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MAJOR ARTICLE

Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir/Abacavir/Lamivudine in Antiretroviral-Naive Adults (SYMTRI): A Multicenter Randomized Open-Label Study (PReEC/RIS-57)

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Background. Darunavir/cobicistat/emtricitabine/tenofovir alafenamide (D/C/F/TAF) is the reference for combination therapy based on protease inhibitors due to its efficacy, tolerability, and convenience. Head-to-head randomized comparisons between D/C/F/TAF and combination therapy based on integrase inhibitors in antiretroviral-naive patients are lacking.

Methods. Adult (>18 years old) human immunodeficiency virus-infected antiretroviral-naive patients (HLA-B*5701 negative and hepatitis B virus negative), with viral load (VL) ≥500 c/mL, were centrally randomized to initiate D/C/F/TAF or dolutegravir/abacavir/lamivudine (DTG/3TC/ABC) after stratifying by VL and CD4 count. Clinical and analytical assessments were performed at weeks 0, 4, 12, 24, and 48. The primary endpoint was VL <50 c/mL at week 48 in the intention-to-treat (ITT)-exposed population (US Food and Drug Administration snapshot analysis, 10% noninferiority margin).

Results. Between September 2018 and 2019, 316 patients were randomized and 306 patients were included in the ITT-exposed analysis (151 D/C/F/TAF and 155 DTG/3TC/ABC). Almost all (94%) participants were male and their median age was 35 years. Forty percent had a baseline VL >100 000 copies/mL, and 13% had <200 CD4 cells/μL. Median weight was 73 kg and median body mass index was 24 kg/m^2. At 48 weeks, 79% (D/C/F/TAF) versus 82% (DTG/3TC/ABC) had VL <50 c/mL (difference, −2.4%; 95% confidence interval [CI], −11.3 to 6.6). Eight percent versus four percent experienced virologic failure but no resistance-associated mutations emerged. Four percent versus six percent had drug discontinuation due to adverse events. In the per-protocol analysis, 94% versus 96% of patients had VL <50 c/mL (difference, −2%; 95% CI, −8.1 to 3.5). There were no differences in CD4 cell count or weight changes.

Conclusions. We could not demonstrate the noninferiority of D/C/F/TAF relative to DTG/ABC/3TC as initial antiretroviral therapy, although both regimens were similarly well tolerated.

Keywords. darunavir/cobicistat; dolutegravir; naive patients; tenofovir alafenamide; virologic efficacy.

Current international guidelines on antiretroviral therapy (ART) agree on recommending integrase inhibitor-containing regimens as the preferred first-line therapy [1–3]. Protease inhibitors (PIs) and nonnucleosides are alternative regimens. Darunavir/cobicistat combined with FTC/TAF (D/C/F/TAF) in a single pill has proven highly efficacious and tolerable in antiretroviral (ARV)-naive patients in the only randomized clinical trial conducted to date with this formulation (AMBER study), where it was compared with darunavir (DRV)/cobicistat plus emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) [4]. To date, the single pill containing D/C/F/TAF has not been compared head-to-head with integrase inhibitor regimens.

Previous studies showed older DRV combinations to be inferior to integrase inhibitors [5, 6]. In the AIDS Clinical Trials Group (ACTG) 5257 study—a large, 3-arm, randomized,

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open-label clinical trial enrolling more than 1800 ARV-naive human immunodeficiency virus (HIV)-infected individuals—a raltegravir (RAL) regimen was superior to ritonavir-boosted atazanavir or darunavir regimens in the combined endpoint of virologic efficacy and tolerability at 96 weeks [5]. In the FLAMINGO study—another phase 3, open-label, randomized clinical trial conducted in antiretroviral-naive patients—dolutegravir (DTG) was superior to ritonavir-boosted darunavir, both combined with investigator-selected TDF/FTC or abacavir/lamivudine (ABC/3TC) [6].

In contrast to previous studies, the AMBER study, in which TAF was substituted for TDF and cobicistat was substituted for ritonavir, revealed the combination of D/C/F/TAF to have higher efficacy rates (91.4% at 48 weeks) and lower adverse event-related discontinuations (2%) than those reported in FLAMINGO or the ACTG 5257 trials. These data encouraged us to compare this combination with another triple-drug regimen based on a second-generation integrase inhibitor.

The objective of this multicenter randomized study was to compare head-to-head 2 single-pill triple regimens based on D/C/F/TAF, a PI-based regimen, and DTG/ABC/3TC, a second-generation integrase inhibitor regimen, as initial ART.

METHODS

Study Design and Population

We performed a randomized, parallel, open-label, multicenter noninferiority trial in 27 hospitals in Spain. The study investigators enrolled the following: ARV-naive patients (≤10 days of prior therapy with any ARV agent after a diagnosis of HIV-1 infection except for pre-exposure prophylaxis [PrEP] or postexposure prophylaxis [PEP], up to 1 month before screening); and HIV-1 infected adults (aged ≥18 years) with plasma HIV-1 ribonucleic acid (RNA) levels ≥500 copies/mL, estimated glomerular filtration rate (eGFR) ≥50 mL/minute according to the Cockcroft-Gault formula, hepatic transaminases (*aspartate aminotransferase* and *alanine aminotransferase*) ≤5 × upper limit of normal, and blood tests showing absolute neutrophil count ≥750/mm^3 (≥0.75 g/L), platelets ≥50 000/mm^3 (≥50 g/L), and hemoglobin ≥8.5 g/dL (≥85 g/L). Females of childbearing potential had to agree to use protocol-specified highly effective contraceptive methods or remain sexually inactive from screening to the end of the study period and for 30 days after the last dose of the study drug.

Individuals were excluded for any of the following reasons: presence of the HLA-B*5701 allele; chronic hepatitis B infection (defined by a positive hepatitis B surface antigen); pregnancy or breastfeeding; current or previous malignant neoplasm; active opportunistic infections or other serious active infections requiring parenteral antibiotics or antifungal therapy in the previous 30 days; or concomitant therapy at risk for clinically significant interactions with the study drugs.

Patient Consent Statement

This trial was performed in accordance with the Declaration of Helsinki and approved by the local ethics committees (AC023/18, approved by Bellvitge University Hospital Clinical Research Ethics Committee reflected in summary 14/18) and the Spanish Agency for Medicines and Medical Devices.

The patient's written consent was obtained. This study was registered at the European Union Clinical Trials Registry (EudraCT 2018-001645-14).

Procedures

Eligible patients were randomized 1:1 centrally using a computer-generated block randomization protocol after stratifying by HIV-1 RNA (≤100 000 or >100 000 copies/mL) and CD4 counts (≤200 or >200/μL).

Patients received oral fixed-dose combinations of either D/C/F/TAF (800 mg, 150 mg, 200 mg, and 10 mg, respectively) or DTG/ABC/3TC (50 mg, 600 mg, and 300 mg, respectively) administered once daily, with no food restrictions. We obtained data during study visits at baseline, and at weeks, 4, 12, 24, and 48, with a follow-up visit at the end of study or after the last visit if the study was discontinued before week 48, where possible.

The laboratory tests were performed at each hospital and included blood cells, serum chemistries, fasting lipids, CD4 counts, renal laboratory parameters (serum creatinine and eGFR), and plasma HIV-1 RNA. Protocol-defined virologic failure was defined as a confirmed viral load (VL) ≥50 copies/mL at week 48, as well as a reduction in VL of less than 1 log plus VL ≥50 copies/mL at week 12 or a confirmed rebound to VL ≥50 copies/mL in a patient with previous VL <50 copies/mL or to a VL ≥1 log from the nadir. Treatment was considered to have failed in patients lost to follow-up with the last VL ≥50 copies/mL.

Genotyping tests at baseline were not required for enrollment, although they were performed as a routine practice in Spain according to national guidelines (https://gesida-seimc.org/wp-content/uploads/2020/07/TAR_GUIA_GESIDA_2020_COMPLETA_Julio.pdf); only 5 of 316 patients did not undergo baseline genotypic resistance tests. Sanger sequencing or ultradeep sequencing-based genotypic resistance tests were used according to routine practice at the participating center.

Safety was assessed at each medical visit through recording of clinical or laboratory adverse events. Specifically, discontinuation due to adverse events was closely monitored with the corresponding clinical investigator.

Outcomes

The primary endpoint was the proportion of participants with plasma HIV-1 RNA <50 copies/mL at week 48 among those who took at least 1 dose of treatment (intention-to treat-exposed [ITTe] analysis) as defined by the US Food and Drug Administration (FDA) snapshot algorithm [7].

Virologic efficacy was also assessed in a per-protocol analysis (patients who continued with the allocated regimen and without protocol deviations) and in 3 sensitivity ITT analyses: ITT analysis (all randomized patients), missing = excluded, and ITTe with an outcome of plasma HIV-1 RNA <200 copies/mL.

Other prespecified outcomes were (1) changes from baseline in $CD4^+$ cell count at week 48, changes in weight and body mass index (BMI), and adverse events and (2) the results of clinical laboratory tests to evaluate safety and tolerability.

Statistical Analysis

We analyzed the primary endpoint for all participants who were randomly assigned to treatment, returned for follow-up assessments, and received at least 1 dose of the study drug.

The primary assessment of noninferiority was with the 95% confidence interval (CI) for the difference in virological rates (D/C/F/TAF group, DTG/ABC/3TC group) with a prespecified noninferiority margin of −10%, based on published FDA regulatory guidance [7].

Estimating a response rate of 90% at week 48 in both treatment groups and expecting 10% losses, a sample size of 316 participants would achieve at least 80% power for detection of noninferiority at a 1-sided α of 0.025 (158 participants in each group). *Ene* v3.0 (Servei d'Estadística Aplicada, Universitat Autònoma de Barcelona, Barcelona, Spain) was used to calculate sample size.

We constructed the baseline stratum-weighted difference in the response rate and its 95% CI based on the Mantel-Haenszel proportion adjusted for baseline HIV-1 RNA stratum (<100 000 or ≥100 000 copies/mL) and baseline CD4 cell count stratum (<200 or ≥200 × 10^6 cells/L).

In the FDA snapshot analysis, participants were classified into 1 of 3 outcomes: (1) HIV-1 RNA <50 copies/mL at week 48 (virological success); (2) HIV-1 RNA ≥50 copies/mL at week 48 or HIV-1 RNA ≥50 copies/mL at the last visit before discontinuing earlier than week 48 for reasons other than adverse events or death; (3) loss to follow-up during the study period with last the HIV-1 RNA <50 copies/mL or discontinuation due to adverse events or death, or continuing in the study but with no analytical data at week 48 (no virological data).

The *P* value and the difference in response rates of the snapshot analysis were calculated on the basis of the dichotomized response (HIV-1 RNA <50 copies/mL at week 48 vs HIV-1 RNA ≥50 copies/mL and no virologic data at week 48). The same analysis was carried out on the basis of age, baseline HIV-1 RNA stratum, and baseline CD4 cell count stratum.

The per-protocol analysis excluded participants in the full analysis set who were lost to follow-up or discontinued due to adverse events or death or for whom no analytical data were available at week 48. In addition, we assessed the proportion of participants with HIV-1 RNA <50 copies/mL using the missing = excluded analysis as a missing data imputation method at week 48. The longitudinal descriptive analysis from baseline in $\log_{10}$ HIV-1 RNA to weeks 24 and 48 was summarized by treatment group based on the per-protocol population.

Changes from baseline in weight, BMI, and CD4 cell count were summarized by treatment group, with descriptive statistics based on the per-protocol population. The *P* value was calculated using a 2-sided Wilcoxon rank-sum test and *t* test, depending on the distribution of the samples in each stratum.

Adherence to therapy was evaluated using the SMAQ questionnaire [8]. The statistical analyses were performed using R (version 3.6.2) under RStudio IDE (version 1.2.5033).

RESULTS

Between September 2018 and 2019, 320 patients were screened for participation in the study, and 316 were randomly assigned to treatment, 158 per arm. Of these, 306 received at least 1 dose of treatment (Figure 1). Baseline characteristics were well balanced between the arms (Table 1). Of note, almost all participants were male, mostly men who have sex with men, 40% had a baseline VL > 100 000 copies/mL, and 13% had <200 CD4 cells/μL. No patient had previously received PrEP or PEP. A total of 11.2 and 9.7 percent of the participants were lost to follow-up in the D/C/F/TAF and DTG/ABC/3TC arms, respectively (Figure 1).

At 48 weeks, the ITTe analysis (n = 306) revealed that 79% (D/C/F/TAF) versus 82% (DTG/ABC/3TC) had VL <50 copies/mL (adjusted treatment difference, −2.4%; 95% CI, −11.3 to 6.6), thus not meeting the predefined noninferiority criterion for D/C/F/TAF versus DTG/ABC/3TC (Figure 2, Table 2). Virologic nonresponse was observed in 8% versus 4% (12 participants in D/C/F/TAF vs 6 in DTG/ABC/3TC); of these, 5 versus 2 were lost to follow-up in the first weeks of therapy (they only came to baseline and 4-week visits), with a VL >50 copies/mL, whereas 7 versus 4 continued therapy up to week 48. Of note, all of these 11 patients but 1 (VL <50 copies/mL at week 24) did not achieve undetectable VL during the study period. Six of the eleven patients had VL <200 copies/L but >50 copies/mL at week 48. Four of them had baseline VL >100 000 copies/mL (2 patients in each arm).

In the per-protocol analysis performed in 258 patients, the proportion of participants with HIV-1 RNA <50 copies/mL at 48 weeks was 94% in the D/C/F/TAF arm and 97% in the DTG arm (adjusted treatment difference, −2%; 95% CI, −8.1 to 3.5). In this analysis, DRV/C/F/TAF was noninferior to DTG (Figure 2, Table 2).

All 3 additional ITT sensitivity analyses were consistent with the main outcome: they did not prove the noninferiority of D/C/F/TAF vs DTG/ABC/3TC (Figure 3). In Figure 4, the proportion of patients with VL <50 copies/mL in the primary endpoint (ITTe analysis) according to stratification by baseline VL, CD4 count, and age is shown.

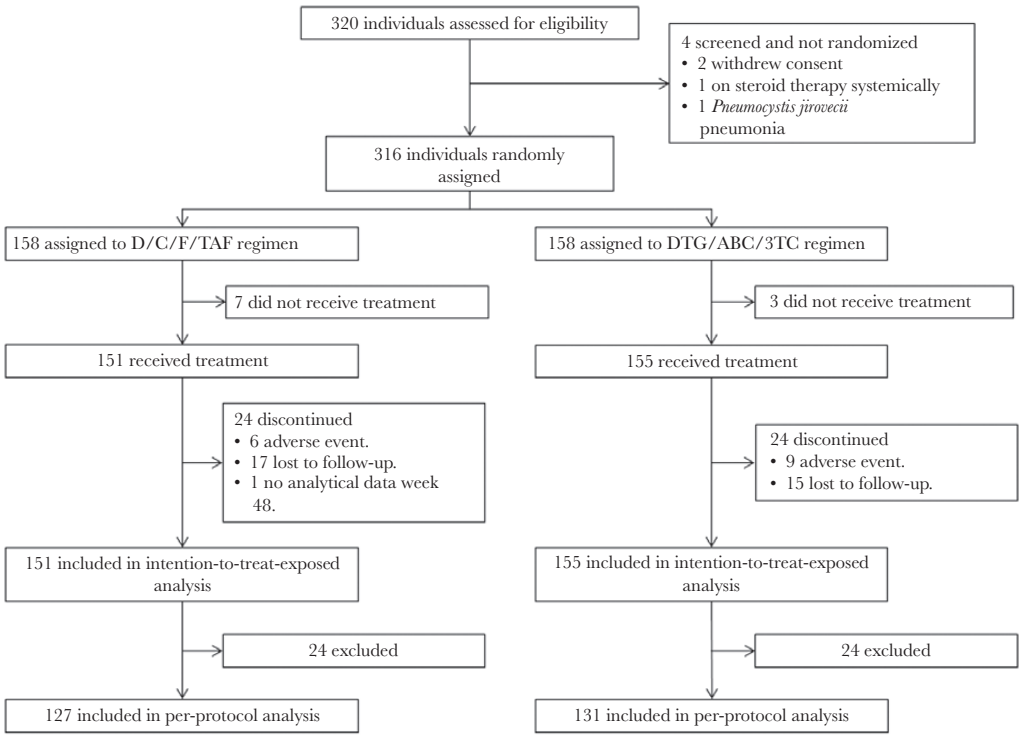

Figure 1. Trial profile. D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine.

Table 1. Baseline Demographic and Clinical Characteristics

Characteristics	D/C/F/TAF (n = 151)	DTG/ABC/3TC (n = 155)
Median age, years	34 (27–41)	36 (31–43)
Sex (n, %)		
Women	5 (3%)	13 (8%)
Men	146 (97%)	142 (92%)
Ethnic Origin (n, %)		
African	0 (0%)	9 (6%)
North African	2 (1%)	0 (0%)
Caucasian	95 (63%)	113 (73%)
Hispanic or Latino	54 (36%)	33 (21%)
Risk Practice (n, %)		
Homosexual sex	127 (84%)	115 (74%)
Heterosexual sex	16 (11%)	31 (20%)
Intravenous drug use	2 (1%)	2 (1%)
Others/Unknown	6 (4%)	7 (4%)
AIDS (opportunistic diseases) (n, %)	0 (0%)	0 (0%)
Median $CD4^+$ cell count ($\times 10E^6$/L)	420 (286–608)	383 (247–569)
$CD4^+$ Cell Count (n, %)		
$<200 \times 10^6$/L	17 (11%)	22 (14%)
$200–350 \times 10^6$/L	40 (26%)	44 (28%)
$>350 \times 10^6$/L	94 (62%)	89 (57%)
Median HIV-1 RNA (copies/mL)	63 096 (13 534–233 000)	65 900 (24 786–212 000)
HIV-1 RNA viral load (n, %)		
<100 000 copies/mL	91 (60%)	93 (60%)
≥100 000 copies/mL	60 (40%)	62 (40%)
Hepatitis C virus infection (n, %)	5 (3%)	5 (3%)
Median weight (kg)	73 (64–80)	72.8 (64.5–80)
Median body mass index (kg/m^2)	23.8 (21.8–26.3)	23.8 (22.0–26.1)

Abbreviations: AIDS, acquired immunodeficiency syndrome; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; HIV, human immunodeficiency virus; RNA, ribonucleic acid.

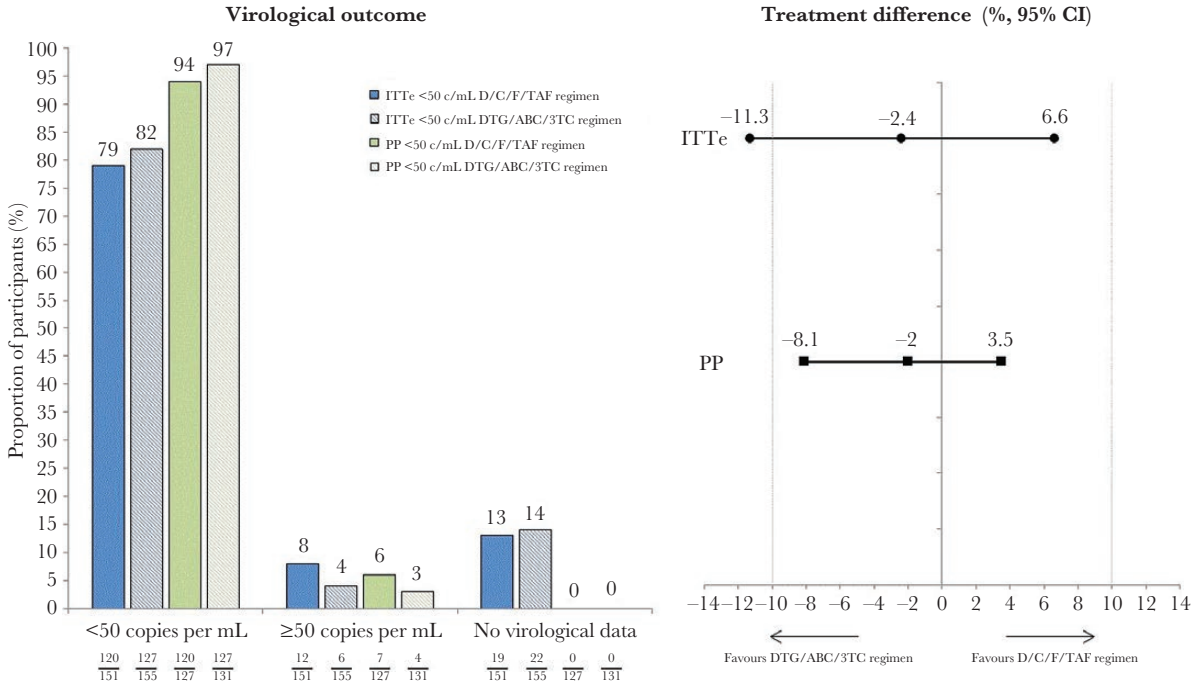

Figure 2. Virological outcome at week 48. CI, confidence interval; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; ITT, intention-to-treat.

Adverse events reported during the study period are detailed in Table 3. Of note, neuropsychiatric symptoms were more frequent in the DTG arm ($P = .005$). The frequency of drug discontinuation due to adverse events at 48 weeks was 4% (n = 6: 5 skin rashes, 1 pulmonary tuberculosis) in the D/C/F/TAF arm versus 6% (n = 9: 3 neuropsychiatric symptoms, 2 muscle complaints, 2 gastrointestinal disturbances, 1 skin rash, 1 neoplasm) in the DTG/ABC/3TC arm.

Regarding laboratory changes from baseline to 48 weeks, total and low-density lipoprotein cholesterol increased significantly more in the D/C/F/TAF arm (+0.71 vs +0.24 mmol/L [$P = .001$] and 0.52 vs 0.11 mmol/L [$P = .003$], respectively). No differences between the arms were found in high-density lipoprotein (HDL) and triglycerides, whereas a trend towards a higher total-to-HDL cholesterol ratio (0.01 vs −0.09, $P = .064$) was observed in the D/C/F/TAF arm. Significantly greater increases were observed in serum creatinine and glucose in the DTG/ABC/3TC arm (+11.49 vs +7.96 μmol/L [$P = .004$] and +0.17 vs −0.1 mmol/L [$P = .021$], respectively). No significant differences were found in CD4 cell counts (+226 vs +260/μL, $P = .10$), weight (+3.0 vs +2.9 kg, $P = .8$) (Figure 5), or BMI (1.0 vs 0.96 kg/m^2, $P = .8$) changes between arms at 48 weeks

Table 2. Virological Outcomes at Week 48

Outcomes	D/C/F/TAF (n = 151)	DTG/ABC/3TC (n = 155)	Treatment Difference (95% CI)
HIV-1 RNA <50 copies/mL	120 (79.5%)	127 (81.9%)	−2.4% (−11.3 to 6.6)[a]
HIV-1 RNA ≥50 copies/mL			
HIV-1 RNA ≥50 copies/mL	7 (4.6%)	4 (2.6%)	
Discontinued due to lack of efficacy	0 (0%)	0 (0%)	
Discontinued due to other reasons and last available HIV-1 RNA ≥50 copies/mL	5 (3.3%)	2 (1.3%)	
No Virological Data			
Discontinued due to adverse events or death	6 (4%)	9 (5.8%)	
Discontinued due to other reasons and last available HIV-1 RNA <50 copies/mL	12 (8%)	13 (8.4%)	
Missing data but on study drug	1 (0.7%)	0 (0%)	

Abbreviations: CI, confidence interval; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; HIV, human immunodeficiency virus; RNA, ribonucleic acid.

[a]Difference in percentages of patients with HIV-1 RNA <50 copies/mL between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted for baseline HIV-1 RNA stratum (<100 000 vs ≥100 000 copies/mL) and baseline CD4 stratum (<200 vs ≥200 × 10^6cells/L).

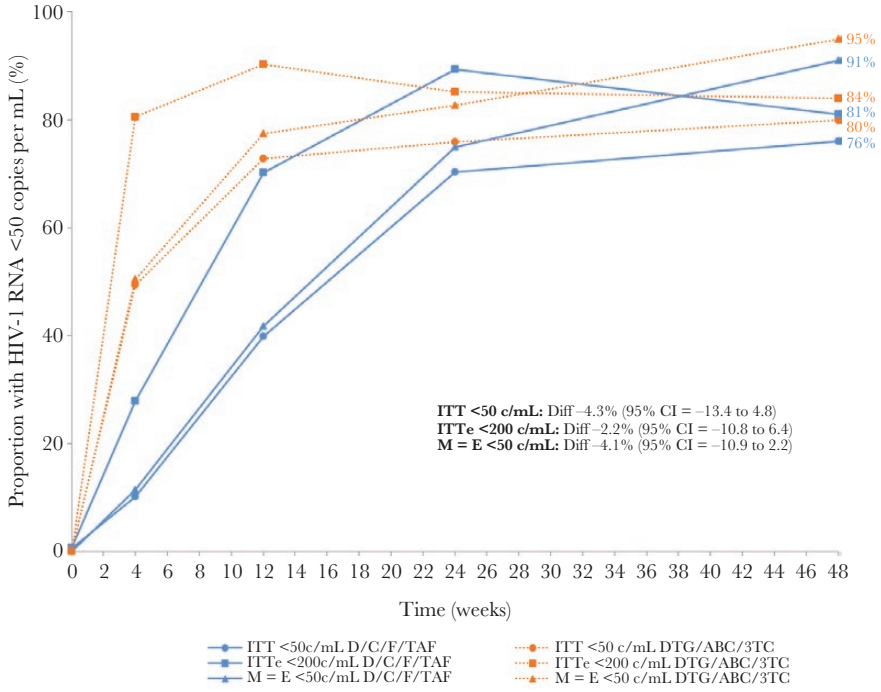

Figure 3. Human immunodeficiency virus (HIV)-1 ribonucleic acid (RNA) 50 or 200 ITT sensitivity analyses performed. CI, confidence interval; D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; ITT, intention-to treat; ITTe, ITT-exposed.

Regarding specific resistance-associated mutations (RAMs) to the study drugs at baseline, mutations were only detected using DSG in <5% of the circulating viral quasispecies. M184 I/V was found in 3 patients (2 in the DTG/ABC/3TC arm and 1 in the D/C/F/TAF arm). K65R was reported in only 1 participant (assigned to DTG/ABC/3TC). No RAMs affecting the activity of darunavir were found. A baseline integrase genotype was available in only 36 participants, and Y143H/C conferring resistance to RAL was reported in 3 patients, whereas S147G, N155H, and Q148H (affecting RAL and elvitegravir) were reported in a patient without RAMs to other ARV families who was randomized to D/C/F/TAF and had VL <50 copies/mL at week 48. No baseline RAMs had been found in the 11 patients who met the protocol-defined criteria for virological failure or were lost to follow-up. In 6 of these 11 patients, VL at failure was <200 copies/mL, with the result that resistance tests were not

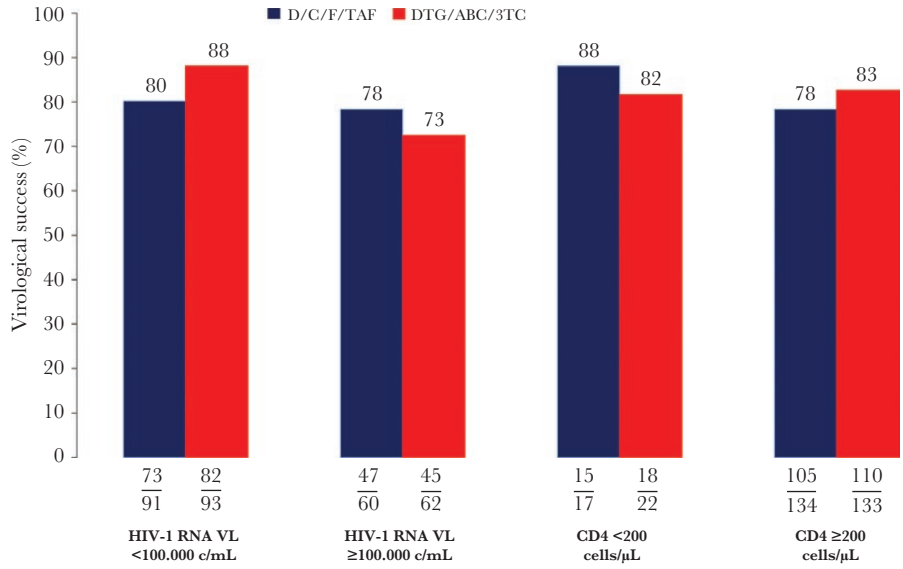

Figure 4. Percentage of patients with viral load <50 copies/mL according to baseline viral load and CD4 count cells. CI, confidence interval; HIV, human immunodeficiency virus; RNA, ribonucleic acid; ITTe, ITT-exposed.

Table 3. Adverse Events[a]

Adverse events	D/C/F/TAF (n = 151)	DTG/ABC/3TC (n = 155)
Any adverse event (n, %)	42 (28%)	35 (23%)
Drug-Related Adverse Event (n, %)	49 (32%)	66 (43%)
Digestive	24 (16%)	31 (20%)
Allergy	16 (11%)	10 (6%)
Neuropsychiatric*	13 (9%)	32 (21%)
Fatigue	10 (7%)	16 (10%)
Other	8 (5%)	5 (3%)
Adverse events leading to permanent discontinuation of treatment or withdrawal from study (n, %)	6 (4%)	9 (6%)

Abbreviations: D/C/F/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; HIV, human immunodeficiency virus; RNA, ribonucleic acid.

[a]Data are represented as number and percentage of positive cases (n, %). Diarrhea, dyspepsia, abdominal pain, constipation, lack of appetite, flatulence, dry mouth, pyrosis, and vomiting were reported as digestive adverse events. Allergy, exanthema, pruritic lesions, pruritus, and grade IV toxicoderma were reported as allergy adverse events. Anxiety, headache, depression, suicidal ideation, insomnia, dizziness, nightmare, concentration problems, and drowsiness were reported as neuropsychiatric adverse events. Arthralgia, arthromyalgia, asthenia, cramps, fatigue, muscle contracture, occasional dysesthesias, bone and muscle pain, fever, discomfort, myositis, paresthesia, and febrile syndrome were reported as bone and muscle and/or generalized discomfort adverse events. Dyslipidemia, weight gain, and transaminitis were reported as other adverse events.

*Significant differences were observed between study regimens for neuropsychiatric adverse events ($P = .005$).

performed. In 3 of 5 patients with VL >200 copies/mL at failure, RNA was amplified, and no RAMs were detected.

DISCUSSION

We performed the first head-to-head comparison of a single-pill regimen of D/C/F/TAF with a nonboosted integrase inhibitor-based regimen (DTG/ABC/3TC) and found that although differences in virologic efficacy were small, D/C/F/TAF did not meet the criterion for noninferiority to DTG/ABC/3TC in the primary endpoint (ITTe) or in the sensitivity ITT analyses. The main difference between the arms was in virologic failure, whereas the number of patients who discontinued the study prematurely due to adverse effects or loss to follow-up was similar between the arms, except for patients who did not return after the baseline visit (7 DRV/c vs 3 DTG). Neither severe toxicity nor resistance selection was seen in study participants.

The efficacy rates in both arms were lower than the expected 90% reported in previous trials conducted in treatment-naive patients with these regimens [4, 9]. The main reason for this was the higher-than-expected number of subjects discontinuing due to causes not related to adverse events or death in both study arms. The relatively high number of patients lost during the study period was related, at least in part, to the coronavirus disease 2019 lockdown and restrictions in Spain in the context of the severe acute respiratory syndrome coronavirus 2 pandemic, as observed in other trials performed during the same period [10]. However, despite the complex circumstances in which the study was conducted, follow-up was good in most cases, and we were eventually able to include 80% of patients in the per-protocol analysis.

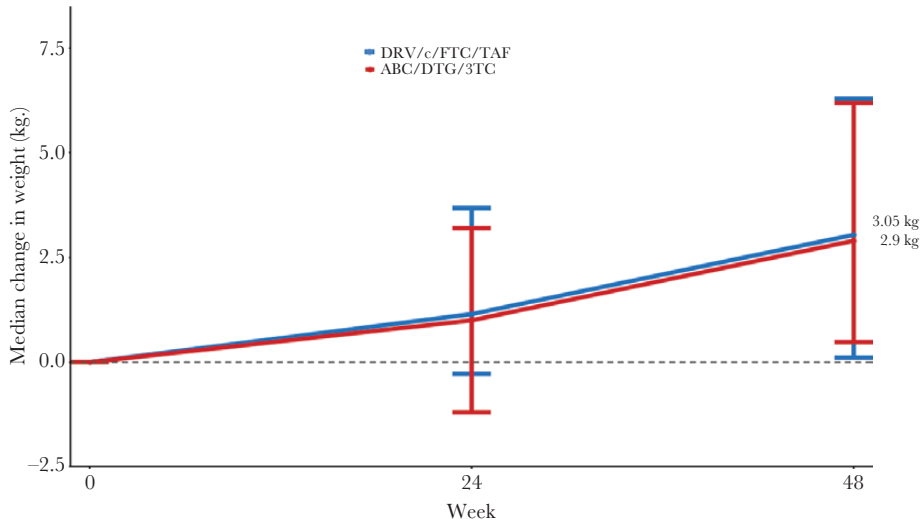

Figure 5. Change from baseline to week 48 in weight. DVR/c/FTC/TAF, darunavir/cobicistat/emtricitabine/tenofovir alafenamide; ABC/DTG/3TC, abacavir/dolutegravir/lamivudine.

Efficacy was approximately 80% for both treatments, and tolerability was similarly good. In addition, no resistance was detected in patients with virological failure. No significant differences were observed between the arms when virologic efficacy was assessed according to baseline VL or CD4 counts. Our results are in agreement with international ART guidelines in which DRV/c regimens are considered an alternative to unboosted integrase inhibitors, the preferred first-line regimens, as well as with findings from previous clinical trials comparing a boosted DRV regimen with an integrase inhibitor in ART-naive patients [5, 6]. This consideration may be expanded to a single-tablet regimen including TAF/FTC and darunavir/cobicistat.

In recent years, weight change has become a hot topic in the HIV field and has been assessed in several clinical trials and cohort studies [11–15]. Second-generation integrase inhibitors—with more data available for dolutegravir [15, 16]—and TAF have been related to increased weight [12, 17], both in ART-naive patients and in switching studies. However, data are controversial and some authors consider weight increase merely a return to normal health, whereas some studies have only found a difference in weight change between nonnucleoside reverse transcriptase inhibitors and integrase strand transfer inhibitor (INSTI) but not between PI and INSTI [11, 12].

It is interesting to note that we found both arms to be associated with the same weight change, supporting a return to normal weight in ART-naive patients initiating therapy, regardless of the given ART [12]. We have shown that the ART containing the booster did just as well as the nonboosted ART. Our data apply only to men of white ethnicity, because only 18 of the 306 participating patients were women. In addition, several studies have shown a more important impact of antiretroviral therapies on weight in women of black ethnicity [17].

Both regimens were well tolerated. Neuropsychiatric symptoms were more frequently reported in the DTG arm. Although such symptoms have not been reported previously in randomized clinical trials, several cohort studies and case series have highlighted this DTG-associated toxicity in routine clinical practice [18, 19], mainly in patients taking ABC concomitantly and in those with a history of neuropsychiatric symptoms. It is unfortunate that we did not collect prior neuropsychiatric history. The open-label design of our trial may have also influenced the reporting of these symptoms in patients taking DTG. Of note, in all patients discontinuing therapy in the D/C/F/TAF arm, the cause was skin rash, which was neither severe nor life-threatening in any case.

In the last years, data coming from the GEMINI study [20] showed that a dual combination of DTG + 3TC is noninferior to a triple drug regimen (DTG + TDF/3TC), and current international Guidelines [1–3] recommend this regimen as one of the preferred regimens for ARV-naive patients, with the exception of those with viral load >500 000 copies/mL and some caveats in patients with CD4 <200 cells/μL (IAS-USA Guidelines [2]). However, most of the preferred regimens still contain 3 drugs, and many physicians still continue to prescribe these regimens to a high number of ARV-naive patients, mainly to those with high viral loads and/or low CD4 counts.

Our study is subject to a series of limitations. The sample size was calculated expecting a 90% virologic efficacy rate as the primary outcome, although efficacy was slightly lower. Pill count, or more accurate methods, were not used to evaluate adherence (eg, the SMAQ questionnaire), and a difference in adherence between arms cannot be ruled out, despite not being expected in a randomized trial with single-tablet regimens in each arm. Finally, because only 6% of participating patients were women, our results cannot be extrapolated to women. In recent years, the number of antiretroviral-naive women in Spain has been very small [21], because most individuals newly infected by HIV are men who have sex with men. In addition, given the results of the TSEPAMO trial at the time the study was designed, some investigators may not have wanted to enroll women owing to the warning against DTG in women of reproductive age [22].

CONCLUSIONS

In summary, D/C/F/TAF was not noninferior to DTG/ABC/3TC in this randomized open-label clinical trial. Both regimens had a high efficacy rate, good tolerability, and a similar increase in CD4 counts, weight, and BMI, and no resistance was detected in the few patients with virological failure in whom genotyping tests could be performed.

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