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Patient-Reported Outcomes Among HIV-1–Infected Adults Randomized to B/F/TAF vs DTG/ABC/3TC in Two Phase 3 Controlled Clinical Trials Over 48 Weeks

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Introduction

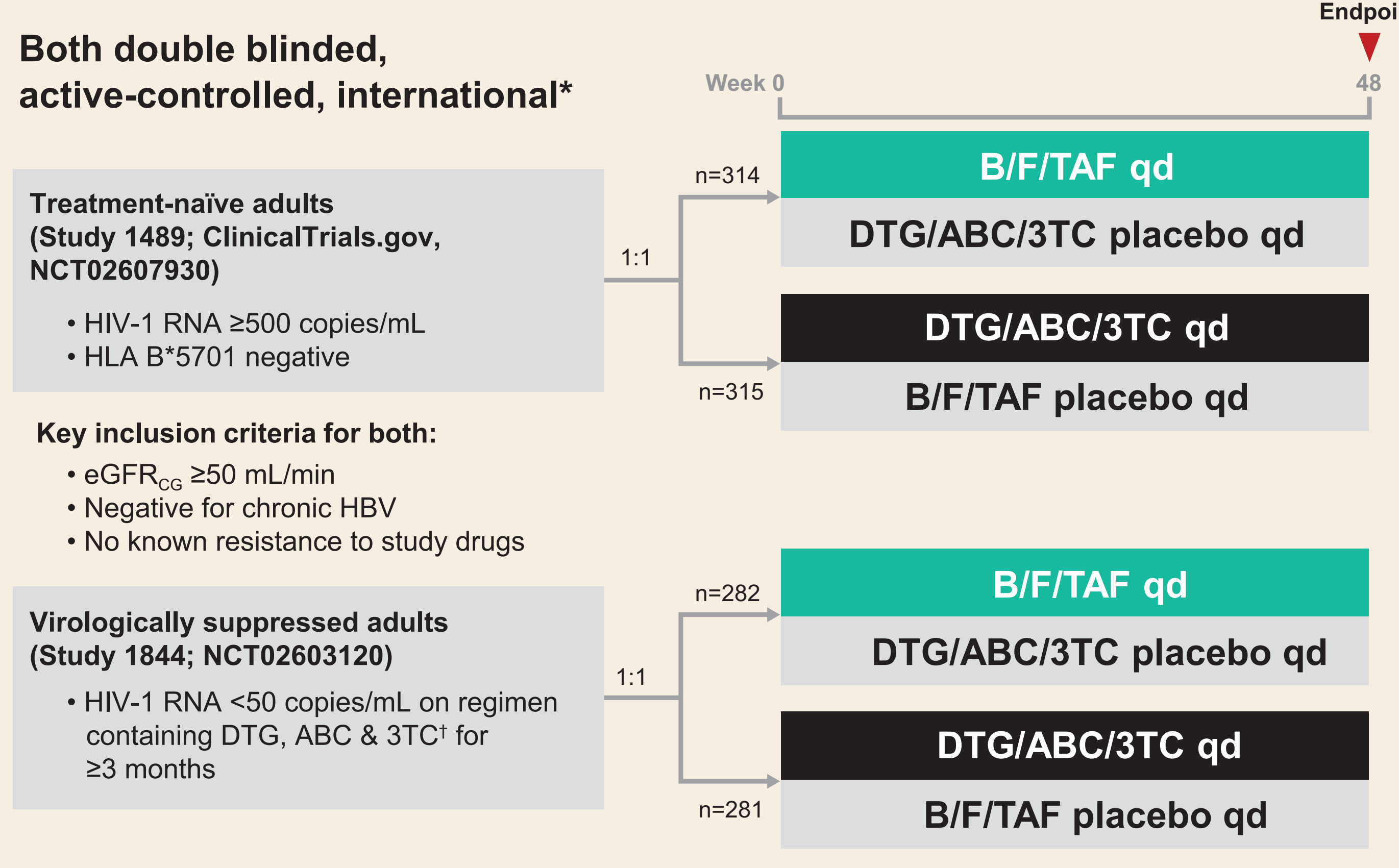
- Integrase strand transfer inhibitors (INSTIs) are recommended for 1st-line antiretroviral therapy (ART) in combination with 2 nucleoside reverse transcriptase inhibitors (NRTIs)[1-3]
- As success of ART largely depends on patient adherence, triple-therapy single-tablet regimens (STRs) have emerged as preferred treatment regimens and are associated with less treatment failure[4]
- In the real-world setting, patient satisfaction and tolerability (eg, patient-reported outcomes [PROs]) may improve adherence, and have become important differentiators among regimens
- Bictegravir (BIC; B) and dolutegravir (DTG) are INSTIs that do not require the coadministration of a pharmaco-enhancer
  - Both have been coformulated with NRTIs as fixed-dose combinations: BIC with emtricitabine (FTC; F) and tenofovir alafenamide (TAF) as B/F/TAF, and DTG with abacavir (ABC) and lamivudine (3TC) as DTG/ABC/3TC
- Nausea has been associated with ABC, while central nervous system adverse events, sometimes leading to discontinuation, have been reported more frequently with DTG[5-9]
- B/F/TAF demonstrated high efficacy and was well tolerated through Week 48, with no treatment-emergent resistance in multiple, Phase 3 studies of treatment-naïve or virologically suppressed adults and adolescents[10-15]
- PROs are valuable as participants do not always report symptoms of this nature as adverse events in clinical studies

Objective

- To characterize changes in measures of self-reported well-being (ie, PROs) in adults with HIV-1 infection after initiating or switching to B/F/TAF vs DTG/ABC/3TC

Methods

Study Design



Both double blinded, active-controlled, international*

Treatment-naïve adults (Study 1489; ClinicalTrials.gov, NCT02607930)
- HIV-1 RNA ≥500 copies/mL
- HLA B*5701 negative

Key inclusion criteria for both:
- $eGFR_{CG}$ ≥50 mL/min
- Negative for chronic HBV
- No known resistance to study drugs

Virologically suppressed adults (Study 1844; NCT02603120)
- HIV-1 RNA <50 copies/mL on regimen containing DTG, ABC & 3TC† for ≥3 months

*Australia, Europe (Belgium, France, Germany, Italy, Spain, and UK), Latin America (Dominican Republic), and North America (Canada and US, including Puerto Rico); †Could be components of STR. $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation; HBV, hepatitis B virus; HLA, human leukocyte antigen.

Patient-Reported Outcome Tools

	HIV-SI[16]	PSQI[17]	SF-36 PCS and MCS[18-20]	WPAI[21]
General description	Validated, 20-item, self-reported questionnaire	Validated, 19-item, self-reported questionnaire	Validated, 8-multi-item (35-item), self-reported questionnaire	Validated, 6-item, self-reported questionnaire
Symptoms/ domains evaluated	Nausea/vomiting; loss of appetite; diarrhea; bloating; nervous/anxious; sad/down/depressed; fatigue; dizzy/lightheaded; trouble remembering; headache; fevers/chills; difficulty sleeping; pain in hands/feet; skin problems; cough; muscle aches; sex problems; weight gain; weight loss; hair loss	Subjective sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbances (nighttime awakening); use of sleeping medication; daytime dysfunction	Physical function; role limitations due to physical health problems; bodily pain; general health; vitality; social functioning; role limitations due to emotional problems; emotional well-being	Health-related, work-productivity loss for employed population measured by current employment, hours missed due to health problems and other reasons, hours actually worked, degree to which health affected productivity while working, and degree to which health affected regular activities
Scores	Range: 0 ("I do not have this symptom") to 4 ("It bothers me a lot.")	Range: 0–21 (lower score = better sleep quality)	Range: 0–100 (higher score = better functioning);	Expressed as impairment % (higher numbers = greater impairment and less productivity)
Responses	Dichotomized as "not present or not bothersome" (score 0–1) or "bothersome" (score 2–4)	Dichotomized as poor (score >5) or good sleep (score ≤5)		
Timepoints	Baseline, and Weeks 4, 12, and 48	Baseline, and Weeks 4, 12, and 48	Baseline, and Weeks 4, 12, and 48	Baseline, and Weeks 4, 12, and 48

HIV-SI, HIV Symptoms Index; MCS, Mental Component Summary; PCS, Physical Component Summary; PSQI, Pittsburgh Sleep Quality Index; SD, standard deviation; SF-36, 36-Item Short Form Health Survey; WPAI, Work Productivity and Activity Impairment.

Statistical Analyses

HIV-SI

- Treatment differences were assessed using logistic regression models adjusted for:
  - BL HIV-SI count, age, sex, BL Veterans Aging Cohort Study (VACS) Index,[16] medical history of serious mental illness (ie, ≥1 of the following investigator-reported diagnoses reported by the study: major depression, anxiety, bipolar disorder, post-traumatic stress disorder, schizophrenia or other psychosis), BL SF-36 PCS and MCS, years since HIV diagnosis (Study 1844 only)
- Longitudinal modeling (ie, the prevalence of HIV-SI bothersome symptoms over time) conducted using generalized, mixed-model including treatment, time, time-by-treatment interaction, and additional covariates as above
- Treatment differences noted if prevalence was statistically significantly different at ≥2 timepoints in adjusted logistic regression model or ≥1 timepoints in adjusted logistic regression model and in longitudinal model

PSQI

- Logistic regression models adjusted for BL PSQI poor sleep quality and BL SF-36 MCS
- Longitudinal modeling (ie, prevalence of poor sleep quality over time) included treatment, time, time-by-treatment interaction, and BL PSQI poor sleep quality and BL SF-36 MCS as covariates

SF-36 PCS/MCS scores and WPAI scores

- Treatment differences assessed using 2–sided Wilcoxon rank sum test
- SF-36 PCS/MCS scores further transformed into norm-based scoring
  - Mean of 50 and SD of 10 using the QualityMetric Health Outcomes™ Scoring Software 4.5

Results

Baseline Characteristics*

	Treatment Naïve: Study 1489		Virologically Suppressed: Study 1844†	
	B/F/TAF n=314	DTG/ABC/3TC n=315	B/F/TAF n=282	DTG/ABC/3TC n=281
Age, y	31 (18–71)	32 (18–68)	47 (21–71)	45 (20–70)
Male	285 (91)	282 (90)	247 (88)	252 (90)
White	180 (58)	179 (57)	206 (73)	202 (73)
VACS index score	17 (13, 24)	14 (13, 23)	12 (0, 18)	10 (0, 18)
FIB-4 score‡	0.8 (0.6, 1.1)	0.7 (0.6, 1.1)	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)
Serious mental illness	91 (29)	90 (29)	122 (43)	112 (40)
HIV-SI count§	4.0 (1.0, 7.0)	3.0 (1.0, 7.0)	3.0 (1.0, 6.5)	3.0 (1.0, 5.0)
Years since HIV diagnosis	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	8.0 (4.0, 13.0)	7.0 (3.0, 14.0)
SF-36 PCS	57.4 (52.6, 60.0)	56.6 (52.2, 59.3)	55.5 (50.5, 59.1)	56.6 (51.0, 59.2)
SF-36 MCS	49.0 (37.7, 55.2)	49.5 (40.0, 56.3)	51.9 (44.5, 57.5)	53.2 (46.6, 57.6)

*Data are reported as median (interquartile range) or n (%), except for age, which is median (range); †Median exposure to the combination of DTG, ABC and 3TC at the time of study entry was 14.4 months; ‡FIB-4 (Fibrosis-4) score derived from age, platelets, aspartate aminotransferase, and alanine aminotransferase values; §Summation of presence of individual HIV-SI items; ranges from 0–20, with higher counts indicating more bothersome symptoms.

Significant Differences in Bothersome Symptoms and PSQI

✓= statistically significant (p <0.05) based on adjusted logistic regression or longitudinal model favoring the B/F/TAF group

🟩 Favors B/F/TAF ▨ No differences between arms ■ Favors DTG/ABC/3TC

	Treatment Naïve: Study 1489				Virologically Suppressed: Study 1844			
	Week			Longitudinal Model	Week			Longitudinal Model
	4	12	48		4	12	48	
HIV-SI Bothersome Symptom*								
Fatigue/loss of energy	✓	✓	✓	✓	✓			
Dizzy/lightheadedness	✓		✓		✓			✓
Nausea/vomiting	✓	✓		✓		✓	✓	✓
Loss of appetite		✓		✓		✓		✓
Sad/down/depressed					✓		✓	✓
Nervous/anxious					✓	✓	✓	✓
Difficulty sleeping		✓	✓			✓		✓
PSQI*								
Poor sleep quality		✓			✓	✓		✓

*Only symptoms where ≥2 time points/models showed significance in either study are presented.

Treatment-Naïve Adults

- **HIV-SI:** fatigue/loss of energy, dizzy/lightheadedness, nausea/vomiting, loss of appetite, and difficulty sleeping significantly favored B/F/TAF
- **PSQI:** no treatment differences were noted
- **SF-36 PCS/MCS and WPAI:** no treatment differences were noted
- No HIV-SI or PSQI symptom favored DTG/ABC/3TC

Virologically Suppressed Adults

- **HIV-SI:** dizzy/lightheadedness, nausea/vomiting, loss of appetite, sad/down/depressed, nervous/anxious, and difficulty sleeping significantly favored B/F/TAF
- **PSQI:** significantly better sleep with switch to B/F/TAF vs remaining on DTG/ABC/3TC
- **SF-36 PCS/MCS and WPAI:** no treatment differences were noted
- No HIV-SI or PSQI symptom favored DTG/ABC/3TC

Conclusions

- Consistently favorable PROs for initiating or switching to B/F/TAF vs initiating or continuing DTG/ABC/3TC were demonstrated in these 2 large, double-blind studies
  - Of note, suppressed participants in Study 1844 had been taking DTG with ABC and 3TC for a median of 14.4 months prior to study entry
- Differences in PROs between B/F/TAF and DTG/ABC/3TC appeared as early as Week 4 and generally continued through 48 weeks for those symptoms found to be significantly different between groups in the longitudinal analysis
- Compared with those starting B/F/TAF, treatment-naïve participants initiating DTG/ABC/3TC reported more of the following symptoms: fatigue/loss of energy, dizzy/lightheadedness, nausea/vomiting, loss of appetite, and difficulty sleeping
- Compared with those who switched to B/F/TAF, virologically suppressed participants continuing DTG/ABC/3TC reported more of the following symptoms: dizzy/lightheadedness, nausea/vomiting, loss of appetite, sad/down/depressed, nervous/anxious, difficulty sleeping, and poor sleep quality
- Patient satisfaction and tolerability may improve adherence to ARVs, become important differentiators among treatment regimens
- Instruments assessing patient-reported outcomes add to spontaneous adverse event reporting in clinical trials and may further differentiate the safety and tolerability of regimens compared in clinical studies

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Disclosures

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