Efficacy, safety and tolerability of switching to dolutegravir/lamivudine in virologically suppressed adults living with HIV on bictegravir/emtricitabine/tenofovir alafenamide -48-week results from the DYAD study

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Abstract THPEB089

BACKGROUND

- The TANGO and SALSA studies demonstrated non-inferior efficacy of switching to dolutegravir (DTG)/lamivudine (3TC) compared to staying on a baseline regimen among virologically suppressed people living with HIV (PLWH) through 196 and 48 weeks repsectively[1,2]
- TANGO did not enroll any switches from bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) and only 50/493 (10%) switched from B/F/TAF in SALSA[1,2]
- We previously demonstrated noninferior efficacy of switching to DTG/3TC vs. continuing B/F/TAF among stably suppressed adults through Week 24 in the DYAD study[3]
- Here, we report updated 48-week efficacy and safety results

METHODS

- DYAD (NCT 04585737) is a Phase IV randomized, open-label, noninferiority study evaluating the efficacy and safety of switching to DTG/3TC compared with continuing B/F/TAF among virologically suppressed adults with HIV-1
- Eligible participants included all PLWH aged ≥18 years seen at the Orlando Immunology Center (OIC) with undetectable viral load (≥2 HIV-1 RNA measurements <50 copies/mL at least 3 months apart) for ≥3 months and on B/F/TAF for ≥3 months
- Other key inclusion criteria included:
  - Stable insurance plan not expected to change in the following 12 months
- Key exclusion criteria included:
  - Chronic hepatitis B virus (HBV) or acute need for hepatitis C virus (HCV) therapy
  - History of prior virologic failure (VF)
  - Suspected or documented major integrase strand transfer inhibitor (INSTI) resistance
  - Major nucleoside reverse transcriptase inhibitor (NRTI) resistance (defined as History of 3 or more thymidine analog mutations (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R), M184V/I, T69-insertions, or K65R/E/N)
  - Severe hepatic impairment (Child-Pugh Class C disease)
- Study utilized commercial insurance to pay for medications and labs and visit schedule was designed to mimic routine clinical care (q3 months)
- Primary endpoint of the study was the proportion of participants with HIV-1 RNA≥50 c/mL at Week 48 using the FDA snapshot algorithm (ITT-E) (assessed by the Farrington-Manning score using a noninferiority margin of 6%)
- Secondary endpoints included efficacy and safety of switching to DTG/3TC vs. continuing B/F/TAF at Weeks 96 and 144 in an observational open-label extension phase
- Mean change in creatinine, glomerular filtration rate, lipid parameters, weight, BMI and waist circumference at Week 48 were compared between treatment groups using 2-sample t-tests

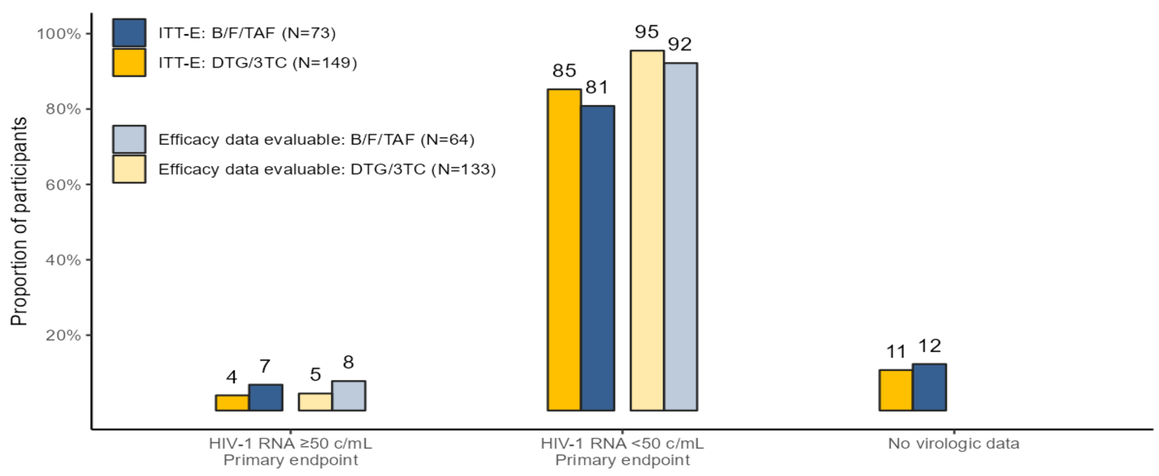
RESULTS

Table 1. Baseline demographic and clinical characteristics

Characteristic	DTG/3TC N=149	B/F/TAF N=73
Age		
Median (range), y	49 (24-73)	51 (20-73)
Age≥50 y, n (%)	74 (50)	44 (60)
Sex		
Female, n (%)	24 (16)	12 (16)
Race		
Caucasian, n (%)	102 (68)	54 (74)
Black, n (%)	44 (30)	18 (25)
Asian, n (%)	1 (1)	0 (0)
Other, n (%)	2 (1)	1 (1)
Ethnicity		
Hispanic/Latino, n (%)	43 (29)	22 (30)
Not Hispanic/Latino, n (%)	106 (71)	51 (70)
BMI, median (range), kg/m^2	29.8 (18.8-56.6)	29.5 (20-49.8)
Weight, median (range), kg	90.4 (53.1-171.9)	88.5 (59.1-123.5)
CD4$^+$ T-cell count, median (range), cells/mm^3	720.5 (214-1479)	734.5 (151-1573)
≥350 cells/mm^3, n (%)	139 (93)	70 (96)
<350 cells/mm^3, n (%)	10 (7)	3 (4)
Duration of HIV infection prior to Day 1, median (range), years	13 (1-36)	14 (1-36)
Duration of ART prior to Day 1, median (range), years	12 (1-32)	9.5 (1-27)
Duration of B/F/TAF prior to Day 1, median (range), years	2 (0.5-7.5)	2.5 (0.5-7.5)
Number of ART regimens prior to Day 1	3 (1-9)	3 (1-10)
Current Insurance Coverage		
Private, n (%)	132 (89)	59 (81)
Medicaid, n (%)	5 (3)	2 (3)
Medicare, n (%)	12 (8)	10 (13)
Ryan White, n (%)	0 (0)	2 (3)
Baseline genotype available, n (%)	60 (40)	37 (51)
NRTI Resistance. n (%)	3 (2)	6 (8)
NNRTI Resistance, n (%)	16 (11)	13 (18)
PI Resistance, n (%)	27 (18)	16 (22)
INSTI Resistance, n (%)	1 (1)[a]	2 (3)[a]

Abbreviations. BMI, Body Mass Index; ART, antiretroviral therapy; HIV, human immunodeficiency virus; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; DTG, dolutegravir; 3TC, lamivudine; B, bictegravir; F, emtricitabine; TAF, tenofovir alafenamide
[a]Minor INSTI resistance associated mutations that did not affect INSTI susceptibility

Figure 1. Virologic outcomes at Week 48 by FDA Snapshot analysis



Abbreviations. B, bictegravir; F, emtricitabine; TAF, tenofovir alafenamide; DTG, dolutegravir; 3TC, lamivudine

Table 2. Snapshot outcomes at Week 48

	DTG/3TC N=149	B/F/TAF N=73	Adjusted Treatment Difference (95% CI)
HIV-1 RNA≥50 c/mL	6 (4)	5 (7)	-2.8% (-11.4%, 3.1%)
HIV-1 RNA<50 c/mL	127 (85)	59 (81)	4.4% (-5.6%. 16.0%)
No virologic data	16 (11)	9 (12)	

Abbreviations. B, bictegravir; F, emtricitabine; TAF, tenofovir alafenamide; DTG, dolutegravir; 3TC, lamivudine; CI, confidence interval; c/ml, copies/mL

At Week 48, 6 (4%) participants on DTG/3TC and 5 (7%) on B/F/TAF had HIV-1 RNA≥50 c/mL (treatment difference -2.8%, 95% confidence interval [-11.4%, 3.1%]) meeting noninferiority criteria

Table 3. Participants with Confirmed Virologic Withdrawal at Week 48

	Study Treatment	HIV-1 RNA at SVW (c/mL)	HIV-1 RNA at CVW[a] (c/mL)	Baseline GT	GT at CVW[b]	Treatment disposition
1	DTG/3TC	60 at W24	151	N/A	No NRTI/INSTI resistance	Continue DTG/3TC
2	DTG/3TC	161,000 at W12	135	N/A	N/A	Continue DTG/3TC
3	DTG/3TC	384 at W24	129	N/A	No NRTI/INSTI resistance	Continue DTG/3TC
4	DTG/3TC	149 at W12	168	N/A	No NRTI/INSTI resistance on study GT but GT ordered by external provider 3 weeks later with M41L, D67N, K70R, M184V, T215F, K219Q, and no INSTI resistance	Stop DTG/3TC (HIV-1 RNA<50 c/mL at DC visit), switched to DTG+DRV/c
5	DTG/3TC	110 at W36	50	N/A	N/A	Continue DTG/3TC
6	DTG/3TC	72 at W36	100	No NRTI/INSTI resistance	No NRTI/INSTI resistance	Continue DTG/3TC
7	DTG/3TC	77 at W36	60	No NRTI/INSTI resistance	No NRTI/INSTI resistance	Continue DTG/3TC
8	DTG/3TC	50 at W36	140	V118I, no INSTI resistance	No NRTI/INSTI resistance	Continue DTG/3TC
9	DTG/3TC	216 at W36	145	No NRTI/INSTI resistance	No NRTI/INSTI resistance	Continue DTG/3TC
10	DTG/3TC	77 at W36	53	N/A	No NRTI/INSTI resistance	Continue DTG/3TC
11	DTG/3TC	151 at W48	67	N/A	No NRTI/INSTI resistance	Continue DTG/3TC
12	DTG/3TC	373 at W48	211	N/A	No NRTI/INSTI resistance	Continue DTG/3TC
13	B/F/TAF	600 at W24	220	N/A	N/A	Continue B/F/TAF
14	B/F/TAF	104 at W4	4580	N/A	No NRTI/INSTI resistance	Continue B/F/TAF
15	B/F/TAF	720 at W12	270	N/A	M184 M/I, G140G/S	Continue B/F/TAF, participant DC'ed from study (HIV-1 RNA<50 c/mL at DC visit)
16	B/F/TAF	120 at W36	360	No NRTI/INSTI resistance	No NRTI/INSTI resistance	Continue B/F/TAF
17	B/F/TAF	190 at W48	50	N/A	N/A	Continue B/F/TAF
18	B/F/TAF	164 at W48	829	N/A	No NRTI/INSTI resistance	Continue B/F/TAF

Abbreviations. SVW, suspected virologic withdrawal; CVW, confirmed virologic withdrawal; GT, genotype; c/mL, copies/mL; DTG, dolutegravir; 3TC, lamivudine; B, bictegravir; F, emtricitabine; TAF, tenofovir alafenamide; W, week; NRTI, nucleoside reverse transcriptase inhibitor; INSTI, integrase strand transfer inhibitor; DC, discontinuation; DRV/c, darunavir/cobicistat
[a]Confirmed virologic withdrawal was defined as two consecutive HIV-1 RNA values≥50 copies/mL
[b]All genotypes at CVW were proviral DNA genotypes

One non-CVW DTG/3TC participant developed SVF at W4 with an HIV-1 RNA of 148 c/mL but did not return for confirmatory testing. At W12, HIV-1 RNA was 87 c/mL and a genotype was inadvertently collected at this initial episode of unconfirmed viremia. GT demonstrated K65R, M184V, T215S, and K219E. The participant was discontinued from the study at W12 at which time an HIV-1 RNA<50 c/mL on DTG/3TC. The participant was subsequently transitioned to DTG+DRV/c. A baseline GT demonstrated no NRTI or INSTI resistance.

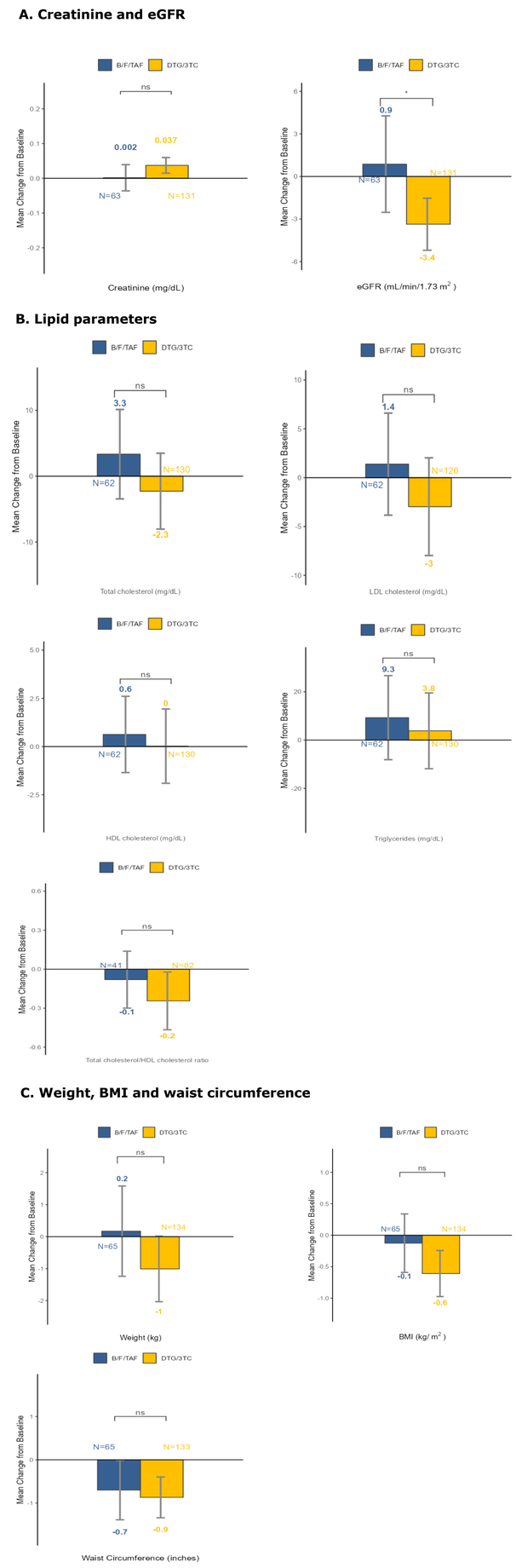
Table 4. Adverse Events through Week 48

	DTG/3TC N=149 n (%)	B/F/TAF N=73 n (%)
Participants reporting drug-related AEs (all grades)	31 (21)	2 (3)
Participants reporting drug-related AEs, grades 2-5	14 (9)	1 (1)
Drug-related AEs (occurring in ≥2%)		
Nausea	7 (5)	0
Fatigue	6 (4)	0
Diarrhea	5 (3)	0
Headache	5 (3)	0
Insomnia	5 (3)	0
Worsening depression	3 (2)	0
Dizziness	3 (2)	0
Constipation	2 (1)	1 (1)
Proteinuria	0	1 (1)
AEs leading to withdrawal	6 (4)	1
Drug-related AEs leading to withdrawal, Day 1-Week 48	6 (4)[a]	0
Drug-related AEs leading to withdrawal, Week 24-48	0	0
SAEs	12 (8)[b]	4 (5)[b]

Abbreviations. AE, adverse event; DTG, dolutegravir; 3TC, lamivudine; B, bictegravir; F, emtricitabine; TAF, tenofovir alafenamide; SAEs, serious adverse events
[a]Drug-related AEs leading to withdrawal included neuropsychiatric complaints (4), pancreatitis (1) and nausea (1)
[b]Incuded one drug-related SAE in the DTG/3TC arm (pancreatitis), all other SAEs unrelated to drug and no fatal SAEs were observed

RESULTS cont'd

Figure 2. Mean change from baseline in renal and metabolic parameters at Week 48



Abbreviations. B, bictegravir; F, emtricitabine; TAF, tenofovir alafenamide; DTG, dolutegravir; 3TC, lamivudine; ns, not significant; eGFR, estimated glomerular filtration rate
*denotes clinical significance

At Week 48, change in eGFR was significantly different between treatment arms, however there were no significant differences in mean change from baseline in creatinine and other metabolic parameters between treatment groups

CONCLUSIONS

- The DYAD study demonstrated noninferior efficacy of switching to DTG/3TC vs. continuing B/F/TAF among stably suppressed adults at Week 48
- Drug-related AEs and withdrawals due to AEs were more frequent in the DTG/3TC arm which is likely consistent with the open-label nature of this study, furthermore there were no additional drug-related AEs in the DTG/3TC arm after Week 24
- These data reinforce findings from TANGO and SALSA and support the use of DTG/3TC as a switch option from contemporary 3-drug integrase inhibitor-based regimens

References
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