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MAJOR ARTICLE

Efficacy, Safety, and Tolerability of Switching From Bictegravir/Emtricitabine/Tenofovir Alafenamide to Dolutegravir/Lamivudine Among Adults With Virologically Suppressed HIV: The DYAD Study

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Background. In TANGO and SALSA, switching to dolutegravir/lamivudine (DTG/3TC) was noninferior to continuing a baseline regimen among adults who were treatment experienced, although few switched from bictegravir (B) / emtricitabine (F) / tenofovir alafenamide (TAF). Here, we present the efficacy and safety of switching to DTG/3TC as compared with continuing with B/F/TAF among adults with virologic suppression.

Methods. DYAD is an open-label clinical trial that randomized adults with HIV-1 RNA <50 copies/mL and no prior virologic failure (2:1) to switch to once-daily fixed-dose DTG/3TC or maintain B/F/TAF. The primary end point is the proportion with HIV-1 RNA ≥50 copies/mL at week 48 (Food and Drug Administration Snapshot algorithm, intention-to-treat exposed population, 6% noninferiority margin).

Results. Overall, 222 adults were randomized (16% women, 51% aged ≥50 years, 28% Black). At week 48, 6 (4%) with DTG/3TC and 5 (7%) with B/F/TAF had HIV-1 RNA ≥50 copies/mL (treatment difference, −2.8%; 95% CI, −11.4% to 3.1%), meeting noninferiority criteria. Through week 48, 18 participants (12 with DTG/3TC, 6 with B/F/TAF) met confirmed virologic withdrawal (CVW) criteria, and 2 of 18 had resistance: 1 with B/F/TAF developed M184M/I and G140G/S at week 12, and 1 with DTG/3TC had M184V at week 12. One participant with DTG/3TC and non-CVW developed M184V and K65R at week 12. Drug-related adverse events (AEs) and withdrawals due to AEs occurred in 31 (21%) and 6 (4%) participants with DTG/3TC and 2 (3%) and 0 participants with B/F/TAF, respectively.

Conclusions. Switching to DTG/3TC was noninferior to continuing B/F/TAF among adults with virologic suppression at week 48. Drug-related AEs and withdrawals were higher in the DTG/3TC arm, which is likely consistent with the open-label nature of this switch study.

Keywords. bictegravir/emtricitabine/tenofovir alafenamide; dolutegravir/lamivudine; randomized clinical trial; switch study; virologically suppressed.

The use of 2-drug regimens with fewer antiretrovirals for the treatment of HIV-1 infection has several hypothesized benefits, including fewer treatment-related toxicities, a lower propensity for drug-drug interactions, and reduced health care costs. This has important implications as the population with HIV grows older, develops more comorbidities, and is at an increased risk of polypharmacy and poor health outcomes due to drug-drug interactions between antiretrovirals and other medications. Several international guidelines, such as those from the US Department of Health and Human Services and International Antiviral Society, recommend the 2-drug regimen dolutegravir/lamivudine (DTG/3TC) as a preferred regimen for HIV-1 treatment in patients who are antiretroviral naive and experienced, with the following exceptions: HIV/hepatitis B virus coinfection (naive and experienced), prior to the availability of resistance testing (naive), baseline HIV-1 RNA >500 000 copies/mL (naive), history of virologic failure (experienced), and history of resistance to DTG or 3TC (experienced) [1, 2]. These recommendations are based on the potent and durable efficacy and favorable safety profile of DTG/3TC as compared with its 3-drug comparators in registrational studies [3, 4]; however, these randomized clinical trials (RCTs)

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included few comparisons with bictegravir (B) / emtricitabine (F) / tenofovir alafenamide (TAF), which is the most widely used therapy in adults who are antiretroviral naive and experienced in the United States [5].

In the open-label phase 3 TANGO study, switching to DTG/3TC was noninferior to continuing a 3- or 4-drug TAF-containing regimen through 144 weeks, with no evidence of treatment-emergent resistance among adults who were virologically suppressed [4]. Drug-related adverse events (AEs) and discontinuations were initially higher in the DTG/3TC arm, but this difference stabilized after week 48, with discontinuation rates of 1% in each study arm between weeks 48 and 144. There were no significant differences in changes in weight, renal function, and inflammatory and bone biomarkers between treatment arms throughout the study period, although changes in total cholesterol, low-density lipoprotein cholesterol, and triglycerides favored DTG/3TC at week 144. Furthermore, 78% of participants in TANGO switched to DTG/3TC from an integrase strand transfer inhibitor (INSTI) plus F/TAF, and baseline regimens did not include B/F/TAF [4].

Similarly, the open-label phase 3 SALSA study demonstrated noninferiority of switching to DTG/3TC vs continuing a stable 3- or 4-drug baseline regimen through 48 weeks among adults who were virologically suppressed, with no evidence of treatment-emergent resistance [6]. Overall, drug-related AEs were more common with DTG/3TC, but this stabilized between weeks 24 and 48 with low and comparable rates between arms (5% for DTG/3TC vs 2% for baseline regimen). Adjusted mean change in weight was higher with DTG/3TC, although 44% switched from a tenofovir disoproxil fumarate–containing regimen. Changes in lipids, insulin resistance, and inflammatory biomarkers were generally small and similar in both arms, whereas markers of proximal tubular renal function and bone turnover favored DTG/3TC at week 48. In this study, only 10% of DTG/3TC switches were from B/F/TAF [6].

Few other studies have evaluated the efficacy and safety of switching from B/F/TAF to DTG/3TC among adults with virologic suppression. SOUND was a prospective open-label pilot study evaluating the efficacy of switching to DTG/3TC from B/F/TAF among patients with suppression and an unknown resistance history. At a week 48 interim analysis, 37 of 40 patients remained virologically suppressed, and there were no drug-related AEs or discontinuations [7]. Observational data were collected from 3713 adults with virologic suppression in the OPERA cohort who switched to B/F/TAF or DTG/3TC and were followed for a median 16 months; findings demonstrated low and similar rates of virologic failure, but discontinuations were less likely with B/F/TAF [8]. These results are consistent with data from a retrospective cohort study of 525 Chinese patients who were virologically suppressed and switched to B/F/TAF or DTG/3TC [9]. At week 48, HIV-1 RNA ≥50 copies/mL was seen in 4.4% with DTG/3TC vs 6.1% with B/F/TAF, with no significant difference in virologic efficacy between groups and no discontinuations due to AEs. These findings are similar to those observed from a retrospective Italian cohort evaluating 324 adults with virologic suppression who switched to DTG/3TC vs B/F/TAF [10]. Over a median follow-up of 19.6 months, 99.1% with DTG/3TC maintained virologic suppression vs 97.2% with B/F/TAF. There were no virologic failures in either group, and 3.6% with DTG/3TC discontinued due to AEs vs 2.3% with B/F/TAF. Changes in lipids and body mass index (BMI) were similar between groups.

Further data from RCTs would be useful to validate these results and determine whether there are any clinical benefits associated with the use of DTG/3TC vs B/F/TAF. Here, we present the efficacy and safety of switching to DTG/3TC as compared with continuing B/F/TAF in adults with virologic suppression through 48 weeks.

METHODS

DYAD is a phase 4, randomized, open-label, noninferiority study evaluating the efficacy and safety of switching to DTG/3TC as compared with continuing B/F/TAF among adults with virologically suppressed HIV-1. Adults aged ≥18 years at the Orlando Immunology Center (OIC) were eligible if they had an undetectable viral load for ≥3 months (≥2 HIV-1 RNA measurements <50 copies/mL) and had taken B/F/TAF for ≥3 months. Participants were required to have a stable insurance plan that was not expected to change in the following 12 months to obtain coverage of the study drugs commercially at a pharmacy of their choice. Key exclusion criteria were as follows: severe hepatic impairment (Child-Pugh class C), hepatitis B virus infection (defined as a reactive test for hepatitis B surface antigen or hepatitis B virus DNA), need for hepatitis C virus therapy, evidence of major nucleoside reverse transcriptase inhibitor (NRTI) or INSTI resistance-associated mutations in any available historical genotype, any plasma HIV-1 RNA value ≥50 copies/mL within 6 months of screening, ≥2 HIV-1 RNA values ≥50 copies/mL or any value >200 copies/mL within 6 and 12 months of screening, and a prior regimen switch due to virologic failure (HIV-1 RNA ≥400 copies/mL).

The study was approved by the Advarra Institutional Review Board and registered on ClinicalTrials.gov (NCT04585737). Written informed consent was obtained from all participants prior to the conduct of any study procedures.

After screening (≤42-day period), eligible participants were randomized 2:1 to switch to a once-daily DTG/3TC fixed-dose combination (50 mg/300 mg) or continue with B/F/TAF. No dose reductions, modifications, or changes in the frequency of any of the regimen components were allowed during the study. Study visits were planned at day 1 and weeks 1 (phone call), 4, 12, 24, 36, and 48. Plasma for HIV-1 RNA was collected

at each visit through week 48 (except at the week 1 phone call) with retesting performed within 2 to 4 weeks if HIV-1 RNA was ≥50 copies/mL. Safety outcomes were assessed at each visit through week 48.

The primary end point was the proportion of participants with HIV-1 RNA ≥50 copies/mL at week 48 per the Food and Drug Administration Snapshot algorithm in the intention-to-treat exposed (ITT-E) population. Another key efficacy end point was the proportion of participants with HIV-1 RNA ≥50 copies/mL among those with an available HIV-1 RNA assessment at week 48 (efficacy data evaluable analysis done to account for those with missing data). Secondary end points through 48 weeks included the proportion with HIV-1 RNA <50 copies/mL (ITT-E and efficacy data evaluable), change from baseline in $CD4^+$ T-cell count and $CD4^+/CD8^+$ ratio, and incidence of genotypic resistance in patients with confirmed virologic withdrawal (CVW; defined in the study as 2 consecutive HIV-1 RNA measurements ≥50 copies/mL). Additional secondary end points included safety and tolerability, which were evaluated through incidence and severity of AEs, laboratory abnormalities, and discontinuations due to AEs at week 48. Changes from baseline in renal markers (serum creatinine and estimated glomerular filtration rate based on serum creatinine), fasting lipids, weight, BMI, and waist circumference were also assessed as safety end points. Study drug adherence was assessed with a visual analog scale, and participants were asked to self-report how many doses of study drug were missed since the last study visit.

All randomized participants who received ≥1 dose of study treatment were included in the ITT-E population and used for the efficacy and safety analyses. The proportion of participants with HIV-1 RNA ≥50 copies/mL and <50 copies/mL was compared between treatment groups at week 48 with a Farrington-Manning test. The noninferiority margin for the difference in the proportion of participants with HIV-1 RNA ≥50 copies/mL was 6% at week 48. Descriptive statistics were used to summarize the incidence and severity of AEs. Median changes in $CD4^+$ T-cell count and $CD4^+/CD8^+$ ratio were assessed. Mean changes from baseline in renal markers, fasting lipid parameters, weight, BMI, and waist circumference at week 48 were compared between treatment groups via 2-sample *t* tests.

RESULTS

The first participant was screened on 5 October 2020, and the last participant's week 48 visit was on 3 August 2023. Of 235 screened, 222 were enrolled and randomized to switch to DTG/3TC (n = 149) or continue with B/F/TAF (n = 73; Figure 1); 222 received the study treatment (ITT-E). Overall, baseline demographic and clinical characteristics were well balanced (Table 1). In the ITT-E population, 16% were cisgender women, 51% were aged ≥50 years, 28% were African American or of African heritage, and 30% self-reported Hispanic ethnicity. Median duration of B/F/TAF prior to study enrollment was 2 years in the DTG/3TC arm and 2.5 years in the B/F/TAF arm. Only 97 (44%) participants had a baseline genotype available, 9 (4%) had NRTI resistance (considered minor), 29 (13%) had non-NRTI resistance, 43 (19%) had protease inhibitor resistance, and 3 (1%) had INSTI resistance (considered minor).

At week 48, 6 (4%) participants with DTG/3TC and 5 (7%) with B/F/TAF had HIV-1 RNA ≥50 copies/mL (treatment difference, −2.8%; 95% CI, −11.4% to 3.1%), meeting noninferiority criteria (Table 2, Figure 2). The proportion of participants with HIV-1 RNA <50 copies/mL was 127 of 149 (85%) with DTG/3TC and 59 of 73 (81%) with B/F/TAF (treatment difference, 4.4%; 95% CI, −5.6% to 16%). In the efficacy data evaluable analysis, 127 of 133 (95%) with DTG/3TC and 59 of 64 (92%) with B/F/TAF maintained HIV-1 RNA <50 copies/mL. At week 48, 16 (11%) with DTG/3TC and 9 (12%) with B/F/TAF were missing virologic data. Mean change (range) from baseline in $CD4^+$ T-cell count was +12 cells/mm^3 (−981 to +469) in the DTG/3TC arm and −67 cells/mm^3 (−806 to +333) in the B/F/TAF arm at week 48. Mean change (range) in $CD4^+/CD8^+$ ratio was −0.3% (−199% to +85%) in the DTG/3TC arm and +9% (−32% to +61%) in the B/F/TAF arm.

At week 48, 12 participants with DTG/3TC and 6 with B/F/TAF met CVW criteria (Table 3). Two had resistance that was not previously documented, 1 with DTG/3TC and 1 with B/F/TAF. The participant with DTG/3TC developed CVW at week 12 (HIV-1 RNA of 149 copies/mL, followed by a confirmatory value of 168 copies/mL) despite self-report of 100% adherence to the study regimen. A proviral DNA genotype performed at the week 12 confirmatory visit did not reveal any resistance; however, the participant's external clinic provider ordered a second proviral DNA genotype 3 weeks later, which demonstrated M41L, D67N, K70R, M184V, T215F, and K219Q but no INSTI resistance. The participant was discontinued from the study 2 weeks later (HIV-1 RNA <50 copies/mL with DTG/3TC at discontinuation) and switched to DTG plus darunavir/cobicistat by the routine clinic provider. A baseline genotype prior to study entry was not available. The participant with B/F/TAF and CVW had an HIV-1 RNA of 720 copies/mL at week 12, followed by a confirmatory value of 270 copies/mL. Adherence by self-report was 100%. A proviral DNA genotype performed at the week 12 confirmatory visit demonstrated an M184M/I and a G140G/S. The participant was discontinued from the study 3 weeks later (HIV-1 RNA <50 copies/mL at discontinuation) and continued with B/F/TAF by the routine clinic provider. A baseline genotype prior to study entry was not available. One participant with DTG/3TC and non-CVW developed suspected virologic failure at week 4 with an HIV-1 RNA of 148 copies/L but did not return for confirmatory testing. The participant returned for a week 12

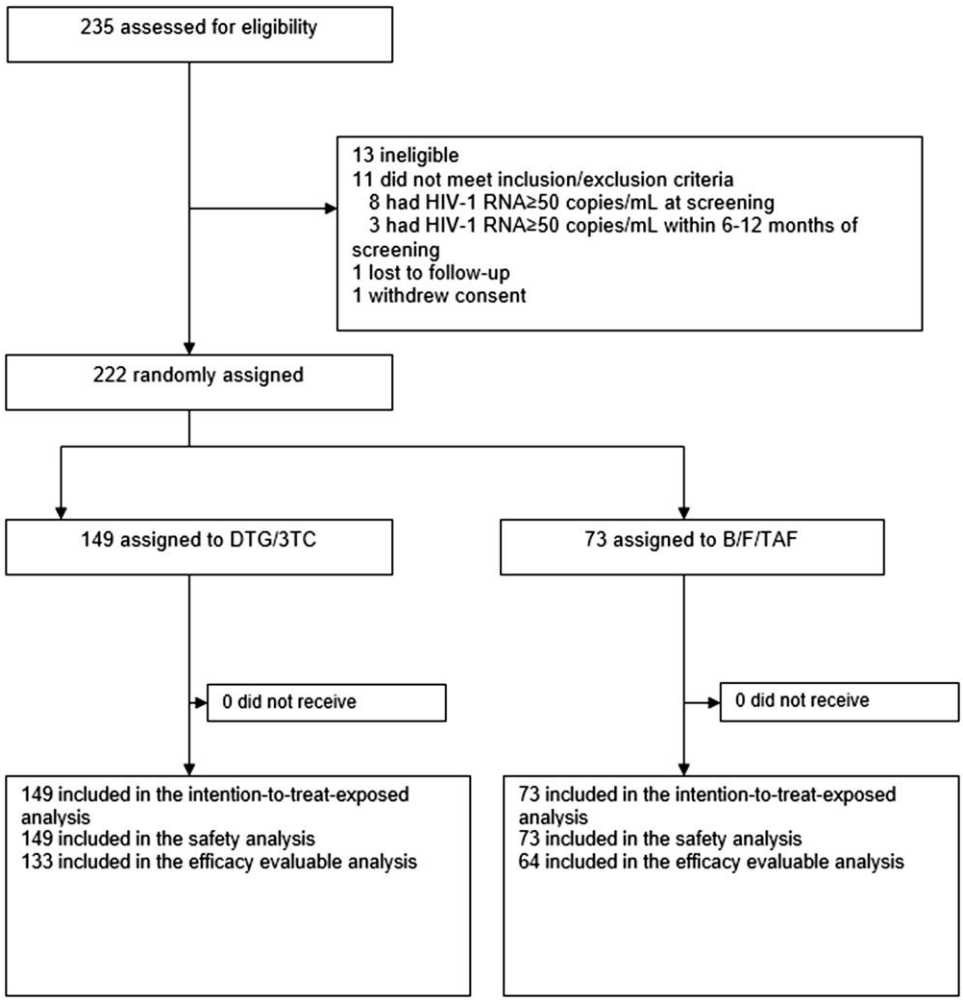

Figure 1. Study participant disposition. Abbreviations: 3TC, lamivudine; B, bictegravir; DTG, dolutegravir; F, emtricitabine; TAF, tenofovir alafenamide.

visit, during which an HIV-1 RNA of 87 copies/mL was observed. Adherence by self-report was 100% at week 4% and 98% at week 12. A proviral DNA genotype was inadvertently collected at this initial episode of unconfirmed viremia and demonstrated K65R, M184V/I, T215S, and K219E. The participant was discontinued from the study (HIV-1 RNA <50 copies/mL with DTG/3TC at the time of discontinuation) and switched to DTG plus darunavir/cobicistat by the routine clinic provider. A baseline genotype prior to study entry was available and demonstrated no NRTI or INSTI resistance.

Through week 48, at least 1 AE was reported by 119 (80%) participants with DTG/3TC and 51 (70%) with B/F/TAF (Table 4). The most common AEs in the DTG/3TC arm were SARS-CoV-2 infection (10%), fatigue (10%), rash (7%), nausea (7%), and lower back pain (6%), whereas SARS-CoV-2 infection (16%), rash (5%), and hyperlipidemia (5%) were most common in the B/F/TAF arm. Drug-related AEs were higher in the DTG/3TC arm than in the B/F/TAF arm through week 48 (21% vs 1%), yet there were no drug-related AEs that occurred in either study arm between weeks 24 and 48. Withdrawals due to AEs (DTG/3TC, 4%; B/F/TAF, 1%) and drug-related AEs (DTG/3TC, 4%; B/F/TAF, 0%) were also higher among the DTG/3TC group, but there were no withdrawals due to AEs in either study arm between weeks 24 and 48. Serious AEs occurred at a similar frequency in both arms (DTG/3TC, 8%; B/F/TAF, 5%), with 1 drug-related serious AE in the DTG/3TC arm. No fatal serious AEs were observed. There were no pregnancies reported in either study arm.

Obesity was reported as a new-onset AE in 2% of those with DTG/3TC and 0% with B/F/TAF. There were no AEs of "weight gain" in either study arm, although weight loss was noted in 1% with DTG/3TC and 3% with B/F/TAF. An AE of appetite increase was cited in 1 participant with DTG/3TC vs 0 with B/F/TAF, whereas appetite decrease was indicated in 1 participant with DTG/3TC and 1 with B/F/TAF. Mean weight

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	DTG/3TC (n = 149)	B/F/TAF (n = 73)
Age, y	49 (24–73)	51 (20–73)
Age ≥50 y	74 (50)	44 (60)
Sex: female	24 (16)	12 (16)
Race		
Caucasian	102 (68)	54 (74)
Black	44 (30)	18 (25)
Asian	1 (1)	0 (0)
Other	2 (1)	1 (1)
Ethnicity		
Hispanic/Latino	43 (29)	22 (30)
Not Hispanic/Latino	106 (71)	51 (70)
Body mass index	29.8 (18.8–56.6)	29.5 (20–49.8)
Weight, kg	90.4 (53.1–171.9)	88.5 (59.1–123.5)
$CD4^+$ T-cell count, cells/mm^3	720.5 (214–1479)	734.5 (151–1573)
$CD4^+$ T-cell count: baseline		
≥350 cells/mm^3	139 (93)	70 (96)
<350 cells/mm^3	10 (7)	3 (4)
Duration prior to day 1, y		
HIV infection	13 (1–36)	14 (1–36)
ART	12 (1–32)	9.5 (1–27)
B/F/TAF	2 (0.5–7.5)	2.5 (0.5–7.5)
No. of ART regimens prior to day 1	3 (1–9)	3 (1–10)
Current insurance coverage		
Private	132 (89)	59 (81)
Medicaid	5 (3)	2 (3)
Medicare	12 (8)	10 (13)
Ryan White	0 (0)	2 (3)
Baseline genotype available: resistance	60 (40)	37 (51)
NRTI	3 (2)	6 (8)
Non-NRTI	16 (11)	13 (18)
Protease inhibitor	27 (18)	16 (22)
INSTI	1 (1)	2 (3)

Data are presented as No. (%) or median (range).

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; B, bictegravir; DTG, dolutegravir; F, emtricitabine; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; TAF, tenofovir alafenamide.

Table 2. Snapshot Outcomes at Week 48

	DTG/3TC (n = 149)	B/F/TAF (n = 73)
HIV-1 RNA		
<50 copies/mL	127 (85)	59 (81)
≥50 copies/mL	6 (4)	5 (7)
Data in window and HIV-1 RNA ≥50 copies/mL	6 (4)	5 (7)
Discontinued for lack of efficacy	0	0
Discontinued for other reason and HIV-1 RNA ≥50 copies/mL	0	0
Change in antiretroviral therapy	0	0
No virologic data	16 (11)	9 (12)
Discontinued because of adverse event or death	6 (4)[a]	1 (1)[b]
Discontinued for other reasons	9 (6)[c]	7 (11)[d]
Enrolled in study but missing data in window[e]	1 (1)	1 (1)

Data are presented as No. (%).

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

[a]Reasons for discontinuation due to adverse events in the DTG/3TC group: headache (1), pancreatitis (1), worsening depression (1), abdominal bloating (1), abdominal upset (1), worsening anxiety (1), and last on-treatment HIV-1 RNA <50 copies/mL (6).

[b]Reasons for discontinuation due to adverse events in the B/F/TAF group: elevated creatinine kinase levels (1).

[c]Other reasons for discontinuation in the DTG/3TC arm: virologic failure (2), lost to follow-up (6), and consent withdrawal (1).

[d]Other reasons for discontinuation in the B/F/TAF arm: consent withdrawal (3), lost to follow-up (3), and virologic failure (1).

[e]Unsuccessful phlebotomy attempts at week 48 in 1 participant with DTG/3TC and 1 with B/F/TAF.

change from baseline to week 48 was −1 kg in the DTG/3TC group and +0.2 kg in the B/F/TAF group ($P = .17$). Similarly, mean BMI change from baseline to week 48 was −0.6 kg/m^2 in the DTG/3TC group and −0.1 kg/m^2 in the B/F/TAF group ($P = .27$). Mean change in waist circumference from baseline to week 48 was −0.9 inches in the DTG/3TC group and −0.7 inches in the B/F/TAF group ($P = .69$; Figure 3). New-onset diabetes or prediabetes was reported in 3% with DTG/3TC and 1% with B/F/TAF. New-onset hypertension was observed in 5% with DTG/3TC and 4% with B/F/TAF. Notably, both study arms enrolled participants from the OIC wellness clinic, which is a program that targets OIC patients experiencing abnormal weight gain and poorly controlled metabolic conditions (ie, diabetes). The program provides exercise counseling, nutritional support, and weight loss pharmacotherapy to appropriate candidates.

Changes in lipids were minimal in both groups through week 48, with no significant differences between the arms in mean change from baseline in total cholesterol, high- and low-density lipoprotein, triglycerides, and ratio of total cholesterol to high-density lipoprotein (Figure 3). New-onset hyperlipidemia was reported in 3% with DTG/3TC and 3% with B/F/TAF. Initiation of lipid-lowering therapy occurred in 12% with DTG/3TC and 23% with B/F/TAF.

At week 48, mean change from baseline in creatinine was 0.04 mg/dL in the DTG/3TC arm and 0.002 mg/dL in the B/F/TAF arm ($P = .11$). However, mean change from baseline in estimated glomerular filtration rate was significantly different in the DTG/3TC arm as compared with the B/F/TAF arm (−3.37 vs 0.87 mL/min, $P = .03$).

DISCUSSION

The DYAD study demonstrated noninferior efficacy of switching to DTG/3TC vs continuing B/F/TAF through 48 weeks among adults with stably suppressed HIV. Low rates of virologic failure were observed in each treatment arm and in the efficacy data evaluable analysis; 95% of those who switched to DTG/3TC maintained virologic suppression at week 48. Among 18 participants with CVW, 2 experienced resistance: 1 with DTG/3TC and 1 with B/F/TAF. A third case of resistance occurred in a participant with DTG/3TC and non-CVW. Importantly, no INSTI resistance was observed with DTG/3TC;

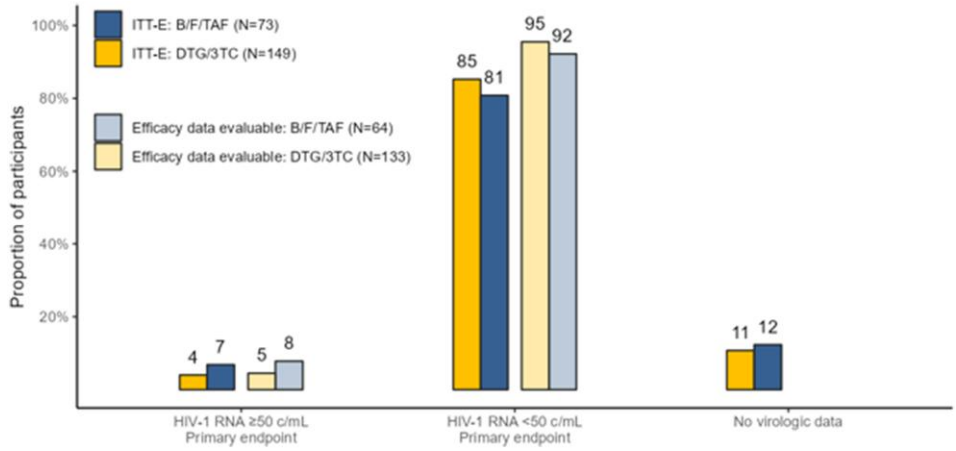

Figure 2. Virologic outcomes at week 48 by Food and Drug Administration Snapshot analysis. Abbreviations: 3TC, lamivudine; B, bictegravir; DTG, dolutegravir; F, emtricitabine; ITT-E, intention to treat exposed; TAF, tenofovir alafenamide.

Table 3. Participants With Confirmed Virologic Withdrawal at Week 48

	HIV-1 RNA, copies/mL		Genotype		
Treatment: No.	At SVW	At CVW	Baseline	At CVW[a]	Treatment Disposition
DTG/3TC					
1	60 at wk 24	151	NA	No NRTI/INSTI resistance	Continue DTG/3TC
2	161 000 at wk 12	135	NA	NA	Continue DTG/3TC
3	384 at wk 24	129	NA	No NRTI/INSTI resistance	Continue DTG/3TC
4	149 at wk 12	168	NA	No NRTI/INSTI resistance on study genotype but genotype ordered by external provider 3 wk later with M41L, D67N, K70R, M184V, T215F, and K219Q and no INSTI resistance	Stop DTG/3TC (HIV-1 RNA <50 copies/mL at discontinuation visit), switched to DTG + DRV/c
5	110 at wk 36	50	NA	NA	Continue DTG/3TC
6	72 at wk 36	100	No NRTI/INSTI resistance	No NRTI/INSTI resistance	Continue DTG/3TC
7	77 at wk 36	60	No NRTI/INSTI resistance	No NRTI/INSTI resistance	Continue DTG/3TC
8	50 at wk 36	140	V118I, no INSTI resistance	No NRTI/INSTI resistance	Continue DTG/3TC
9	216 at wk 36	145	No NRTI/INSTI resistance	No NRTI/INSTI resistance	Continue DTG/3TC
10	77 at wk 36	53	NA	No NRTI/INSTI resistance	Continue DTG/3TC
11	151 at wk 48	67	NA	No NRTI/INSTI resistance	Continue DTG/3TC
12	373 at wk 48	211	NA	No NRTI/INSTI resistance	Continue DTG/3TC
B/F/TAF					
13	600 at wk 24	220	NA	NA	Continue B/F/TAF
14	104 at wk 4	4580	NA	No NRTI/INSTI resistance	Continue B/F/TAF
15	720 at wk 12	270	NA	M184 M/I, G140G/S	Continue B/F/TAF, participant discontinued (HIV-1 RNA <50 copies/mL at discontinuation visit)
16	120 at wk 36	360	No NRTI/INSTI resistance	No NRTI/INSTI resistance	Continue B/F/TAF
17	190 at wk 48	50	NA	NA	Continue B/F/TAF
18	164 at wk 48	829	NA	No NRTI/INSTI resistance	Continue B/F/TAF

Abbreviations: 3TC, lamivudine; B, bictegravir; CVW, confirmed virologic withdrawal; DRV/c, darunavir/cobicistat; DTG, dolutegravir; F, emtricitabine; INSTI, integrase strand transfer inhibitor; NA, not available; NRTI, nucleoside reverse transcriptase inhibitor; SVW, suspected virologic withdrawal; TAF, tenofovir alafenamide.

[a]All genotypes at CVW were proviral DNA genotypes.

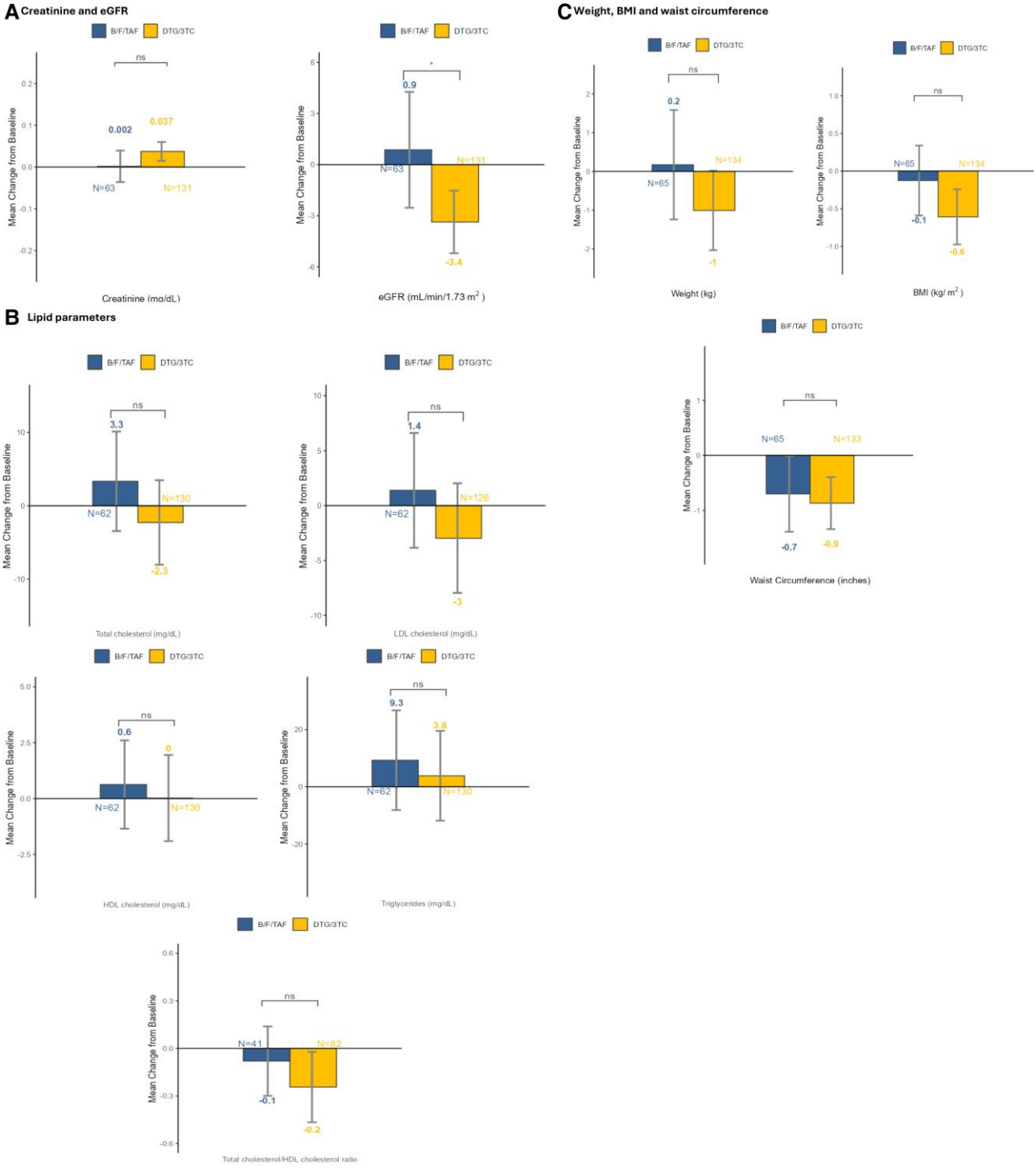

Figure 3. Mean change from baseline in renal and metabolic parameters at week 48. Data are presented as mean change (standard deviation). Abbreviations: 3TC, lamivudine; B, bictegravir; DTG, dolutegravir; eGFR, estimated glomerular filtration rate; F, emtricitabine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ns, not significant; TAF, tenofovir alafenamide.

however, the participant with B/F/TAF and CVW did have a G140G/S INSTI resistance-associated mutation, which in isolation does not significantly affect the activity of BIC or DTG [11]. Drug-related AEs and withdrawals due to AEs were more frequent with DTG/3TC in this open-label switch study, but no additional drug-related AEs occurred after week 24 in the DTG/3TC arm. Changes in renal and metabolic parameters were small and similar in both treatment arms, except for

Table 4. Adverse Events Through Week 48

	DTG/3TC (n = 149)	B/F/TAF (n = 73)
Any AE	119 (80)	51 (70)
AEs occurring in ≥5% of either arm		
COVID-19 infection	15 (10)	12 (16)
Fatigue	15 (10)	3 (4)
Rash	11 (7)	4 (5)
Nausea	11 (7)	0
Lower back pain	10 (6)	2 (3)
Headache	8 (5)	2 (3)
Dizziness	8 (5)	0
Depression	8 (5)	2 (3)
Hypertension	8 (5)	3 (4)
Hyperlipidemia	7 (4)	4 (5)
Drug-related AEs	31 (21)	2 (3)
Grades 2–5	14 (9)	1 (1)
≥2% of either arm		
Nausea	7 (5)	0
Fatigue	6 (4)	0
Diarrhea	5 (3)	0
Headaches	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	6 (4)[a]	0
Any SAEs	12 (8)	4 (5)
Drug related	1 (1)[b]	0

Data are presented as No. (%).

Abbreviations: 3TC, lamivudine; AE, adverse event; B, bictegravir; DTG, dolutegravir; F, emtricitabine; SAE, serious adverse event; TAF, tenofovir alafenamide.

[a]Drug-related AEs leading to withdrawal: neuropsychiatric complaints (4), pancreatitis (1), and nausea (1).

[b]Drug-related SAE in the DTG/3TC arm was pancreatitis.

changes in estimated glomerular filtration rate, which were significantly different between the arms (ie, increased in the B/F/TAF arm and decreased in the DTG/3TC arm). These findings align with the increase in serum creatinine observed in the DTG/3TC arm, likely due to the inhibition of OCT2 renal transport by DTG, which results in small and reversible increases in serum creatinine and does not represent a nephrotoxic effect [12]. Though BIC is also an inhibitor of OCT2, clinical pharmacology studies suggest that inhibition by DTG is more potent, as evidenced by the changes in metformin concentrations when administered with DTG (metformin area under the curve increased by 79%) vs BIC (metformin area under the curve increased by 39%) [13–15]. This may explain why increases in serum creatinine were observed with a switch from BIC to DTG in our study.

Findings from the DYAD study support the noninferior efficacy of DTG/3TC among adults with virologic suppression in the TANGO and SALSA trials, but these studies included few participants switching from B/F/TAF [4, 6]. DYAD is the first head-to-head RCT evaluating the efficacy of the 2-drug regimen DTG/3TC vs B/F/TAF, a 3-drug regimen with high efficacy, a high barrier to resistance, and a well-tolerated safety profile. Study findings support data from observational cohorts that have demonstrated high rates of virologic suppression among treatment-experienced patients switching to DTG/3TC vs B/F/TAF [8–10, 16, 17]. Yet, these studies have reported few cases of virologic failure and none with treatment-emergent resistance. In fact, there are few cases of treatment-emergent resistance with DTG/3TC or B/F/TAF in the literature. Clinical trials of these agents report no cases of treatment-emergent resistance with B/F/TAF and a single case of treatment-emergent resistance in a participant with DTG/3TC from the GEMINI studies who also reported nonadherence to the separate components of the study regimen [3, 4, 6, 18–22]. Real-world data similarly confirm a high barrier to resistance of both regimens, with few reports of treatment-emergent resistance [8–10, 23–30].

In the DYAD study, 18 (8%) participants experienced CVW through week 48, and there were 2 cases of resistance, 1 participant with DTG/3TC and 1 with B/F/TAF. A participant with DTG/3TC and non-CVW was also found to have resistance after a genotype was collected erroneously. In all 3 cases, resistance tests performed were proviral DNA genotypes (due to low viral loads), and all were undetectable with the study drug at the discontinuation visit. These cases highlight one of the possible limitations of proviral DNA genotypes, which is the potential detection of mutations in nonreplicating variants that are not clinically significant [31]. In addition, proviral DNA assays may "miss" low-frequency resistance mutations; hence, our study findings should be interpreted with these caveats [31]. Both participants with CVW with resistance did not have historical genotypes available prior to study entry for comparison, but neither had documentation of prior resistance or virologic failure. A baseline genotype was available for the participant with DTG/3TC and non-CVW and did not reveal any resistance mutations. All 3 participants self-reported adherence rates of 98% to 100% at the time of viremia; however, formal adherence assessments, such as pill counts or drug-level testing, were not performed in this study; as such, reports of high adherence could not be confirmed.

Overall, DYAD demonstrated higher rates of virologic withdrawal and resistance than what has been previously observed in RCTs of DTG/3TC and B/F/TAF, but this is likely due to the conservative definition of CVW used in this study (2 consecutive HIV-1 RNA values ≥50 copies/mL) when compared with other RCTS, such as TANGO and SALSA, which used a CVW definition of an initial HIV-1 RNA ≥50 copies/mL, followed by an HIV-1 RNA ≥200 copies/mL [4, 6]. Our definition of CVW could be viewed as too strict given that HIV-1 RNA values between 50 and 200 copies/mL are considered by many to be viral blips in routine clinical practice and are generally not a cause for concern. However, given that we were

comparing 2 of the most potent regimens commercially available and there is still some controversy regarding the clinical relevance of viral blips [32–34], we chose to utilize a more strict definition of CVW than used in other RCTs, and our findings should be interpreted with this caveat. Notably, the more frequent observance of HIV-1 RNA values ≥50 copies/mL in DYAD may also be due to the "real world" nature of the visit schedule, which was less intensive than a typical RCT and therefore may have been accompanied by less frequent adherence counseling and monitoring.

Safety results from DYAD revealed a higher rate of drug-related AEs and withdrawals due to AEs in the DTG/3TC arm, but after week 24 there were no additional drug-related AEs in either study arm. Similar findings have been observed in other open-label switch studies where participants were switching from a therapy in which they had generally been stable for a while [4, 6, 35]. In DYAD, the median duration of B/F/TAF prior to study enrollment was 2 years in the DTG/3TC arm and 2.5 years in the B/F/TAF arm. Additionally, the finding of no further drug-related AEs in the DTG/3TC arm after week 24 suggests that there may have been a transient "adjustment period" to the new study regimen following switch. The safety profile of DTG/3TC in this study is, however, consistent with that in other RCTs and observational cohorts [3, 4, 6, 17, 24]. The increased frequency of drug-related AEs in our study, which started enrolling after Food and Drug Administration approval in 2020, may simply reflect improved knowledge of the clinical safety profile of DTG/3TC and thereby a greater likelihood of investigators to assign certain AEs as drug related.

Changes in weight and lipids were minimal and comparable in the study arms through week 48; however, in contrast to other cohorts, participants with DTG/3TC lost weight following switch, and participants in both study arms had less central obesity at week 48. Generally, prior data have demonstrated increased weight, BMI, and waist circumference following switch to second-generation INSTIs [36–39], and some studies have linked these changes to adverse cardiometabolic complications [38, 40–42]. The unusual findings in our study may be due to enrollment of participants from both treatment arms in the OIC wellness clinic, which as previously mentioned is a dedicated program for the management of obesity and metabolic conditions.

Limitations of the DYAD study include the single-center nature of the trial and the fact that cisgender men represented 84% of the study population, which may limit generalizability to other populations, including cisgender women. The study was conducted during the COVID-19 pandemic, which likely contributed to missing data for some of the 23% of the study population that did not have an HIV-1 RNA assessment at week 48. As previously noted, all participants with CVW had resistance testing performed with proviral DNA genotypes, which may not provide a completely accurate profile of resistance mutations and their significance. Last, our study did not perform formal adherence assessments, which may limit our ability to fully characterize episodes of viremia in those experiencing CVW.

In conclusion, the DYAD study is the first RCT to evaluate the efficacy and safety of DTG/3TC as compared with B/F/TAF in adults with virologic suppression. Our findings of noninferior efficacy and a consistent safety profile of DTG/3TC reinforce findings from TANGO and SALSA and support use of this agent as a switch option from contemporary INSTI-based 3-drug regimens.

Notes

Author contributions. All authors have contributed sufficiently to the project to be included as authors, and all have agreed to be fully accountable for the work, ensuring its accuracy and integrity. C.-P. R.: responsible for the conception and design of the study; gathered, analyzed, and interpreted the data necessary for the writing of this article; drafted and heavily revised the manuscript; provided final review for the approval of submission. J. C.: gathered, analyzed, and interpreted the data necessary for the writing of this article; provided the final review for the approval of submission. V. N.: responsible for the conception and design of the study, assisted in revision of the article, provided the final review for the approval of submission. F. H.: responsible for the conception and design of the study, assisted in revision of the article, provided the final review for the approval of submission. E. D.: responsible for the conception and design of the study, assisted in revision of the article, provided the final review for the approval of submission.

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