3 values, regardless of sex

B/F/TAF Use During Pregnancy

- Cumulative to 17 October 2019, 30 cases of B/F/TAF exposure during pregnancy in Gilead-sponsored clinical trials

Prospective Reports N=25 (83%)			Retrospective Reports N=4 (13%)			Unknown if Retrospective or Prospective Reports N=1 (3%)		
Timing of Exposure in Pregnancy								
Preconception or 1 st Trimester	After 1 st Trimester	Unknown	Preconception or 1 st Trimester	After 1 st Trimester	Unknown	Preconception or 1 st Trimester	After 1 st Trimester	Unknown
21 (84.0%)	2 (8.0%)	2 (8.0%)	4 (16.0%)	0	0	1 (4.0%)	0	0

- Live birth without congenital anomaly (n=15)
 - Live birth with congenital anomaly (n=1; patent urachus*)
 - Not reported / outcome pending / unknown (n=3)
- Spontaneous abortion during T1 (n=7)
 - Still birth (n=1)
 - Elective termination (n=3)
- No cases of CNS congenital malformations or neural tube defects

No prevalence rate could be derived as many exposures originated from retrospective reports drawn from a population in which the number of exposed pregnancies is unknown.

T1, trimester 1 of pregnancy

* Connection between the bladder and the umbilicus which was not confirmed on repeat ultrasound and there was no intervention

Conclusions

- ◆ Week 48 outcomes from this large analysis of 373 diverse female participants demonstrate the safety, tolerability, and efficacy of B/F/TAF
 - High rates of viral suppression
 - No treatment-emergent resistance
 - Well tolerated and safe
 - 0.1% discontinuation due to AEs; no discontinuations for bone and renal AEs
 - Low rates of serious AEs, Grade 3-4 AEs and Grade 3-4 laboratory abnormalities
 - Improvements in renal tubular markers with switch from TDF
 - Small median eGFR change of ≤ 5 mL/min decrease in women
 - BMD changes were comparable to DTG/ABC/3TC through Week 144
 - Similar median weight changes from baseline to Week 48 for B/F/TAF and comparators in ART-naïve women ($p=NS$) and small differences (<1.5 kg) in virologically suppressed women ($p<0.001$)
- ◆ B/F/TAF is an important treatment option for women and girls living with HIV globally, regardless of age and race

Acknowledgements

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1474	1961	4449	1489	1490
South Africa Thailand Uganda US	Dominican Republic Russia Thailand Uganda US	Belgium France Italy Spain United Kingdom	Belgium Canada Dominican Republic France Germany Italy Puerto Rico Spain United Kingdom US	Australia Belgium Canada Dominican Republic France Germany Italy Puerto Rico Spain United Kingdom US

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