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Week 96 subgroup analyses of the phase 3, randomized AMBER and EMERALD trials evaluating the efficacy and safety of the once daily darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) single-tablet regimen in antiretroviral treatment (ART)-naïve and -experienced, virologically-suppressed adults living with HIV-1

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Week 96 subgroup analyses of the phase 3, randomized AMBER and EMERALD trials evaluating the efficacy and safety of the once daily darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) single-tablet regimen in antiretroviral treatment (ART)-naïve and -experienced, virologically-suppressed adults living with HIV-1

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Background: Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg was investigated in AMBER (treatment-naïve adults; NCT02431247) and EMERALD (treatment-experienced, virologically-suppressed adults; NCT02269917).

Objective: To describe a Week 96 pre-planned subgroup analysis of D/C/F/TAF arms by demographic characteristics (age ≤/>50 years, gender, black/non-black race), and baseline clinical characteristics (AMBER: viral load [VL], $CD4^+$ count, WHO clinical stage, HIV-1 subtype and antiretroviral resistance; EMERALD: prior virologic failure [VF], antiretroviral experience, screening boosted protease inhibitor [PI], and boosting agent).

Methods: Patients in D/C/F/TAF and control arms could continue on/switch to D/C/F/TAF in a single-arm, open-label extension phase after Week 48 until Week 96. Efficacy endpoints were percentage cumulative confirmed VL ≥50 copies/mL (virologic rebound; EMERALD), and VL <50 (virologic response), or ≥50 copies/mL (VF) (FDA snapshot; both trials).

Results: D/C/F/TAF demonstrated high Week 96 virologic responses (AMBER: 85% [308/362]; EMERALD: 91% [692/763]) and low VF rates (AMBER: 6% [20/362]; EMERALD: 1% [9/763]). In EMERALD, D/C/F/TAF showed low virologic rebound cumulative through Week 96 (3% [24/763]). Results were consistent across subgroups, including prior antiretroviral experience in EMERALD. No darunavir, primary PI, or tenofovir resistance-associated mutations were observed post-baseline. Study-drug-related serious adverse events (AEs) and AE-related discontinuations were <1% and 2%, respectively (both D/C/F/TAF arms), and similar across subgroups. $eGFR_{cyst}$ and bone mineral density improved or were stable and lipids increased through Week

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96 across demographic subgroups, with small changes in total-cholesterol/HDL-cholesterol ratio.
Conclusions: D/C/F/TAF was effective with a high barrier to resistance and bone/renal safety benefits, regardless of demographic or clinical characteristics for treatment-naïve and treatment-experienced, virologically-suppressed adults.

Keywords: D/C/F/TAF, HIV-1, darunavir, single-tablet regimen, tenofovir alafenamide, subgroup analysis, Phase III

Introduction

Once-daily, single-tablet regimens (STRs) for HIV-1 infection are a convenient treatment option for patients with improved adherence and satisfaction, a reduced rate of virologic failure (VF) and resistance, and a higher probability of viral load (VL) suppression, compared with multi-tablet regimens.[1–3]

The oral, once-daily, STR darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) 800/150/200/10 mg, currently approved in Europe, the US, and Canada[4,5] is based on the protease inhibitor (PI) darunavir (DRV), which has demonstrated a high, durable virologic response (VL <50 copies/mL), high barrier to resistance, and long-term safety in a broad range of patients.[6–9] International HIV-1 treatment guidelines include D/C/F/TAF or DRV boosted with ritonavir (RTV) or cobicistat (COBI) combined with two nucleoside or nucleotide analogs reverse transcriptase inhibitors (N(t)RTIs).[10–12] DRV is also recommended for rapid initiation of treatment, when resistance test results are not available,[11] and when treatment adherence may be unpredictable.[11,12]

Week 48 primary analyses of two Phase 3, randomized studies, AMBER and EMERALD, showed that D/C/F/TAF had a high, non-inferior antiviral efficacy, no primary PI, DRV, or tenofovir (TFV) resistance and favorable bone and renal biomarker safety versus control arms.[13,14] AMBER included antiretroviral treatment (ART)-naïve adults[13] and EMERALD ART-experienced, virologically suppressed patients, including those with a history of non-DRV VF.[14] Antiviral efficacy was maintained through Week 96 in the D/C/F/TAF arms of both studies.[15,16]

Pre-planned subgroup analyses demonstrated that D/C/F/TAF was effective and well-tolerated through Week 48 regardless of demographic characteristics (age, gender, and race) in both studies,[17,18] clinical characteristics (baseline VL, $CD4^+$ cell count, and World Health Organization [WHO] clinical stage) in AMBER,[17] and prior ART experience in EMERALD.[18] The current paper reports the results of the same pre-planned subgroup analyses cumulative through Week 96 in the D/C/F/TAF arms of each study.

Methods

Study designs and patients

AMBER (TMC114FD2HTX3001; ClinicalTrials.gov Identifier: NCT02431247)[13] and EMERALD (TMC114IFD3013; NCT02269917)[14] are Phase 3, international, randomized, active-controlled, non-inferiority studies conducted at 121 sites across 10 countries, and 106 sites across nine countries, respectively (Figure 1).

The AMBER study included ART-naïve adults with HIV-1 and a screening plasma VL ≥1,000 copies/mL, $CD4^+$ cell count >50 cells/mm^3 and genotypic susceptibility to DRV, emtricitabine (FTC), and TFV (Figure 1). Patients were randomized (1:1) to double-blind treatment with D/C/F/TAF 800/150/200/10 mg once daily or D/C 800/150 mg fixed-dose combination (FDC) co-administered with emtricitabine/tenofovir disoproxil fumarate (F/TDF) 200/300 mg FDC once daily (control arm) over at least 48 weeks. Randomization was stratified by VL (≤ or >100,000 copies/mL) and $CD4^+$ cell count (< or ≥200 cells/mm^3) at screening.

The EMERALD study included ART-experienced adults with HIV-1 who were virologically suppressed (VL <50 copies/mL for ≥2 months before screening; one VL 50–200 copies/mL within 12 months prior to screening was allowed) on stable boosted PI (bPI, DRV/RTV or DRV/COBI once daily, atazanavir (ATV)/RTV or ATV/COBI once daily, or lopinavir (LPV)/RTV twice daily) plus F/TDF regimens for ≥6 months (Figure 1). Previous ART VF was allowed, with no history of VF on DRV-based regimens and if historical genotype was available, absence of only DRV resistance-associated mutations (RAMs).[19] There was no exclusion of patients with historical TFV or FTC RAMs. Patients were randomized (stratified by bPI at screening) (2:1) in an open-label fashion to switch to D/C/F/TAF 800/150/200/10 mg once daily or continue on a bPI combined with F/TDF (control arm).

After Week 48 unblinding (AMBER) or at Week 52 (EMERALD), patients in the D/C/F/TAF and control arms of both trials continued on or switched to D/C/F/TAF in a single-arm, open-label extension phase until Week 96, provided they consented and continued to derive benefit (Figure 1). To preserve blinding in AMBER, switching to D/C/F/TAF was done at different

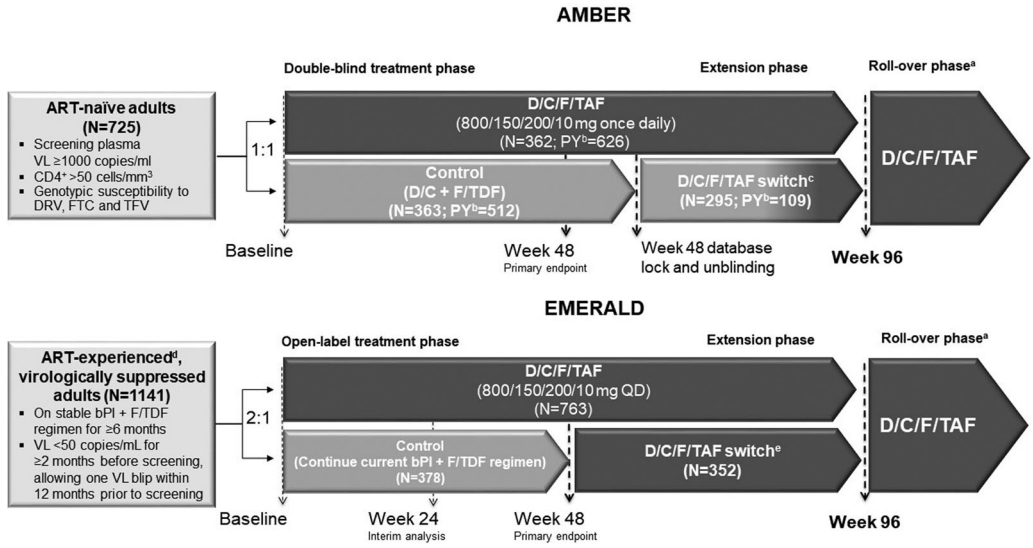

Figure 1 AMBER and EMERALD study designs.

AMBER was a Phase 3, randomized, active-controlled, double-blind, international, noninferiority study conducted at 121 sites across ten countries in North America (Canada and USA) and Europe (Belgium, France, Germany, Italy, Poland, Russia, Spain, and UK).

EMERALD was a Phase 3, randomised, active-controlled, open-label, international, non-inferiority study conducted at 106 sites across nine countries in North America (Canada and USA) and Europe (Belgium, France, Poland, Spain, Sweden, Switzerland, and UK).

ART, antiretroviral therapy; bPI, boosted protease inhibitor; DRV, darunavir; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide once-daily; D/C + F/TDF, darunavir/cobicistat plus emtricitabine/tenofovir disoproxil fumarate once-daily; FTC, emtricitabine; QD, once-daily; RAMs, resistance-associated mutations; TFV, tenofovir; VF, virologic failure; VL, viral load.

[a]After Week 96, participants were given the opportunity to remain in the trial until the study drug became commercially available.

[b]PY = Patient-years of exposure = sum of treatment duration (weeks) x 7/365.25.

[c]Patients switched to D/C/F/TAF at different time points (not uniformly) leading to a lack of uniform D/C/F/TAF exposure post-switch.

[d]Previous ART VF allowed, with no history of VF on DRV-based regimens and absence of DRV RAMs[19] if historical genotypes were available; No restriction on any other RAMs, including FTC or TFV RAMs.

[e]Patients switched to D/C/F/TAF at Week 52.

time points (not uniformly) leading to a lack of uniform D/C/F/TAF exposure post-switch (Figure 1).

Week 96 endpoints

In AMBER, the Week 96 efficacy endpoint was virologic outcome (proportion of patients with virologic response, VL <50 copies/mL, and VF, VL ≥50 copies/mL; FDA snapshot). VF was defined as last VL in the Week 96 window ≥50 copies/mL, or discontinuations for efficacy reasons, or premature discontinuations not due to efficacy with a last VL ≥50 copies/mL. In EMERALD, Week 96 efficacy endpoints were protocol-defined virologic rebound (PDVR), defined as the proportion of patients with confirmed VL ≥50 copies/mL or premature discontinuations irrespective of reason with last VL ≥50 copies/mL cumulative through Week 96, and virologic outcome at Week 96 by FDA snapshot.

Other secondary endpoints included safety and tolerability, treatment-emergent resistance and changes from baseline in estimated glomerular filtration rate based on serum cystatin C ($eGFR_{cyst}$, Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI)[20] and eGFR based on serum creatinine ($eGFR_{cr}$, CKD-EPI)[21], ratios of total urine protein, urine albumin, fasted retinol binding protein and fasted β-2-microglobulin to creatinine (UPCR, UACR, RPB:Cr and B2M:Cr, respectively), lipid laboratory parameters, and, for patients in the bone investigation dual energy x-ray absorptiometry (DXA) sub-studies, changes over time in bone mineral density (BMD) at the hip, lumbar spine (L1–L4), and femoral neck.

Post-baseline samples for genotyping/phenotyping were analyzed in patients with protocol-defined virologic failure (PDVF) in AMBER (virologic non-response, virologic rebound, and/or viremic at final timepoint) or EMERALD (PDVRs) with viral load ≥400 copies/mL at failure or later timepoints.

Week 96 subgroup analyses

This analysis, based on descriptive statistics, focuses on long-term efficacy and safety over 96 weeks in the D/C/F/TAF arm only for each study. No Week 96 comparisons were made between arms during the open-label phase due to the lack of an appropriate comparator in the control arm.

Prespecified subgroup analyses were performed on all randomized patients who received ≥1 dose of study drug.

In AMBER, demographic subgroups analyzed were age (≤50 vs >50 years), gender (men vs women) and race (non-black/African American vs black/African American). Subgroups for clinical characteristics at baseline were based on VL (≤100,000 vs >100,000 copies/mL), $CD4^+$ cell count (<200 vs ≥200 cells/mm^3), WHO clinical stage of HIV infection (1 [asymptomatic] vs 2 [mild symptoms]), and analyzed for efficacy only, HIV-1 subtype (B, non-B), the presence or absence at screening of ≥1 primary and/or DRV RAMs, N(t)RTI RAMs, non-nucleoside reverse transcriptase inhibitor (NNRTI) RAMs or M184V/I. Data were not reported for WHO clinical stage 3 and 4 subgroups due to the small sample sizes.

In EMERALD, demographic subgroups analyzed were age, gender, and race. Regarding clinical characteristics, prior ART experience subgroups analyzed were: number of antiretrovirals (ARVs) previously used (4, 5, 6, 7, and >7, including screening ARVs and PI booster counted as a separate ARV), prior VF (0; ≥1 prior VF), screening bPI (DRV with RTV or COBI; ATV with RTV or COBI; LPV with RTV) and screening boosting agent (RTV with DRV, ATV or LPV; COBI with DRV or ATV).

In both studies, changes in markers of proteinuria and lipids and BMD in the bone investigation substudies are presented for the demographic subgroups. As some subgroups are small, especially in AMBER and in the bone investigation substudies, results should be interpreted with caution.

Results

AMBER D/C/F/TAF arm: ART-naïve patients

Patient baseline characteristics

Patient baseline characteristics have been presented previously[13,17] and are shown in Supplementary Table 1. Of 362 patients in the D/C/F/TAF treatment arm at baseline, 36/362 (10%) were aged >50 years, 44/362 (12%) patients were women, and 40/345 (12%) were black/African American.

Regarding clinical characteristics, 60/362 (17%) patients had baseline VL ≥100,000 copies/mL and 22 (6%) had a baseline $CD4^+$ cell count <200 cells/mm^3. For WHO clinical stage of HIV infection at baseline, 314/362 (87%) patients had stage 1 and 42 (12%) patients had stage 2. Only six (2%) patients were WHO stage 3 and none were stage 4, so these patients were not included in the subgroup analyses.

Efficacy

In the overall population, a high virologic response (85%; 308/362) was observed in the D/C/F/TAF arm at Week 96 (Figure 2).[13] Virologic responses at Week 96 ranged from 70% to 94% (FDA snapshot) across subgroups by age, gender and race, baseline VL, baseline $CD4^+$ cell count, WHO clinical Stage (Figure 2), HIV-1 subtype and baseline resistance (Supplementary Table 3). However, results for certain subgroups with very small sample sizes, such as age >50 years, women, Black/African American race, baseline VL >100,000 copies/mL, baseline $CD4^+$ cell count <200 cells/mm^3, WHO clinical Stage 2 (Figure 2), and presence at screening of ≥1 primary PI and/or DRV RAMs, ≥1 N(t)RTI RAMs and ≥1 NNRTI RAMs (Supplementary Table 3), should be interpreted with caution. In Black/African American patients, the relative fall in virologic response rate at Week 96 compared with that observed in non-black/African American patients was partly due to higher VF (10% versus 5%, respectively; FDA snapshot), but mainly a result of a higher frequency of missing virologic data (20% versus 8%) (Figure 2). The higher VF rate in Black/African American patients could be due to a lower proportion who reported >95% adherence (measured by drug accountability, based on pill count[15]) than for non-black/African American patients (47.5% versus 76%, respectively).

VF (FDA snapshot) was low across the majority of these patient subgroups (ranging from 2% to 18% across subgroups) (Figure 2 and Supplementary Table 3). The VF rate of 18% (4/22) was observed in the subgroup with baseline $CD4^+$ cell count <200 cells/mm^3; only one of the four VFs was efficacy related with VL ≥50 copies/mL at last on-treatment visit (Figure 2). One patient had VL <50 copies/mL at last on-treatment visit, and two patients discontinued due to other reasons (lost to follow-up and non-compliance with study medication) with last available VL ≥50 copies/mL.

Resistance

No emerging DRV, primary PI or TFV RAMs were observed post-baseline in nine patients (7 men; 2 women) with PDVF in the D/C/F/TAF arm.

The N(t)RTI RAM M184I/V, conferring FTC and 3TC resistance, was detected at Week 36 in one female patient in the D/C/F/TAF arm who discontinued due to treatment non-compliance. This patient had HIV-1 with transmitted NNRTI resistance at screening, and in a post-hoc analysis, M184V was detected pre-treatment as a minority variant (9%).[22] The patient had a baseline VL of 20,100 copies/mL, a $CD4^+$ cell count of 126 cells/mm^3 and was WHO clinical Stage 1.

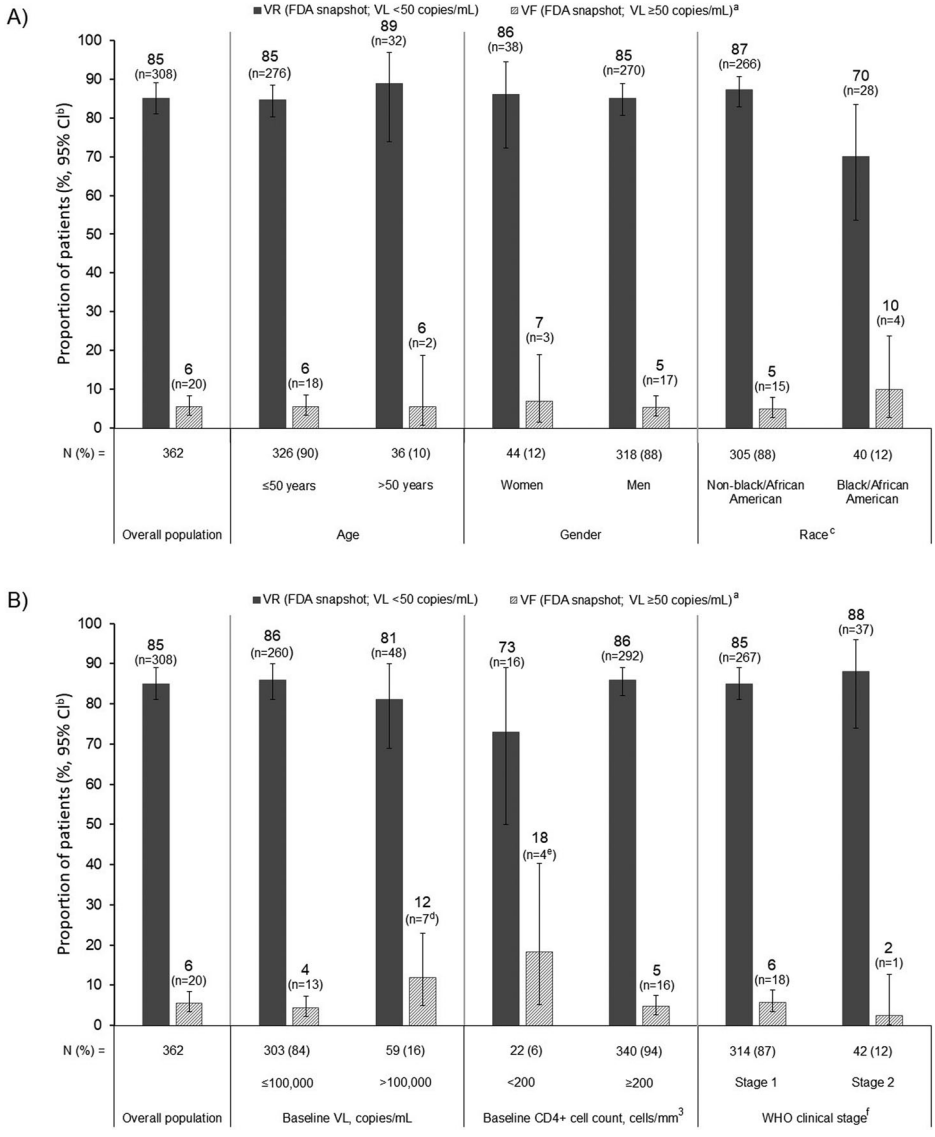

Figure 2 AMBER virologic outcomes at Week 96 (by FDA snapshot) in the D/C/F/TAF arm by A) Demographic characteristics and B) Clinical characteristics at baseline.

D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; VR, virologic response; VF, virologic failure; VL, viral load; WHO, World Health Organization; CI, confidence interval; FDA, Food and Drug Administration.

For each subgroup, patients with missing virologic data (per FDA snapshot) in the D/C/F/TAF arm was: 10% for those ≤50 years, 6% for those >50 years, 7% for women, 10% for men, 8% for those who are non-black/African American, and 20% for those who are black/African American, 10% of those with VL ≤100,000 copies/mL, 7% of those with VL >100,000 copies/mL, 9% of those with $CD4^+$ cell count <200 cells/mm^3, 9% of those with $CD4^+$ cell count ≥200 cells/mm^3, 9% of those with WHO clinical stage 1, and 10% of those with WHO clinical stage 2.

[a]VF was defined as last VL in the Week 96 window ≥50 copies/mL, or discontinuations for efficacy reasons, or premature discontinuations not due to efficacy, adverse events or death with a last VL ≥50 copies/mL.

[b]Two-sided Exact Clopper-Pearson 95% CI.

[c]Percentages calculated excluding patients with 'unknown' or 'not reported' race.

[d]One patient had last VL in the Week 96 window ≥50 copies/mL; Four patients discontinued for efficacy reasons; Two patients discontinued due to other reasons (both lost to follow up) with last available VL ≥50 copies/mL.

[e]Two patients discontinued for efficacy reasons, although one patient had VL <50 copies/mL at last on-treatment visit; Two patients discontinued due to other reasons (lost to follow-up and non-compliance with study medication) with last available VL ≥50 copies/mL.

[f]Data not reported for WHO clinical stage 3 and 4 subgroups due to small sample sizes; 16 patients were categorized as WHO clinical stage 3 and 1 patient was categorized as WHO clinical stage 4.

Safety and tolerability

AEs were similar in occurrence in the overall population and across subgroups by age, gender and race, baseline VL, baseline $CD4^+$ cell count and WHO clinical Stage through Week 96 in the D/C/F/TAF arm (Table 1). Study drug-related serious AEs and AEs leading to discontinuation were low and similar across subgroups, and no deaths were reported (Table 1).

Table 1 Overview of adverse events through Week 96 in the D/C/F/TAF arm of the AMBER study by patient subgroup

		Age		Gender		Race		Baseline VL		Baseline CD4$^+$ count		WHO clinical stage[a]	
Incidence, *n* (%)	Overall population *N* = 362	≤50 years *N* = 326	>50 years *N* = 36	Women *N* = 44	Men *N* = 318	Non-black/ African American *N* = 305	Black/ African American *N* = 40	≤100,000 copies/ mL *N* = 303	>100,000 copies/ mL *N* = 59	<200 cells/mm^3 *N* = 22	≥200 cells/ mm^3 *N* = 340	Stage 1 *N* = 314	Stage 2 *N* = 42
≥1 AE, any grade	334 (92)	298 (91)	36 (100)	41 (93)	293 (92)	279 (91)	38 (95)	280 (92)	54 (92)	19 (86)	315 (93)	289 (92)	39 (93)
Study drug-related	142 (39)	123 (38)	19 (53)	26 (59)	116 (36)	119 (39)	16 (40)	119 (39)	23 (39)	10 (46)	132 (39)	117 (37)	21 (50)
Most common AEs, any grade (≥10% in overall D/C/F/TAF arm)													
Diarrhea	83 (23)	75 (23)	8 (22)	7 (16)	76 (24)	75 (25)	6 (15)	70 (23)	13 (22)	4 (18)	79 (23)	78 (25)	4 (10)
Nasopharyngitis	58 (16)	47 (14)	11 (31)	4 (9)	54 (17)	53 (17)	2 (5)	53 (17)	5 (8)	1 (5)	57 (17)	46 (15)	10 (24)
Headache	54 (15)	48 (15)	6 (17)	6 (14)	48 (15)	45 (15)	7 (18)	45 (15)	9 (15)	5 (23)	49 (14)	44 (14)	9 (21)
≥1 grade 3 or 4 AE	45 (12)	38 (12)	7 (19)	6 (14)	39 (12)	38 (12)	6 (15)	39 (13)	6 (10)	4 (18)	41 (12)	35 (11)	9 (21)
Study drug-related	11 (3)	7 (2)	4 (11)	3 (7)	8 (3)	10 (3)	1 (3)	8 (3)	3 (5)	1 (5)	10 (3)	7 (2)	3 (7)
≥1 serious AE	39 (11)	34 (10)	5 (14)	5 (11)	34 (11)	35 (11)	4 (10)	36 (12)	3 (5)	2 (9)	37 (11)	32 (10)	6 (14)
Study drug-related	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)	0	1 (<1)	0	0	1 (<1)	1 (<1)	0
≥1 AE leading to discontinuation	10 (3)	10 (3)	0	3 (7)	7 (2)	9 (3)	1 (3)	10 (3)	0	0	10 (3)	8 (3)	2 (5)
Study drug-related	8 (2)	8 (2)	0	2 (5)	6 (2)	8 (3)	0	8 (3)	0	0	8 (2)	6 (2)	2 (5)
Median Δ $eGFR_{cyst}$ at Week 84[b], mL/min/1.73m^2	n = 204 +3	n = 186 +3	n = 18 +10	n = 24 +4	n = 180 +3	n = 179 +3	n = 19 +4	n = 172 +3	n = 32 +8	n = 12 +6	n = 192 +3	n = 169 +3	n = 32 +6

D/C/F/TAF: darunavir/cobicistat/emtricitabine/tenofovir alafenamide; VL: viral load; WHO: World Health Organization; AE: adverse event; $eGFR_{cyst}$: eGFR based on serum cystatin C (CKD-EPI formula).

[a]Data not reported for WHO clinical stage 3 and 4 subgroups due to small sample sizes; 16 patients were categorized as WHO clinical stage 3 and 1 patient was categorized as WHO clinical stage 4.

[b]Cystatin C was only collected up to and including the unblinding visit, therefore was not routinely collected during the open-label phase so only 22 patients had results for the Week 96 time point.

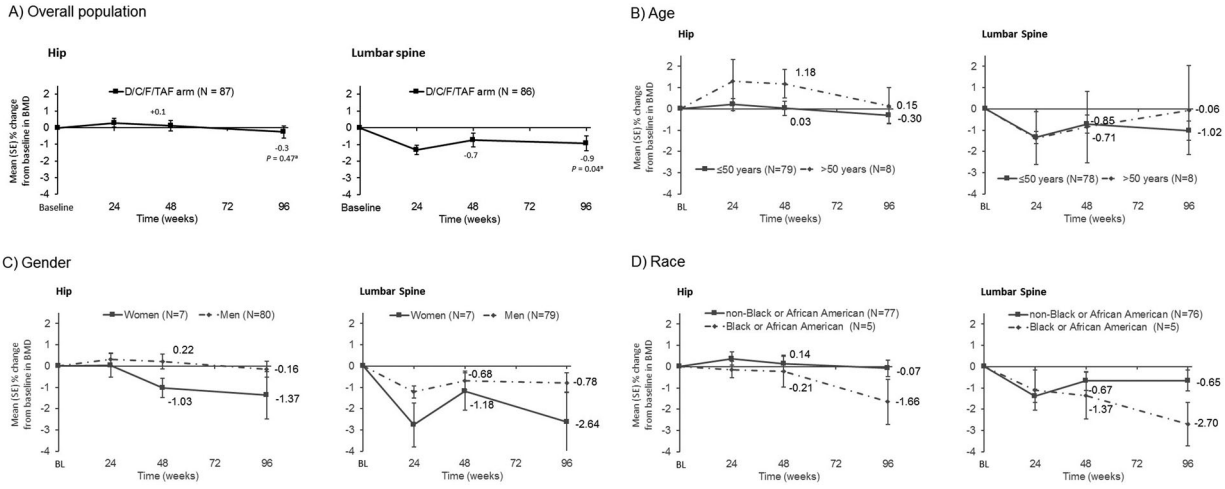

Figure 3 AMBER mean (SE) percent change from baseline to Week 96 in hip and lumbar spine BMD in the D/C/F/TAF arm by A) Overall population; B) Age; C) Gender; D) Race.

BMD, bone mineral density; SE, standard error; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide.

Data are from the bone investigation substudy, which included 113 patients in the D/C/F/TAF arm; N is the number of evaluable patients at Week 96.

[a]Within treatment arm for change at Week 96 from baseline assessed by paired t-test.

The most common AEs (≥10% overall D/C/F/TAF arm through 96 weeks), diarrhea, nasopharyngitis, and headache, each occurred with a similar incidence across subgroups (Table 1).

Laboratory parameters. Renal function, as assessed by changes in $eGFR_{cyst}$ over time, improved from baseline to Week 96 with D/C/F/TAF overall, and results were generally consistent across subgroups (Table 1 and Supplementary Figure 1). No cases of Fanconi syndrome or subclinical proximal renal tubulopathy were observed.

At Week 48, mean changes in markers of proteinuria versus baseline improved in the D/C/F/TAF arm versus the control arm.[13] Mean changes in proteinuria markers continued to improve through Week 96 in the D/C/F/TAF arm consistently across demographic subgroups (Supplementary Figure 2).

Median lipid parameter values tended to increase with D/C/F/TAF at Week 96 versus baseline across baseline demographic subgroups (Supplementary Figure 3), with only small median changes in TC/HDL-C ratio from baseline at Week 96 across age (+0.23 ≤ 50 years; +0.41 > 50 years), gender (+0.02 women; +0.28 men) and race subgroups (-0.04 black/African American; +0.3 non-black/African American). Low and similar proportions of patients across demographic subgroups (3% ≤50 years; 6% >50 years; 2% women; 4% men; and 5% black/African American; 4% non-black/African American) initiated lipid-lowering therapy during the study.

Bone investigation sub-study. The bone sub-study included 113 patients in the D/C/F/TAF arm and 99 in the control arm at baseline.[13] At Week 48, mean change in BMD at each site was statistically favorable for the D/C/F/TAF arm versus the control arm.[13] In the D/C/F/TAF arm through Week 96, there were small decreases in hip and lumbar spine BMD across demographic subgroups (Figure 3). Femoral neck BMD changes followed the same pattern at Week 96 (Supplementary Figure 4).

EMERALD D/C/F/TAF arm: Virologically-suppressed, ART-experienced patients

Patient baseline characteristics

Patient baseline characteristics[14,18] of the 763 patients in the D/C/F/TAF treatment arm at baseline are shown in Supplementary Table 1. Overall, 256/763 (34%) of patients were aged >50 years, 140/763 (18%) were women and 155/752 (21%) were black/African American.

Regarding previous ART use (including screening ART and PI booster counted as a separate ARV), 447/763 patients (59%) previously used ≥5 ARVs (Supplementary Table 1), 318 (42%) ≥ 2 PIs, 328 (43%) ≥ 3 N(t)RTIs, 225 (29%) ≥ 1 NNRTI, and 39 (5%) ≥ 1 integrase inhibitor.[14] Overall, 252/763 patients (33%) discontinued prior ARVs (including screening ARVs) due to convenience, 220 (29%) discontinued due to AEs and 116 (15%) had prior non-DRV VF (51 [7%] patients on a PI, 90 [12%] on an N(t)RTI, 50 [7%] on an NNRTI, and seven [1%] on an integrase

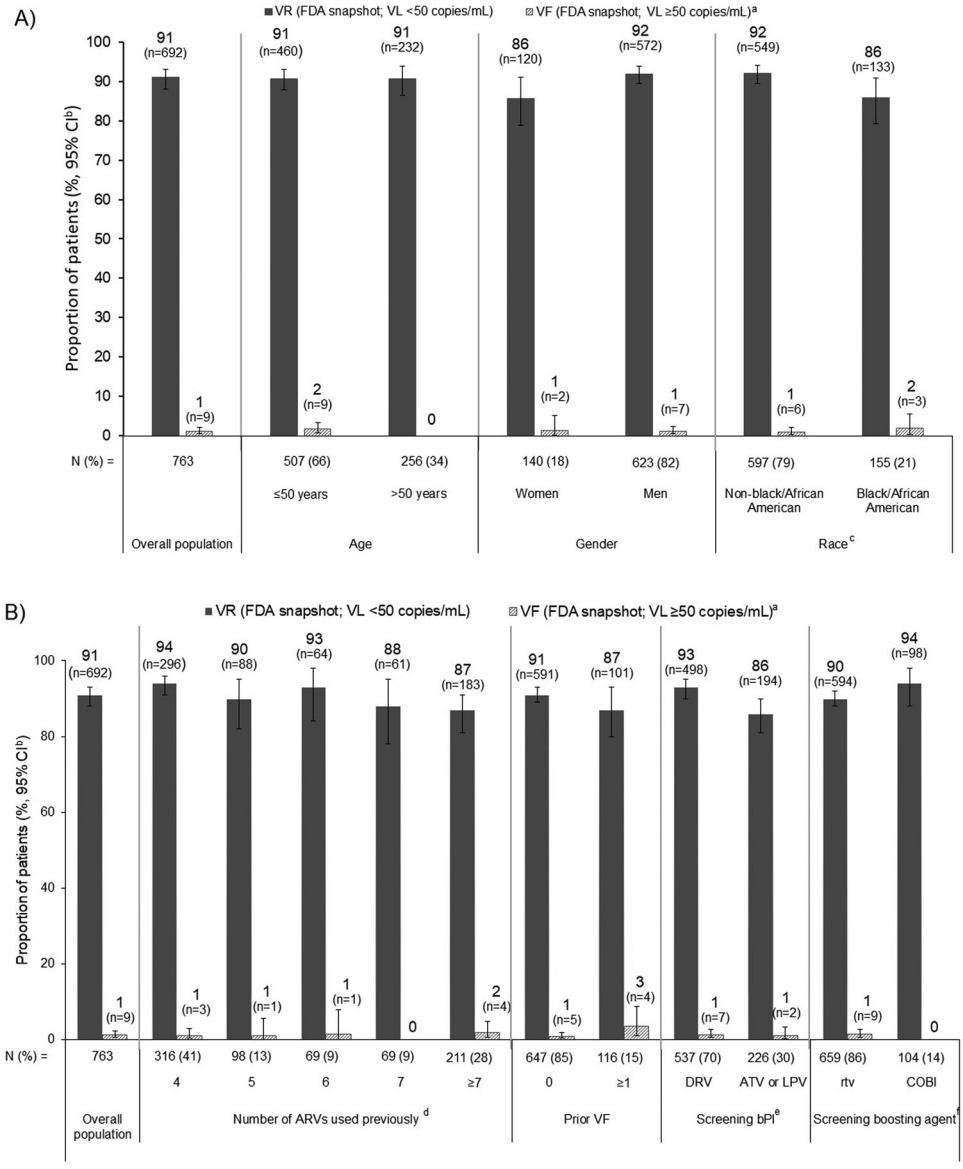

Figure 4 EMERALD virologic outcomes at Week 96 (by FDA snapshot) in the D/C/F/TAF arm by A) Demographic characteristics and B) Clinical characteristics at baseline.

D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; VR, virologic response; VF, virologic failure; VL, viral load; CI, confidence interval; FDA, Food and Drug Administration.

For each subgroup, patients with missing virologic data (per FDA snapshot) in the D/C/F/TAF arm was: 7% for those ≤50 years, 9% for those >50 years, 13% for women, 7% for men, 7% for those who are non-black/African American, and 12% for those who are black/African American, 5% of those who used 4 prior ARVs, 9% of those who used 5 prior ARVs, 6% of those who used 6 prior ARVs, 12% of those who used 7 prior ARVs, 11% of those who used >7 prior ARVs, 8% of those with 0 prior VFs, 9% of those with ≥1 prior VF, 6% for the DRV group, 13% for the ATV or LPV group, 8% for the rtv group, and 6% for the COBI group.

[a]VF was defined as last VL in the Week 96 window ≥50 copies/mL, or discontinuations for efficacy reasons, or premature discontinuations not due to efficacy, adverse events or death with a last VL ≥50 copies/mL.

[b]Two-sided Exact Clopper-Pearson 95% CI.

[c]Percentages calculated excluding patients with 'unknown' or 'not reported' race.

[d]Includes ARVs and booster used at screening. Data not reported for the one patient who had previously used 3 ARVs prior to baseline.

[e]DRV with rtv or COBI, ATV with rtv or COBI, and LPV with rtv.

[f]rtv with DRV, ATV, or LPV; and COBI with DRV or ATV.

inhibitor).[14] Regarding boosted PI use at screening, 537/763 patients (70%) used boosted DRV, 167 boosted ATV (22%) and 59 boosted LPV (8%), with 104 (14%) receiving COBI and 659 (86%) receiving RTV as a boosting agent (Supplementary Table 2).[14]

Efficacy

In the overall population, a high sustained virologic response (91%; 692/763; FDA snapshot) was maintained in the D/C/F/TAF arm at Week 96 (Figure 4).[14] High virologic responses were seen across all subgroups by

age, gender and race, number of previously used ARVs, prior VF, screening bPI, and screening boosting agent (ranging from 86% to 94%) at Week 96 (Figure 4). VF (FDA snapshot) at Week 96 was low in all these patient subgroups (ranging from 0% to 3%) (Figure 4).

The PDVR rate cumulative through Week 96 was low in the D/C/F/TAF arm, and results were consistent across these patient subgroups (ranging from 0% to 7%) (Table 2).

Resistance

Post-baseline genotype data was available for four PDVFs (2 men; 2 women) in the D/C/F/TAF arm. No DRV, primary PI, FTC, or TFV RAMs were observed post-baseline across subgroups.

Safety and tolerability

The overall incidence of AEs in the D/C/F/TAF arm through Week 96 was generally similar in the overall population and across patient subgroups by age, gender and race, screening bPI, and screening boosting agent (Table 3). The Week 96 analysis by prior VF or antiretroviral treatment experience was not preplanned so data are not presented.

Rates of study drug-related Grade 3 or 4 AEs, serious AEs and discontinuations due to AEs were low and generally similar across all patient subgroups (Table 3). The most common AEs (≥10% overall D/C/F/TAF arm through 96 weeks), upper respiratory tract infection, viral upper respiratory tract infections, diarrhea, headache, and back pain, each occurred with a similar incidence across subgroups (Table 3).

Laboratory parameters. Median change in $eGFR_{cyst}$ was stable in the D/C/F/TAF arm through Week 96 across age, gender and race, screening bPI and screening boosting agent subgroups (Table 3 and Supplementary Figure 1), and no cases of Fanconi syndrome or subclinical proximal renal tubulopathy were detected.

Mean changes in markers of proteinuria at Week 48 compared with baseline improved in the D/C/F/TAF arm versus the control arm.[14] Mean changes in proteinuria markers continued to improve in the D/C/F/TAF arm through Week 96, and results were similar across demographic subgroups (Supplementary Figure 2).

Median lipid parameter values at Week 96 tended to increase compared with baseline in the D/C/F/TAF arm across demographic subgroups (Supplementary Figure 3), with only small median changes in TC/HDL-C ratio across age (+0.2 ≤ 50, and >50 years), gender (+0.2 both genders), and race subgroups (+0.3 black/African American; +0.2 non-black/African

Table 2 EMERALD PDVR cumulative through Week 96 in the D/C/F/TAF arm by subgroup

EMERALD	Overall population	Age		Gender		Race[a]		Number of ARVs previously used[b]				Prior VF		Screening bPI[c]			Screening boosting agent[d]	
		≤50 years	>50 years	Women	Men	Non-black/ African American	Black/ African American	4	5	6	7	>7	0	≥1	DRV	ATV or LPV	rtv	COBI
N (%)	763	507 (66)	256 (34)	140 (18)	623 (82)	597 (79)	155 (21)	316 (41)	98 (13)	69 (9)	69 (9)	211 (28)	647 (85)	116 (15)	537 (70)	226 (30)	659 (86)	104 (14)
PDVR (VL ≥50 copies/mL[e]) cumulative through Week 96, *n* (%) (95% CI)[f]	24 (3) (2; 5)	18 (4) (2; 6)	6 (2) (1; 5)	4 (3) (1; 7)	20 (3) (2; 5)	17 (3) (2; 5)	7 (5) (2; 9)	9 (3) (1; 5)	4 (4) (1; 10)	5 (7) (2; 16)	0	6 (3) (1; 6)	19 (3) (2; 5)	5 (4) (1; 10)	16 (3) (2; 5)	8 (4) (2; 7)	22 (3) (2; 5)	2 (2) (<1; 7)

PDVR: protocol-defined virologic rebound; D/C/F/TAF: darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ARV: antiretroviral; VF: virologic failure; bPI: boosted protease inhibitor; DRV: darunavir; ATV: atazanavir; LPV: lopinavir; rtv: ritonavir; COBI: cobicistat; CI: confidence interval.

[a]Percentages calculated excluding patients with 'unknown' or 'not reported' race.

[b]Includes ARVs and booster used at screening. Data not reported for the one patient who had previously used 3 ARVs prior to baseline.

[c]DRV with rtv or COBI, ATV with rtv or COBI, and LPV with rtv.

[d]rtv with DRV, ATV, or LPV; and COBI with DRV or ATV.

[e]Confirmed VL ≥50 copies/mL or premature discontinuation with last VL ≥50 copies/mL (cumulative through Week 96).

[f]Two-sided Exact Clopper-Pearson 95% CI.

Table 3 Overview of adverse events through Week 96 in the D/C/F/TAF arm of the EMERALD study by subgroup[a]

		Age		Gender		Race		Screening bPI[b]		Screening boosting agent[c]	
Incidence, *n* (%)	Overall population *N* = 763	≤50 years *N* = 507	>50 years *N* = 256	Women *N* = 140	Men *N* = 623	Non-black/African American *N* = 597	Black/African American *N* = 155	DRV *N* = 537	ATV or LPV *N* = 226	rtv *N* = 659	COBI *N* = 104
≥1 AE, any grade	690 (90)	456 (90)	234 (91)	122 (87)	568 (91)	545 (91)	136 (88)	495 (92)	195 (86)	600 (91)	90 (87)
Study drug-related	165 (22)	120 (24)	45 (18)	33 (24)	132 (21)	137 (23)	24 (15)	111 (21)	54 (24)	154 (23)	11 (11)
Most common AEs, any grade (≥10% in overall D/C/F/TAF arm)											
URTI	122 (16)	90 (18)	35 (14)	23 (16)	99 (16)	104 (17)	17 (11)	91 (17)	31 (14)	112 (17)	10 (10)
Viral URTI	98 (13)	63 (12)	32 (13)	19 (14)	79 (13)	86 (14)	11 (7)	75 (14)	23 (10)	91 (14)	7 (7)
Diarrhea	80 (11)	60 (12)	20 (8)	11 (8)	69 (11)	66 (11)	11 (7)	63 (12)	17 (8)	71 (11)	9 (9)
Headache	79 (10)	61 (12)	18 (7)	22 (16)	57 (9)	59 (10)	17 (11)	55 (10)	24 (11)	72 (11)	7 (7)
Back pain	76 (10)	47 (9)	29 (11)	13 (9)	63 (10)	58 (10)	18 (12)	56 (10)	20 (9)	67 (10)	9 (9)
≥1 grade 3 or 4 AE	98 (13)	61 (12)	37 (14)	18 (13)	80 (13)	80 (13)	17 (11)	64 (12)	34 (15)	88 (13)	10 (10)
Study drug-related	14 (2)	10 (2)	4 (2)	2 (1)	12 (2)	12 (2)	2 (1)	11 (2)	3 (1)	14 (2)	0
≥1 serious AE	66 (9)	37 (7)	29 (11)	13 (9)	53 (9)	51 (9)	15 (10)	42 (8)	24 (11)	58 (9)	8 (8)
Study drug-related	2 (<1)	1 (<1)	1 (<1)	0	2 (<1)	2 (<1)	0	1 (<1)	1 (<1)	2 (<1)	0
≥1 AE leading to discontinuation	17 (2)	9 (2)	8 (3)	3 (2)	14 (2)	13 (2)	4 (3)	6 (1)	11 (5)	15 (2)	2 (2)
Study drug-related	12 (2)	8 (2)	4 (2)	2 (1)	10 (2)	11 (2)	1 (1)	4 (1)	8 (4)	11 (2)	1 (1)
Fatal AEs[d]	3 (<1)	1 (<1)	2 (1)	0	3 (<1)	3 (1)	0	2 (<1)	1 (<1)	3 (<1)	0
Median Δ $eGFR_{cyst}$ at Week 96, mL/min/1.73m^2	n = 686 -1	n = 458 -0.4	n = 228 -2	n = 118 -0.5	n = 568 -1	n = 543 -1	n = 133 +1	n = 494 -1	n = 192 -1	n = 588 -1	n = 98 +2

D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; AE, adverse event; URTI, upper respiratory tract infection; bPI: boosted protease inhibitor; DRV: darunavir; ATV: atazanavir; LPV: lopinavir; rtv: ritonavir; COBI: cobicistat.

$eGFR_{cyst}$, eGFR based on serum cystatin C (CKD-EPI formula).

[a]Week 96 analysis by prior virologic failure or antiretroviral treatment experience subgroups was not preplanned so data are not presented.

[b]DRV with rtv or COBI, ATV with rtv or COBI, and LPV with rtv; [c]rtv with DRV, ATV, or LPV; and COBI with DRV or ATV.

[d]Two cases of myocardial infarction (one in a patient who was a smoker with ongoing medical history of hyperlipidemia and hypertension, and one in a patient with ongoing medical history of obesity and hypertension), and one metastatic pancreatic cancer.

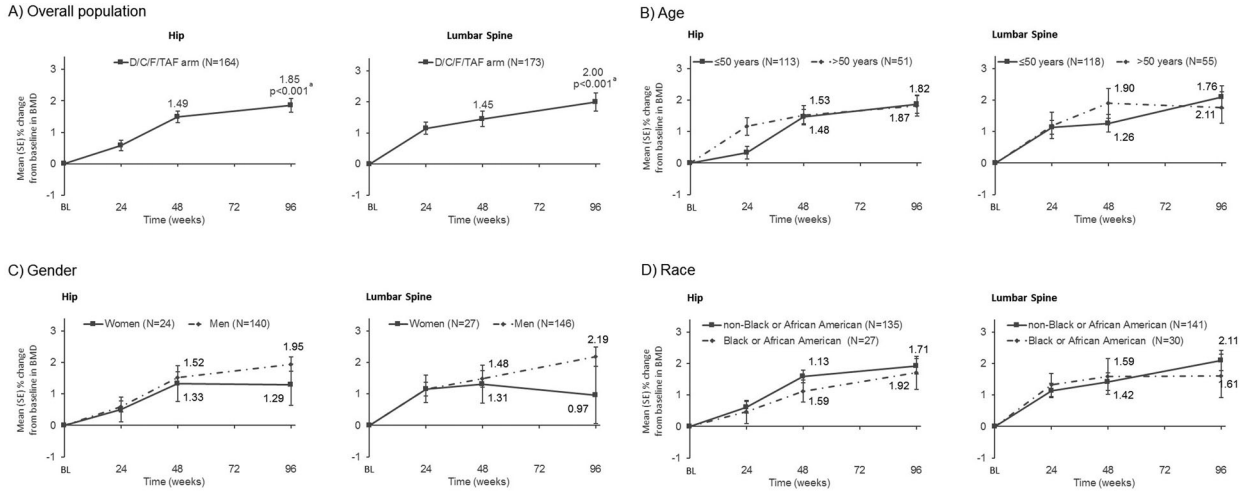

Figure 5 EMERALD mean (SE) percent change from baseline to Week 96 in hip and lumbar spine BMD in the D/C/F/TAF arm by A) Overall population; B) Age; C) Gender; D) Race.

BMD, bone mineral density; SE, standard error; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide.

Data are from the bone investigation substudy, which included 209 patients in the D/C/F/TAF arm; *N* is the number of evaluable patients at Week 96.

[a]Within treatment arm for change at Week 96 from baseline assessed by paired t-test.

American). Proportions of patients who initiated lipid-lowering therapy were low and similar across demographic subgroups during the study: 6% ≤50 years; 4% >50 years; 4% women; 6% men; and 1% black/African American; 7% non-black/African American.

Bone investigation sub-study. The bone substudy included 209 patients in the D/C/F/TAF arm and 108 in the control arm.[14] At Week 48, mean change in BMD at each site was statistically favorable for the D/C/F/TAF arm versus the control arm.[14] In the D/C/F/TAF arm through Week 96, there were numerical increases in hip and lumbar spine BMD versus baseline across subgroups based on age, gender, and race, with overall numerically smaller increases in women compared with in other subgroups (Figure 5). Femoral neck BMD changes followed the same pattern at Week 96 (Supplementary Figure 4).

Discussion

When selecting an ART regimen, clinicians need to consider the varied HIV-1 patient population, with a range of demographic and clinical characteristics and treatment histories.[10–12] In the current Week 96 analyses of AMBER and EMERALD, the efficacy and safety of D/C/F/TAF were consistent across subgroups of ART-naïve patients based on demographic (age, gender, race) and baseline clinical characteristics (VL, $CD4^+$ cell count, WHO clinical stage, HIV-1 subtype and ART resistance) and in virologically suppressed patients based on demographic characteristics, prior treatment experience and ART regimen used at baseline.

Entry criteria were less restrictive in EMERALD than in other switch studies.[23–30] Regarding prior resistance, the only patients excluded were those with a history of VF on DRV-based regimens or the presence of DRV RAMs (if historical genotypes were available). There was no exclusion based on other PI or N(t)RTI RAMs, including FTC or TFV RAMs.[14,22,31] As such, ART-experienced, virologically suppressed patients with varied treatment histories, including history of VF, were allowed to enroll, so the population was more treatment-experienced than in most reported clinical switch studies.[14,22,31]

In AMBER and EMERALD, D/C/F/TAF maintained high sustained virologic response rates at Week 96 across patient subgroups, ranging from 70% to 89% in ART-naïve patients in AMBER and 86% to 94% in ART-experienced, virologically suppressed patients in EMERALD. Responses were comparable to Week 96 responses with STRs in overall populations of ART-naïve patients from previous Phase 3 trials (66% to 88%)[32–40] and other studies evaluating switching to integrase inhibitor-based regimens.[41,42] However, direct comparisons are difficult due to differences in study designs, inclusion criteria and the resulting study populations. Low VF rates were also observed in the D/C/F/TAF arm at Week 96 across patient subgroups in both studies. In EMERALD, low PDVR rates cumulative through Week 96 were observed regardless of demographic characteristics, prior VF, prior ART experience and ART regimen at baseline, and were consistent with the overall Week 96 results.[16]

In both studies through 96 weeks across patient subgroups, no treatment-emergent DRV, primary PI or TFV RAMs were observed in 1,125 patients. In only one patient in the D/C/F/TAF arm of AMBER, an FTC RAM (M184I/V) was identified post-VF (<0.1%). As described previously, M184V was detected pretreatment at screening by deep sequencing as a minority variant (9%).[22] These results are consistent with previous DRV and D/C/F/TAF studies and the established high genetic barrier to resistance of DRV.[9,43,44] The lack of emergence of significant resistance mutations over time for virologically suppressed, treatment-experienced patients is important, particularly given concerns for re-emergence of archived RAMs in patients with prior VF. D/C/F/TAF demonstrated a high genetic barrier to resistance in ART-experienced adults in EMERALD through 96 weeks, even in patients with HIV-1 virus harboring archived study drug RAMs at baseline.[31] Archived RAMs to study drugs had no effect on virologic response and VF rates.

D/C/F/TAF was associated with a favorable safety and tolerability profile through 96 weeks, with low incidences of study drug-related serious AEs and discontinuations due to AEs observed across all subgroups of both studies. Most commonly reported AEs, upper respiratory tract infection, nasopharyngitis, diarrhea, and headache were reported previously with DRV and COBI.[6,7,43–46] In AMBER, the incidence of study drug-related AEs was higher in some subgroups (age >50 years; women; $CD4^+$ cell count <200 cells/mm^3; WHO stage 2), although these results should be interpreted with caution due to the small sample sizes.

Renal, bone, and lipid safety results in both studies were consistent with the established effects of TAF vs TDF[13,14,32,44,47,48] including a pooled analysis of 5 Phase 3 studies.[49] Renal function improved or was stable through Week 96 across subgroups in both trials, and no cases of Fanconi syndrome or subclinical proximal renal tubulopathy were observed. Favorable renal tubular proteinuria and BMD at each site seen in the D/C/F/TAF arm at Week 48 versus control were maintained through Week 96 in the D/C/F/TAF arm across demographic subgroups in both studies. Importantly, the D/C/F/TAF bone safety profile was generally consistent in patients aged ≤50 and >50 years. In the D/C/F/TAF arm of each study, there were increases in fasting lipids from baseline to Week 96 across demographic subgroups. However, changes in TC/HDL-C ratio were small, and low and similar proportions of patients in each demographic subgroup initiated lipid-lowering therapy during the studies. Combined with these factors, concerns around weight gain in patients are important attributes to consider as the HIV patient population ages. Recently the integrase inhibitor class has been associated with significant weight gain.[11] D/C/F/TAF has only demonstrated a median increase of weight from baseline of 2 kg through 96 weeks in both AMBER[15] and EMERALD.[16]

Limitations were the small numbers of patients in some subgroups. These small sample sizes were sometimes associated with large 95% CIs in the FDA snapshot analysis of virologic outcome, thereby limiting the interpretation of the virologic outcome data in these subgroups, and of the changes in lipid parameters from baseline. For example, in the AMBER D/C/F/TAF arm, the subgroup with baseline $CD4^+$ cell count <200 cells/mm^3 only included 22 patients. These later presenters, while frequent in clinical practice are very difficult to enroll in clinical trials, as shown in a Phase 3 trial comparing abacavir/lamivudine plus DRV/r vs abacavir/lamivudine plus raltegravir in ART-naïve patients with baseline $CD4^+$ cell count <200 cells/mm^3 and VL < 500,000 copies/mL.[50] In AMBER, of the four snapshot VFs in the subgroup with baseline $CD4^+$ cell count <200 cells/mm^3, only one was efficacy related. Similarly, in the Phase 3 GEMINI-1 and −2 trials, a lower virologic response in patients with $CD4^+$ cell count <200 cells/mm^3 was observed in patients receiving dolutegravir and lamivudine compared with patients receiving dolutegravir with F/TDF, but most snapshot VFs were considered unrelated to efficacy or treatment failure.[51,52] In AMBER, the number of Black/African American patients in the D/C/F/TAF arm was very low (N = 40), however, the relative fall in virologic response rate at week 96 compared with that observed in non-black/African American patients is consistent with the findings of several previous trials with other ARVs.[53–58] VF was higher in Black/African American patients than in non-black/African American patients, which could be explained by the lower proportion of Black/African American patients who reported >95% adherence, as observed in other studies.[53,55,56,58] However, in our study, the lower response in Black/African American patients was mainly a result of a higher frequency of missing virologic data.

Despite these limitations, the analysis of AMBER demonstrated that a diverse patient population could consider initiating ART with D/C/F/TAF. D/C/F/TAF may have an important role for rapid initiation of treatment in newly diagnosed patients as shown in the DIAMOND study,[59] particularly those with uncertain adherence or who plan to start treatment prior to the availability of baseline VL, $CD4^+$ or resistance test results.[11,12] The EMERALD analysis showed that switching to D/C/F/TAF may be an option for a broad

range of virologically suppressed HIV-1 patients, including those who have previously received multiple ARV agents and/or have had prior VF, and those currently on multi-tablet regimens of LPV, ATV, or DRV, given the consistent results by screening bPI subgroup and the advantages of DRV compared with other PIs.[11,60]

In conclusion, through 96 weeks in AMBER and EMERALD across patient subgroups in ART-naïve and -experienced virologically suppressed adults, once-daily D/C/F/TAF STR resulted in high virologic response rates, few discontinuations due to AEs, no primary PI, DRV or TFV resistance development and favorable bone and renal outcomes. These findings continue to support the use of D/C/F/TAF in HIV-1 patients who are ART-naïve, or virologically suppressed on a stable ART regimen and require a switch in therapy.

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Disclosure of interest

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Author contributions

G.D.H, A.W., C.M., and C.D.S. contributed to the conduct of the studies as investigators and to the interpretation of the data. J.J. contributed to statistical analysis and interpretation of the data. E.V.L., E.L., K.B., and B.B. contributed to the design of the analysis and interpretation of the data. All authors were involved in the development of the primary manuscript, interpretation of data, and have read and approved the final version, and have met the criteria for authorship as established by the ICMJE.

Data availability statement

Week 96 subgroup data were presented in part at the Conference on Retroviruses and Opportunistic Infections (CROI); Seattle, WA, USA, March 4–7, 2019 (abstract and poster 0500) and the 9th International Workshop on HIV & Women; Seattle, WA, USA, March 2–3, 2019 (abstract and poster 23). The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

Ethics approval and consent to participate

The AMBER and EMERALD protocols were reviewed and approved by institutional review boards or independent ethics committees. The studies were conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. All patients provided written, informed consent prior to the start of the studies.

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