

A Randomized, Open-Label Trial to Evaluate Switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Plus Darunavir in Treatment-Experienced HIV-1-Infected Adults

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Background: HIV-infected, treatment-experienced adults with a history of prior resistance and regimen failure can be virologically suppressed but may require multitablet regimens associated with lower adherence and potential resistance development.

Methods: We enrolled HIV-infected, virologically suppressed adults with 2-class to 3-class drug resistance and at least 2 prior regimen failures into this phase 3, open-label, randomized study. The primary endpoint was the percentage of participants with HIV-1 RNA <50 copies per milliliter at week 24 [Food and Drug Administration (FDA) snapshot algorithm].

Results: For 135 participants [elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) plus darunavir (DRV), n = 89;

baseline regimen, n = 46], most of whom were taking a median of 5 tablets/d, simplification to E/C/F/TAF plus DRV was noninferior to continuation of baseline regimens at week 24 (plasma HIV-1 RNA <50 copies per milliliter: 96.6% vs. 91.3%, difference 5.3%, 95.001% CI: -3.4% to 17.4%). E/C/F/TAF plus DRV met prespecified criteria for noninferiority and superiority at week 48 for the same outcome. E/C/F/TAF plus DRV was well tolerated and had an improved renal safety profile compared with baseline regimens, with statistically significant differences between groups in quantitative total proteinuria and markers of proximal tubular proteinuria. Compared with baseline regimens, participants who switched to E/C/F/TAF plus DRV reported higher mean treatment satisfaction scale total scores and fewer days with missed doses.

Conclusions: This study demonstrated that regimen simplification from a 5-tablet regimen to the 2-tablet, once-daily combination of E/C/F/TAF plus DRV has durable maintenance of virologic suppression and improvements in specific markers of renal safety. Such a strategy may lead to greater adherence and improved quality of life.

Key Words: HIV, regimen simplification, tenofovir alafenamide, darunavir

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INTRODUCTION

Morbidity and mortality in HIV infection have dramatically improved after the introduction of antiretroviral therapy (ART),^{1–3} even among patients with extensive treatment experience and multiclass drug resistance.⁴ With the approval of new drugs, particularly the integrase strand transfer inhibitors (INSTIs) and more potent protease inhibitors (PIs) [ie, darunavir (DRV)], construction of fully suppressive “salvage” regimens, containing at least 2 effective drugs from different classes, was possible.⁵ Despite these advances, “salvage” regimens are often complicated regimens with high pill burden, high dosing frequency, and/or dietary restrictions, factors resulting in higher cost, more side effects, poorer quality of life, and greater risk for nonadherence that may lead to virologic failure and accumulation of additional drug resistance.^{4,6} Current treatment guidelines recommend

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regimen simplification to maintain viral suppression if future treatment options are not compromised,^{7,8} but simplification is challenging in treatment-experienced patients with a history of drug resistance. Newer combination tablets enable simplification of these regimens; however, concerns of potential drug interactions in the absence of pharmacokinetic (PK) and pharmacodynamic data have limited their use.⁹

The single-tablet coformulation of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) has demonstrated high efficacy and improved renal and bone safety compared with tenofovir disoproxil fumarate (TDF)-containing regimens in phase 3 clinical trials of HIV-infected participants.^{10–12} E/C/F/TAF has been approved by the United States (US) Food and Drug Administration (FDA), European Medicines Agency, and other health authorities for treatment of naïve and stably suppressed patients age 12 and older and is one of the recommended initial regimens in guidelines in the USA and in Europe.^{13–17} DRV is a recommended protease inhibitor with a high genetic barrier to resistance, well-established safety profile at a once-daily dose in treatment-experienced patients without DRV-associated resistance mutations, and can be boosted by either ritonavir or cobicistat.^{18,19} The 2-tablet, once-daily combination of E/C/F/TAF plus DRV may be an effective treatment option in select treatment-experienced patients with multiclass resistance. The goal of our phase 3, open-label, randomized trial (GS-US-292-0119) was to evaluate the efficacy, safety, and PK parameters of switching virologically suppressed participants with a history of treatment failure to a 2-tablet, once-daily antiretroviral regimen combining E/C/F/TAF plus DRV. We report results through week 48.

METHODS

Study Design and Participants

We enrolled participants into this phase 3, open-label, randomized trial at 62 academic, private practice, and community health centers in the USA and Canada between September 2013 and September 2014 (Study Protocol available in Supplemental Digital Content 1, <http://links.lww.com/QAI/A932>). Eligible participants were HIV-infected adults (aged ≥ 18 years) who were virologically suppressed (plasma HIV-1 RNA < 50 copies per milliliter) on a current antiretroviral regimen containing DRV boosted by ritonavir (600/100 mg twice daily or 800/100 mg once daily) continuously for at least 4 months before screening. Treatment history included failing at least 2 prior antiretroviral regimens and confirmed resistance by historical genotype to at least 2 different classes of antiretrovirals. Participants must have had no history of integrase inhibitor resistance or be INSTI naïve, or be currently suppressed on the following INSTIs [raltegravir, elvitegravir, or dolutegravir (50 mg once daily, but not twice daily)]. We allowed a history of up to 3 thymidine analogue mutations and/or K65R, but no history of Q151M or T69 insertion mutations. Eligible participants could not have any DRV-associated resistance mutations, including V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, and L89V. The Stanford HIVdb algorithm v8.01 was used to calculate genotypic susceptibility scores (GSS). For each

drug, a 5-point scale was used: susceptible, potential low-level resistance, low-level resistance, intermediate-level resistance, and high-level resistance were scored as 1, 0.75, 0.5, 0.25, and 0, respectively. The total genotypic susceptibility scores for a given regimen were calculated as the sum of the scores for each individual drug. Participants had an estimated glomerular filtration rate (eGFR) by the Cockcroft-Gault formula of at least 50 mL/min.

We randomized participants in a 2:1 ratio using an interactive voice/web response system to switch to coformulated E/C/F/TAF 150/150/200/10 mg (Gilead Sciences, Foster City, CA) plus DRV 800 mg (Janssen) once daily or to stay on their baseline regimen. E/C/F/TAF plus DRV was supplied by Gilead; participants who continued their baseline regimen obtained treatment by prescription.

This study was conducted in accordance with the Declaration of Helsinki. Central or site-specific institutional review boards or ethics committees reviewed and approved the protocol. We obtained written informed consent from all participants before screening. This study was registered with ClinicalTrials.gov (Identifier NCT01968551).

Procedures

Randomized participants were seen at screening, baseline, weeks 2, 4, 8, 12, 16, 24, 36, 48, and every 12 weeks thereafter. Laboratory tests included hematological analysis, serum chemistry tests, fasting lipid parameters, CD4 counts, measures of renal function [eGFR by Cockcroft-Gault, urine protein-to-creatinine ratio, retinol binding protein-to-creatinine ratio, beta-2-microglobulin-to-creatinine ratio (Covance Laboratories, Indianapolis, IN)], and measurement of HIV RNA concentration (Roche TaqMan 2.0; Roche Diagnostics, Rotkreuz, Switzerland). Fasting lipid parameters were not measured in this study. Participants with confirmed virologic rebound (HIV-1 RNA ≥ 400 copies per milliliter) had confirmatory samples sent for resistance analysis by GeneSeq Integrase, PhenoSense GT, and PhenoSense Integrase (Monogram Biosciences, South San Francisco, CA). Patient-reported outcomes included validated instruments such as visual analog scale adherence and HIV-treatment satisfaction questionnaires.^{20–22}

For those receiving E/C/F/TAF plus DRV who agreed to participate, we performed an intensive PK substudy (sample collection predose up to 24 hours postdose at weeks 2, 4, or 8) to assess plasma concentrations of select analytes using fully validated high-performance liquid chromatography–tandem mass spectroscopy bioanalytical methods (Quest Pharmaceutical Services LLC, Newark, DE).

Statistical Analysis

The primary efficacy endpoint was the percentage of participants with HIV-1 RNA < 50 copies per milliliter at week 24 using the US FDA-defined snapshot algorithm^{23,24} using the full analysis set (all randomized participants who received at least one dose of study drug). We planned to randomize 100 participants to E/C/F/TAF plus DRV and 50 to remain on their baseline regimen, resulting in 53% power to show switching to E/C/F/TAF plus DRV was noninferior to remaining on baseline regimens with respect to the primary

endpoint. We assessed noninferiority of E/C/F/TAF plus DRV vs. baseline regimens using a 2-sided exact 95% confidence interval (CI) approach (alpha level of 0.025), with a prespecified margin of 12%. Because an alpha of 0.00001 was spent on interim analyses at week 12, the significance level for the 2-sided test was adjusted to 0.04999 (corresponding to 95.001% CI). We estimated the exact CI based on unconditional exact methods using 2 inverted one-sided tests with the standardized statistic and calculated the *P*-value using Fisher's exact test. We also performed a secondary per-protocol analysis (full analysis set excluding those who had any major protocol violation). Secondary efficacy endpoints included the percentage of participants with HIV-1 RNA <50 copies per milliliter at week 48 using the US FDA-defined snapshot algorithm and the change from baseline in CD4 cell count at weeks 24 and 48. We conducted prespecified subgroup analyses for virologic response at weeks 24 and 48 to assess treatment differences by age, sex, and race.

We used descriptive statistics for the safety analysis set, which included all who received at least one dose of study drug. Adverse events were coded with the Medical Dictionary for Regulatory Activities (version 18.0). We evaluated change from baseline in eGFR (Cockcroft-Gault), retinol binding protein-to-creatinine ratio, and beta 2 microglobulin-to-creatinine ratio and used the 2-sided Wilcoxon rank-sum test to compare the 2 groups. We compared percent change from baseline in urine protein-to-creatinine ratio between the 2 groups, adjusting for baseline value using rank analysis of covariance.

For the PK analyses, we used descriptive statistics to summarize plasma concentrations and calculated geometric mean (95% CI) and mean (SD) of select natural log-transformed PK parameters.

We compared HIV treatment satisfaction total scores at weeks 24 and 48 between the 2 groups using an ANCOVA model, adjusting for baseline score.

RESULTS

Of the 199 screened participants, 135 enrolled and received at least one dose of study drug (89 randomized to switch to E/C/F/TAF plus DRV, 46 randomized to remain on their baseline regimen) (Fig. 1). Fewer participants in the E/C/F/TAF plus DRV group prematurely discontinued study drug compared with the baseline regimen group (2% vs. 11%).

Baseline demographic and antiretroviral regimen characteristics are shown in Table 1. Although overall most participants were men (75%) and white (50%), women (25%) and black (45%) participants were well represented. Compared with the baseline regimen group, more men (E/C/F/TAF plus DRV, 82% vs. baseline regimen, 61%) and fewer black participants (E/C/F/TAF plus DRV, 39% vs. baseline regimen, 57%) were randomized to the E/C/F/TAF plus DRV group. The median age was 49 years (range, 23–70 years). Comorbid conditions included hyperlipidemia (40%), hypertension (35%), diabetes mellitus (9%), and cardiovascular disease (6%). At baseline, participants were taking a median of 5 tablets per day (range, 2–10 tablets per day). Thirty-nine percent of participants were taking 6 or more tablets per day; 65% were taking at least one antiretroviral medication twice daily with 37% taking DRV twice daily. Overall, 59% of participants were on a TDF-based regimen, 11% on an abacavir-based regimen, and 57% on an integrase inhibitor. The distribution of genotypic susceptibility scores at study entry was similar across treatment groups.

All participants had at least 2-class genotypic resistance per eligibility criteria, the most prevalent being M184V/I for 95% of participants with nucleoside reverse transcriptase inhibitor mutations and K103N/S for 88% of participants with nonnucleoside reverse transcriptase inhibitor resistance-associated mutations (Supplemental Digital Content, Table 1, <http://links.lww.com/QAI/A932>). The tenofovir signature mutation K65R was present at 20% and 30% in the E/C/F/TAF plus DRV and baseline regimen

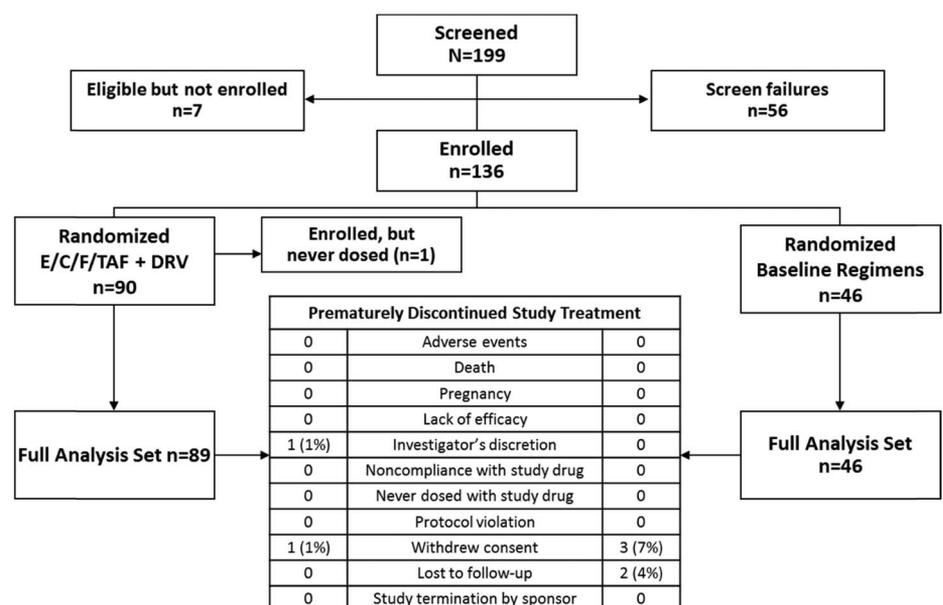


FIGURE 1. Consort flow diagram.

TABLE 1. Baseline Demographic and Antiretroviral Regimen Characteristics

	E/C/F/TAF + DRV (n = 89)	Baseline Regimens (n = 46)
Baseline characteristics		
Age, median (range), yrs	49 (29–70)	47 (23–64)
Male, n (%)	73 (82)	28 (61)
Black (or African descent), n (%)	35 (39)	26 (57)
CD4 count, median (range), cells/ μ L	519	518
eGFR by Cockcroft-Gault, median (range), mL/min	99	100
Comorbidities, n (%)		
Diabetes mellitus	7 (8)	5 (11)
Hypertension	30 (34)	17 (37)
Cardiovascular disease	6 (7)	2 (4)
Hyperlipidemia	41 (46)	13 (28)
Antiretroviral Regimen History		
No. pills per day, median (range)	5	5
≥ 6 pills per day, n (%)	36 (40)	17 (37)
At least twice-daily dosing, n (%)	58 (65)	30 (65)
Prior regimens containing, n (%)		
TDF	54 (61)	25 (54)
ABC	10 (11)	5 (11)
Other NRTIs	11 (12)	6 (13)
Resistance history		
2-class resistance, n (%)	62 (70)	34 (74)
3-class resistance, n (%)	23 (26)	9 (20)
M184V/I, n (%)	76 (85)	36 (78)
K65R, n (%)	18 (20)	14 (30)
NNRTI-R, n (%)	79 (89)	40 (87)
PI-R, n (%)	34 (38)	13 (28)
TAM, n (%)	39 (44)	18 (39)
GSS at study entry (mean)	2.45	2.56

ABC, abacavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; R, resistant; TAM, thymidine analogue mutation; TDF, tenofovir disoproxil fumarate.

groups. Participants with thymidine analogue mutations (up to 3) represented 44% and 39% of the E/C/F/TAF plus DRV and baseline regimen groups, respectively (Table 1).

Pharmacokinetics

Fifteen participants who received E/C/F/TAF plus DRV participated in the PK substudy. Mean steady-state trough plasma concentrations (C_{trough}) for elvitegravir (464 ng/mL) and DRV (1250 ng/mL) were >10 -fold and >22 -fold higher than the protein-adjusted IC_{95} value of elvitegravir (45 ng/mL) and protein adjusted EC_{50} value for DRV for virus with no DRV resistance-associated mutations (55 ng/mL), respectively (Fig. 2). Plasma exposure of TAF (mean AUC of 89.9 ng·h·mL⁻¹) was within the range of safe and efficacious TAF exposure established in the phase 3 pivotal E/C/F/TAF studies (mean AUC_t 47.2–1869.3 ng·h·mL⁻¹). Consistent with findings from the phase 3 pivotal E/C/F/TAF vs. E/C/F/TDF studies, the plasma tenofovir exposure in the current

study after administration of E/C/F/TAF plus DRV (mean AUC: 367 ng·h·mL⁻¹) was markedly lower than the tenofovir exposure after administration of E/C/F/TDF. The primary PK parameters for elvitegravir, DRV, cobicistat, TAF, and its metabolite tenofovir are presented in Supplemental Digital Content, Table 2, <http://links.lww.com/QAI/A932>.

Efficacy

E/C/F/TAF plus DRV was noninferior to baseline regimens for the primary outcome (HIV-1 RNA <50 copies per milliliter at week 24; FDA-snapshot algorithm) using the full analysis set (96.6% vs. 91.3%; difference 5.3%; 95.001% CI: -3.4% to 17.4%) (Fig. 3). Virologic success rates at week 24 using the per-protocol analysis set were consistent with the full analysis set (97.6% vs. 100.0%; difference -2.4%; 95.001% CI: -8.6% to 5.9%). At week 48, E/C/F/TAF plus DRV met the prespecified criteria for noninferiority and superiority using the full analysis set (94.4% vs. 76.1%, difference 18.3%; 95.001% CI: 3.5% to 33.0%) (Fig. 2), with consistent results using the per-protocol analysis set (97.6% vs. 85.4%; difference 12.3%; 95.001% CI: 1.8% to 26.4%). Through week 48, no participants discontinued because of lack of efficacy. Seven participants discontinued (E/C/F/TAF plus DRV, n = 2; baseline regimen, n = 5) because of investigator's discretion (n = 1 on E/C/F/TAF plus DRV), lost to follow-up (n = 2 on baseline regimen), or withdrawal of consent (n = 4; 1 on E/C/F/TAF plus DRV, 3 on baseline regimen). Virologic failure and treatment discontinuation (because of withdrawal of consent or loss to follow-up) contributed to the lower percentage of virologic success in the baseline regimen group, with each factor accounting for 11% of participants. CD4 cell counts remained stable through week 48 in both groups, with a mean (SD) change from baseline at week 48 of 5 (162.6) cells per microliter for E/C/F/TAF plus DRV and 41 (104.2) cells per microliter for baseline regimens ($P = 0.21$).

No differences in virologic success at week 24 were seen in the predefined subgroups of age, sex, and race; however, at week 48, virologic success was higher for the E/C/F/TAF plus DRV-treated participants aged <50 years (difference 22.5%, 95% CI: 3.6% to 43.6%) and male (difference 15.9%, 95% CI: 1.5% to 35.0%) (Supplemental Digital Content, Fig. 1, <http://links.lww.com/QAI/A932>).

Resistance

Because no participants in the E/C/F/TAF plus DRV group had confirmed virologic rebound with HIV-1 RNA >400 copies per milliliter through week 48, none were tested for resistance. One participant in the baseline regimen group, on raltegravir, ritonavir-boosted DRV, and etravirine, had viral rebound (week 36) and was tested for resistance. Historical genotyping confirmed 2-class resistance, with PR (L10V, M36I) and RT (D67N, K70R, K103N, Y181I, T215Y) mutations. Resistance results showed newly detected resistance mutations (K65R and M184V); these resistance mutations were likely preexisting as this participant had a history of treatment with TDF and emtricitabine.

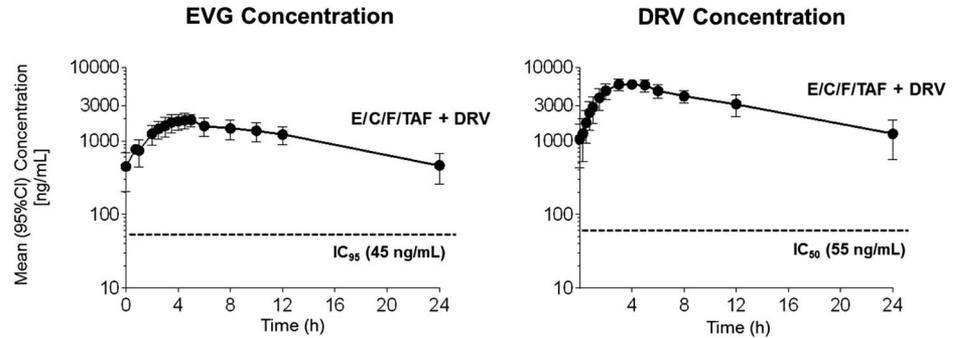


FIGURE 2. Pharmacokinetic substudy results (N = 15).

Safety

Participants in the E/C/F/TAF plus DRV group had a higher rate of any adverse events [92% (n = 82) vs. 78% (n = 36)]. Most adverse events were mild or moderate in severity, and no participants discontinued study drug because of an adverse event. The most commonly reported adverse events ($\geq 5\%$) were back pain and upper respiratory tract infection [10% (n = 9) each] and bronchitis [8% (n = 7)] for E/C/F/TAF plus DRV and diarrhea [9% (n = 4)] and back pain, cough, influenza-like illness, musculoskeletal pain, and sinusitis [7% (n = 3) each] for baseline regimens. Ten percent of participants (n = 9) in the E/C/F/TAF plus DRV and 2% (n = 1) in the baseline regimen group had a serious adverse event (Supplemental Digital Content, Table 3, <http://links.lww.com/QAI/A932>), none of which was related to study drug. A similar percentage of participants in each treatment group had grade 3 or 4 laboratory abnormalities [E/C/F/TAF plus DRV, 11% (n = 10); baseline regimens, 9% (n = 4)]. No treatment-related deaths occurred; 1 participant (E/C/F/TAF plus DRV group) with diffuse large B cell lymphoma died of sepsis. Two participants (2%) in the E/C/F/TAF plus DRV group and 1 participant (2%) in the baseline regimen group had traumatic fractures, considered unrelated to study drug.

Renal Safety

No participants had any serious renal adverse event nor discontinued study drugs because of a renal adverse event; no participant developed proximal renal tubulopathy. There were no differences between the 2 groups in median changes from

baseline in eGFR (week 48: +7.4 mL/min vs. +3.9 mL/min; $P = 0.18$). Participants in the E/C/F/TAF plus DRV group had statistically significant declines in both measures of quantitative proteinuria (urine protein-to-creatinine ratio) and tubular proteinuria (retinol binding protein-to-creatinine ratio and beta 2 microglobulin-to-creatinine ratio) at week 48 vs. increases in the baseline regimen group (Fig. 4).

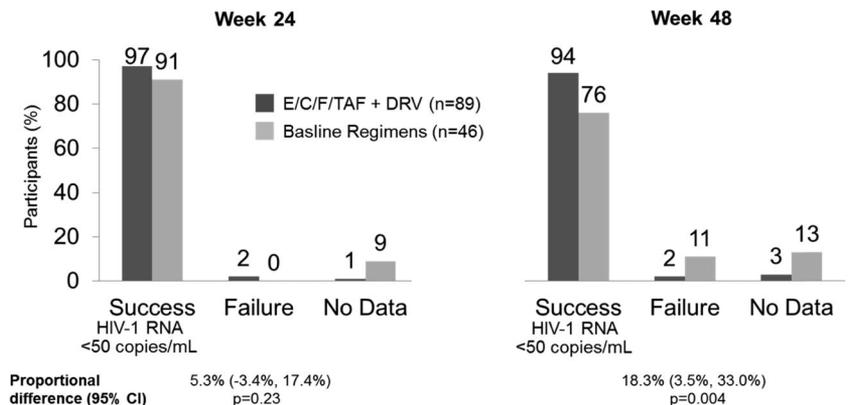
Patient-Reported Outcomes

Although both arms showed improved patient-reported outcome scores, participants in the E/C/F/TAF plus DRV group reported statistically significantly higher mean HIV treatment satisfaction total scores at weeks 24 and 48 (Fig. 5) and answered questions specific to the flexibility or convenience of and the patient’s satisfaction with the treatment more favorably. Based on the visual analog scale adherence questionnaire, participants on E/C/F/TAF plus DRV consistently reported fewer days with missed doses, whereas those on their baseline regimen reported a higher number of days with missed doses as the study progressed: more participants in the E/C/F/TAF plus DRV group reported <2 days with missed doses in the 30 days before week 24 (90% vs. 74%) or 48 (86% vs. 59%) and no days with missed doses in the 4 days before weeks 24 (98% vs. 83%) or 48 (99% vs. 73%).

DISCUSSION

This was the first randomized trial of a simplified, 2-tablet, once-daily regimen combining a boosted protease inhibitor with

FIGURE 3. Virologic outcome at weeks 24 and 48. At week 48, all virologic failure was due to plasma HIV-1 RNA ≥ 50 copies/mL. One participant in the baseline regimens group had confirmed viral rebound (HIV-1 RNA > 400 copies/mL). The remaining participants had subsequent plasma HIV-1 RNA < 50 copies/mL.



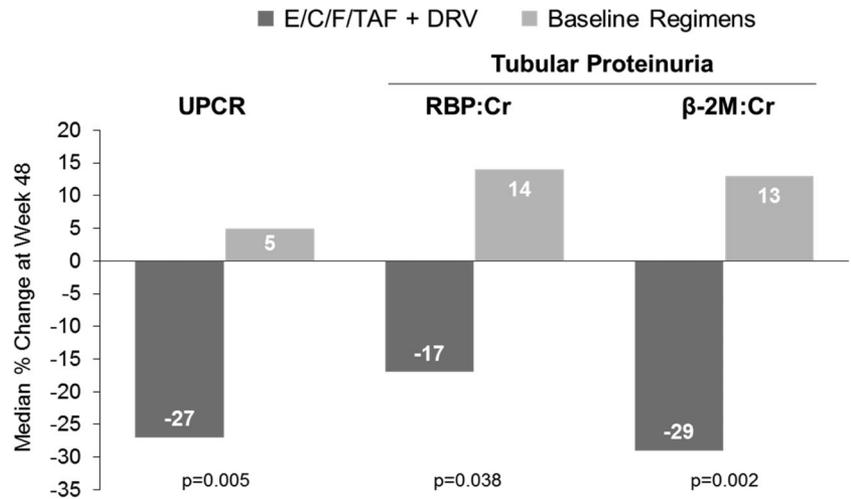


FIGURE 4. Renal safety: urine protein-to-creatinine ratios. Differences between treatment groups in changes in quantitative total proteinuria (UPCR) and in specific markers of proximal tubular proteinuria (RBP:Cr and β-2M:Cr) were statistically significant, favoring E/C/F/TAF + DRV.

an integrase inhibitor and 2 nucleoside reverse transcriptase inhibitors in virologically suppressed, treatment-experienced adults with 2-class to 3-class drug resistance. Overall, steady-state plasma exposure for the components of E/C/F/TAF and DRV was within the safe and efficacious ranges of these analytes. Importantly, PK results of this study demonstrated that the pharmacodynamic (“boosting”) effect of cobicistat on elvitegravir and DRV was maintained upon coadministration of E/C/F/TAF plus DRV, yielding trough concentration levels 10-fold to 22-fold greater than inhibitory and effective concentration thresholds for adequate elvitegravir and DRV antiviral activity.

Treatment with E/C/F/TAF plus DRV resulted in high rates of virologic suppression. E/C/F/TAF plus DRV was noninferior to continuing on baseline regimens at week 24 and met prespecified criteria for noninferiority and superiority at week 48. No participant discontinued because of lack of efficacy. Virologic failure and treatment discontinuation (because of withdrawal of consent or loss to follow-up) contributed to the lower percentage of virologic success in the baseline regimen group. At week 48, E/C/F/TAF plus DRV was superior for the subgroups of participants either aged

<50 years or male; more men were randomized to the E/C/F/TAF plus DRV group than to the baseline regimen group. No new virologic resistance was detected among participants who switched to E/C/F/TAF plus DRV.

Treatment with E/C/F/TAF plus DRV was well tolerated. Participants in the E/C/F/TAF plus DRV group reported a higher rate of adverse events, which was not unexpected for individuals initiating a novel therapy in comparison with those continuing their well-tolerated baseline regimen in an open-label study. Indeed, as assessed by a validated survey tool, although treatment satisfaction was evenly matched between randomized groups at baseline, satisfaction improved among participants who switched to E/C/F/TAF plus DRV. This observation underscores that, for a population with extensive ART experience including prior complicated regimens, there is an unmet need for more convenient treatment options. Simplified regimens improve adherence, as demonstrated in the current study in which participants who switched to E/C/F/TAF plus DRV consistently reporting fewer days with missed doses and greater virologic success at 48 weeks than those remaining on their baseline regimens.

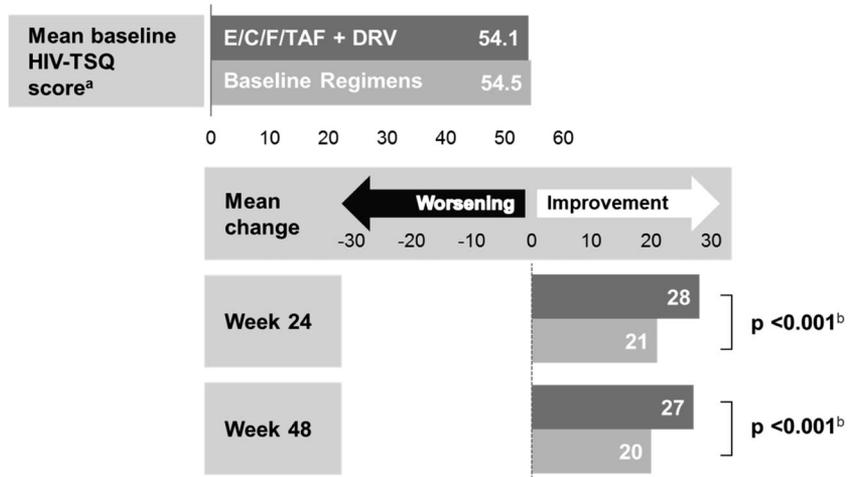


FIGURE 5. Overall HIV treatment satisfaction (HIV-TSQ). ^aANCOVA HIV-TSQ at baseline 0–6 response range, n = 10 questions, higher score = better satisfaction in recent weeks; HIV-TSQ (change) post-baseline: –3–3 response range, higher–better satisfaction. ^bFrom ANCOVA model (treatment as fixed effect; baseline total HIV-TSQ score as covariate).

Long-term safety considerations are an important element in antiretroviral simplification strategies. Proteinuria and specifically proximal tubular proteinuria have been shown to increase risk of mortality or cardiovascular events in both the general population and in HIV-infected individuals.^{25–27} Upon entry into the current study, most participants were receiving regimens containing TDF. Switching to a regimen containing TAF improved glomerular and tubular function, including decreases in overall and tubular proteinuria, consistent with results of other TDF to TAF switch studies.^{11,12,28} Tenofovir (but not TAF) is actively transported from the blood into renal proximal tubule cells by the organic anion transporters (OAT) 1 and OAT3, resulting in tenofovir accumulation in the proximal tubule.^{29,30} The marked (>90%) reduction in circulating tenofovir after switching to TAF is likely the reason for the improvements in clinical renal toxicity compared with continuing on TDF.¹⁰ Participants in our study were representative of the treatment-experienced population who started treatment before the HAART era, with a median age of 49 years, approximately 15 years older than in treatment-naïve trials,¹⁰ and high rates of comorbid conditions, including hyperlipidemia, hypertension, diabetes mellitus, and cardiovascular disease. This improved renal safety profile is important in a population of treatment-experienced individuals, who are likely to be older and have more cardiovascular and renal risk factors than a naïve population.

Limitations to this study include the open-label study design; as such, between-group differences in adverse events and subjective safety reports should be interpreted with caution. More robust reporting of adverse events for the experimental arm (E/C/F/TAF plus DRV) may have occurred in this open-label trial. In addition, approximately one-fourth of participants who switched to E/C/F/TAF plus DRV were newly exposed to a new drug class (INSTI), which may have also contributed to additional reporting of adverse events in this group. Another limitation of our study is the relatively small sample size and hence the inability to control for potential imbalance of important factors, such as comorbidities, impacting safety outcomes between the 2 arms. Participants who switched to E/C/F/TAF plus DRV received drugs provided by Gilead; those who continued their baseline regimen obtained treatment by prescription. This difference in study drug supply might have contributed to the difference in the rates of early discontinuation of study drugs. Because this study excluded participants with DRV mutations or more than 3 thymidine analogue mutations, results should not be extrapolated to such individuals.

Our study provides important guidance for the management of treatment-experienced individuals with multiclass resistance who have traditionally required multi-tablet “salvage” regimens to maintain virologic suppression. Single-tablet regimens have generally been options only for treatment-naïve individuals or those switching therapy without a history of prior resistance. Strategic regimen simplification to the 2-tablet, once daily combination E/C/F/TAF plus DRV was noninferior at 24 weeks and virologically superior at 48 weeks, to remaining on baseline regimens, and was associated with greater patient satisfaction and adherence.

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REFERENCES

1. Palella FJ Jr, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr*. 2006;43:27–34.
2. Lee LM, Karon JM, Selik R, et al. Survival after AIDS diagnosis in adolescents and adults during the treatment era, United States 1984–1997. *JAMA*. 2001;285:1308–1315.
3. Valdez H, Chowdhry TK, Asaad R, et al. Changing spectrum of mortality due to human immunodeficiency virus: analysis of 260 deaths during 1995–1999. *Clin Infect Dis*. 2001;32:1487–1493.
4. Lucas G. Antiretroviral adherence, drug resistance, viral fitness and HIV disease progression: a tangled web is woven. *J Antimicrob Chemother*. 2005;55:413–416.
5. Taiwo B, Murphy RL, Katlama C. Novel antiretroviral combinations in treatment-experienced patients with HIV infection. *Drugs*. 2010;70:1629–1642.
6. Imaz A, Falcó V, Ribera E. Antiretroviral salvage therapy for multiclass drug-resistant HIV-1-infected patients: from clinical trials to daily clinical practice. *AIDS Rev*. 2011;13:180–193.
7. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected adults and Adolescents: Department of Health and Human Services; Washington, DC: 2016. Available at: <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed April 15, 2016.
8. European AIDS Clinical Society (EACS). *Guidelines Version 8.0 (English)*; 2015. Available at: http://www.eacsociety.org/files/2015_eacsguidelines_8_0-english_rev-20160124.pdf. Accessed April 15, 2016.
9. Ricard F, Wong A, Lebouché B, et al. Low darunavir concentrations in patients receiving Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) and darunavir once daily. Poster presented at: 16th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy; May 26–28, 2015; Washington, DC.
10. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385:2606–2615.
11. Wohl D, Oka S, Clumeck N, et al. Brief report: a randomized, double-blind comparison of tenofovir alafenamide versus tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine for initial HIV-1 treatment: week 96 results. *J Acquir Immune Defic Syndr*. 2016;72:58–64.
12. Mills A, Arribas JR, Andrade-Villanueva J, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis*. 2016;16:43–52.
13. Rivero A, Pulido F, Caylá J, et al; Grupo de Estudio de Sida (GESIDA); Secretaría del Plan Nacional sobre el Sida. The Spanish AIDS Study Group and Spanish National AIDS Plan (GESIDA/Secretaría del Plan Nacional sobre el Sida) recommendations for the treatment of tuberculosis in HIV-infected individuals (Updated January 2013) [in Spanish]. *Enferm Infecc Microbiol Clin*. 2013;31:672–684.
14. Ministry of Health, National Committee on AIDS – Commissione Nazionale per la lotta contro l’AIDS, Linee Guida Italiane sull’utilizzo dei farmaci antiretrovirali e sulla gestione diagnosticoclinica delle persone con infezione da HIV-1, Ministero della Salute, luglio, December 2015 [in Italian]. Available at: http://www.salute.gov.it/imgs/C_17_publicazioni_2442_allegato.pdf. Accessed April 15, 2016.

15. Danish Society of Infectious Diseases. Antiviral behandling af HIV smittede personer, Odense C, DK, August 2015 [in Danish]. Available at: <http://www.inmed.dk/guidelines>. Accessed April 15, 2016.
16. Snopková S, Rozsypal H, Aster V, et al. Doporučený postup péče o dospělé infikované HIV a postexpoziční profylaxe infekce HIV. 2016.
17. DAIG Deutsche AIDS-Gesellschaft e.V. Deutsch-Österreichische Leitlinien zur antiretroviralen Therapie der HIV-Infektion, Version 6. Hamburg, DE. Dezember 2015 [in German]. Available at: <http://www.daignet.de/site-content/hiv-therapie/leitlinien-1>. Accessed April 15, 2016.
18. Mills A, Crofoot G Jr, McDonald C, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate in the first protease inhibitor-based single-tablet regimen for initial HIV-1 therapy: a randomized phase 2 study. *J Acquir Immune Defic Syndr*. 2015;69:439–445.
19. Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet*. 2007;369:1169–1178.
20. Kalichman SC, Amaral CM, Swetzes C, et al. A simple single item rating scale to measure medication adherence: further evidence for convergent validity. *J Int Assoc Physicians AIDS Care (Chic)*. 2009;8:367–374.
21. Woodcock A, Bradley C. Validation of the HIV treatment satisfaction questionnaire (HIVTSQ). *Qual Life Res*. 2001;10:517–531.
22. Amico KR, Fisher WA, Cornman DH, et al. Visual analog scale of ART adherence: association with 3-Day self-report and adherence barriers. *J Acquir Immune Defic Syndr*. 2006;42:455–459.
23. Smith F, Hammerstorm T, Soon G, et al. A meta-analysis to assess the FDA DAVP's TLOVR algorithm in HIV submissions. *Drug Inf J*. 2011;45:291–300.
24. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). *Guidance for Industry Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment (Revision 1)*; 2015;1–43. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM355128.pdf>. Accessed April 15, 2016.
25. George E, Lucas GM, Nadkarni GN, et al. Kidney function and the risk of cardiovascular events in HIV-1 infected patients. *AIDS*. 2010;24:387–394.
26. Currie G, Delles C. Proteinuria and its relation to cardiovascular disease. *Int J Nephrol Renovasc Dis*. 2013;7:13–24.
27. Agrawal V, Marinescu V, Agarwal M, et al. Cardiovascular implications of proteinuria: an indicator of chronic kidney disease. *Nat Rev Cardiol*. 2009;6:301–311.
28. Gallant J, Brunetta J, Crofoot G, et al. Efficacy and safety of switching to a single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in HIV-1/hepatitis B coinfecting adults. *J Acquir Immune Defic Syndr*. 2016;73:294–298.
29. Ray AS, Cihlar T, Robinson KL, et al. Mechanism of active renal tubular efflux of tenofovir. *Antimicrob Agents Chemother*. 2006;50:3297–3304.
30. Bam RA, Yant SR, Cihlar T. Tenofovir alafenamide is not a substrate for renal organic anion transporters (OATs) and does not exhibit OAT-dependent cytotoxicity. *Antivir Ther*. 2014;19:687–692.