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Simplification of PI + RTV + FTC/TDF to E/C/F/TDF Maintains HIV Suppression and is Well-Tolerated

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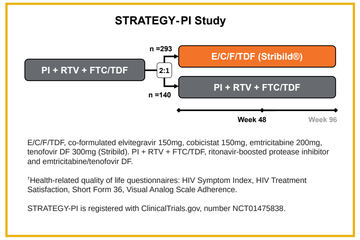
Background

- Co-formulated elvitegravir 150mg, cobicistat 150mg, emtricitabine 200mg, and tenofovir disoproxil fumarate 300mg (E/C/F/TDF) has been shown to be efficacious, safe, and well-tolerated in HIV-infected, treatment-naïve adults[1,2]
- Observational studies indicate that virologic and clinical outcomes are better for patients treated with single-tablet versus multi-tablet regimen, even among the most difficult to treat patient population[3,4]
- Virologically suppressed patients on a multi-tablet ritonavir-boosted protease inhibitor regimen may benefit from switching to single-tablet regimen E/C/F/TDF

Methods

- Multicenter, prospective, randomized, open-label 96-week study
- Eligibility criteria
  - On ritonavir-boosted (PI + RTV) plus emtricitabine/ tenofovir DF (FTC/TDF) with HIV-1 RNA <50 copies/mL for at least six months
  - On first or second antiretroviral regimen
  - No history of virologic failure and no resistance to FTC or TDF on historical genotype
  - $eGFR_{CG}$ ≥70 mL/min
- Primary endpoint
  - Proportion of subjects who maintains HIV-1 RNA < 50 copies/mL at W48 by FDA snapshot algorithm (12% noninferiority margin). If noninferiority is established, then test for superiority per a prespecified sequential testing procedure
- Secondary/tertiary endpoints
  - Change in CD4 cell count, safety, and tolerability of the two regimens through Week 96
  - Patient reported outcomes from health-related quality of life questionnaires†
- Exploratory subgroup analyses
  - Virologic success and difference by percentages
  - Changes from baseline in fasting lipid parameters at Week 48

Figure 1. Study Design



E/C/F/TDF, co-formulated elvitegravir 150mg, cobicistat 150mg, emtricitabine 200mg, tenofovir DF 300mg (Stribild). PI + RTV + FTC/TDF, ritonavir-boosted protease inhibitor and emtricitabine/tenofovir DF.

†Health-related quality of life questionnaires: HIV Symptom Index, HIV Treatment Satisfaction, Short Form 36, Visual Analog Scale Adherence.

STRATEGY-PI is registered with ClinicalTrials.gov, number NCT01475838.

Results

Table 1. Reasons for Enrollment

Reasons subject choose to enroll in study[a]	At Screening (n =433)
Desire to simplify current regimen	86%
Concerned about long-term side effects of current regimen	12%
Have trouble taking current regimen on a regular basis	3%
Have trouble tolerating current regimen well due to side effects	3%

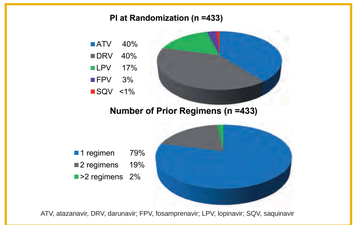
a. Subject can provide more than one reasons for enrollment in study

Table 2. Baseline Characteristics

	E/C/F/TDF (n =293)	PI + RTV + FTC/TDF (n =140)
Age, median years (Q1, Q3)	41 (33, 48)	40 (35, 47)
Male	85%	86%
Non-White	20%	19%
Black or African descent	15%	14%
Time since HIV diagnosis, median years (Q1, Q3)	4 (3, 7)	4 (3, 7)
Time since first ART use, median years (Q1, Q3)	3 (2, 4)	3 (1, 4)
On 1st ART regimen at randomization	77%	83%
Asymptomatic HIV disease status	73%	75%
CD4 cell count, mean cells/mm³ (SD)	604 (275)	624 (270)
HBV: HCV Seropositive[a]	3% : 7%	2% : 7%
$eGFR_{cg}$, median mL/min (Q1, Q3)	111 (96, 128)	111 (98, 127)

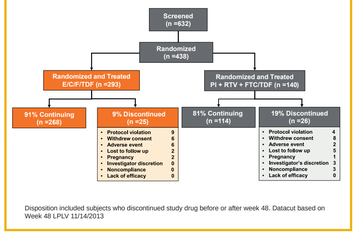
a. Positive HBV surface antigen or HCV antibody

Figure 2. PI and Number of Prior Regimens at Randomization



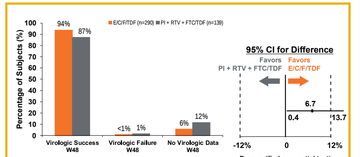
ATV, atazanavir, DRV, darunavir; FPV, fosamprenavir; LPV, lopinavir; SQV, saquinavir

Figure 3. Study Disposition



Disposition included subjects who discontinued study drug before or after week 48. Datacut based on Week 48 LPLV 11/14/2013

Figure 4. Primary Endpoint: HIV-1 RNA < 50 c/mL



CD4 Cell Count (cells/mm³)	Baseline (mean)	ΔWeek 48 (mean)	P-value (Δ W48 - BL)
E/C/F/TDF	603	+40	<0.001
PI + RTV + FTC/TDF	625	+32	=0.025

Full analysis set excluded subjects with protocol-prohibited mutations on historical genotype and those not on PI at randomization.

Table 3. Virologic Outcome at Week 48 (Snapshot)

	E/C/F/TDF (n =290)[c]	PI + RTV + FTC/TDF (n =139)[b]
Virologic Success at Week 48 HIV-1 RNA < 50 copies/mL	272 (93.8%)	121 (87.1%)
Virologic Failure (VF) at Week 48	2 (0.7%)	2 (1.4%)
HIV-1 RNA ≥ 50 copies/mL[a]	2	1
Discontinued study drug due to lack of efficacy	0	0
Discontinued study drug due to other reasons and last available HIV-1 RNA ≥ 50 copies/mL[d]	0	1
No Virologic Data in Week 48 Window	16 (5.5%)	16 (11.5%)
Discontinued study drug due to AE	5	2
Discontinued study drug due to other reasons and last available HIV-1 RNA < 50 copies/mL[e]	11 (3.8%)	14 (10.1%)
Missing data during window but on study drug	0	0

a. Subjects with protocol-prohibited mutations (M184V, n =2; M41L + L210W + T215Y, n =1) in reverse transcriptase on historical genotype were excluded from the full analysis set.
b. One subject was randomized on baseline regimen of efavirenz/emtricitabine/tenofovir DF and was removed from the full analysis set.
c. Two subjects were documented to be off study drug (one in each arm) and one had HIV-1 RNA 50-400 copies/mL (E/C/F/TDF).
d. One subject in the PI + RTV + FTC/TDF group withdrew consent at study day 9 with no samples drawn and had last visit (baseline) HIV-1 RNA of 2,890 c/mL. Screening HIV-1 RNA =50 c/mL.
e. E/C/F/TDF group: protocol violation (n=6)[1], withdrew consent (n=2), lost to follow-up (n=2), and pregnancy (n=1); PI + RTV + FTC/TDF group: protocol violation (n=4)[2], withdrew consent (n=2), lost to follow-up (n=4), pregnancy (n=1), subject noncompliance (n=2), and investigator's discretion (n=1).
[1] On HCV therapy or anticipated to receive HCV therapy (n=1) ; On more than 2 prior ARV regimen and/or history of virologic failure (n=2); Had an eGFRCG below eligible threshold (n=3).
[2]On more than 2 prior ARV regimen and/or history of virologic failure (n=2); Had an eGFRCG below eligible threshold (n=2). Some subjects had more than one protocol violation.

Table 5. Summary of Adverse Events

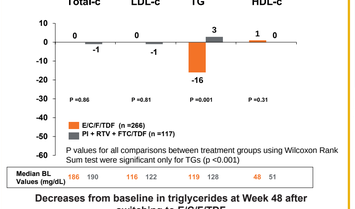
	E/C/F/TDF (n =293)	PI + RTV + FTC/TDF (n =140)
Adverse events (AEs)	79%	74%
Grade 3 or 4	4%	8%
Serious AEs	6%	6%
AEs leading to DC of study drug	2%†	3%**
Death	0	<1%¥

† Nausea, myalgia, headache (in 1 subject); major depression, suicide attempt (1); reduced visual acuity (1); Hodgkin's disease (1); anxiety (1); depression (1)
** Bipolar I disorder (1); decreased eGFR (1); diarrhea (1)
** ¥ Bronchial carcinoma with liver metastases, not related to study drugs

- Most adverse events were grade 1 or 2 in severity
- No SAE reported by >1 subject
- Adverse events leading to discontinuation were uncommon
  - No cases of proximal renal tubulopathy in either treatment group
  - Isolated decrease in eGFR in the PI + RTV + FTC/TDF group (1)

Safety analysis set includes subjects who were randomized and received at least one dose of study drug.

Figure 7. Change From Baseline in Fasting Lipids at Week 48



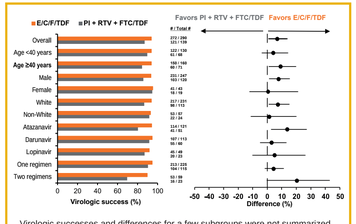
P values for all comparisons between treatment groups using Wilcoxon Rank Sum test were significant only for TGs (p <0.001)

Median BL Values (mg/dL)				
	186	116	119	48
	190	122	128	51

Decreases from baseline in triglycerides at Week 48 after switching to E/C/F/TDF

Changes from baseline in total cholesterol/HDL ratios were not statistically significant. HDL-c, high density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; Total-c, total cholesterol; TG, triglycerides

Figure 5. Virologic Success and Difference By Subgroups



Virologic successes and differences for a few subgroups were not summarized due to small sample sizes.

Table 6. Adverse Events (≥5%) in Either Treatment Arm

	E/C/F/TDF (n =293)	PI + RTV + FTC/TDF (n =140)
Nasopharyngitis	12%	10%
Upper respiratory infection	8%	4%
Diarrhea	7%	8%
Nausea	7%	3%
Headache	6%	6%
Back pain	5%	1%
Anxiety	6%	4%
Cough	5%	3%
Depression	4%	6%
Insomnia	3%	5%

Treatment-emergent adverse events occurring in ≥5% of subjects in either treatment arm

Adverse events consistent with known safety profile of E/C/F/TDF

Table 7. Grade 3 or 4 Laboratory Abnormalities (≥2%)

	E/C/F/TDF (n =293)	PI + RTV + FTC/TDF (n =140)
Grade 3 or 4 lab abnormalities*	14%	23%
GGT (>5 x ULN)	3%	1%
Creatine kinase (≥10 x ULN)	2%	6%
ALT (>5 x ULN)	2%	<1%
Hematuria (>75 RBC/HPF)	2%	1%
Total bilirubin (>2.5 x ULN)	0	12%**

*Treatment-emergent grade 3 or 4 lab abnormalities occurring in ≥2% subjects in either treatment arm
** 17 subjects on ATV with elevated indirect bilirubin
No subject discontinued study drug due to pancreatic, hepatic, or urinary disorders

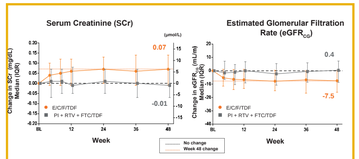
Table 4. No Treatment-Emergent Resistance

	E/C/F/TDF (n =290)	PI + RTV + FTC/TDF (n =139)
Subjects Analyzed for Resistance*, n (%)	0	0
Subjects with Data Available, n	0	0
Subjects with Resistance to ARV Regimen, n (%)	0	0
Any Primary Integrase-R, n	0	0
Any Primary NNRTI-R or PI-R, n	0	0
Any Primary NRTI-R, n	0	0

* Subjects on study drugs who experienced virologic rebound (two consecutive visits with HIV-1 RNA ≥50 c/mL and the second is ≥400 c/mL), or had HIV-1 RNA is ≥400 c/mL at Week 48 or their last visit and on study drugs.

No subject met the protocol defined criteria* for treatment-emergent resistance testing with virologic rebound ≥400 c/mL

Figure 6. Changes From Baseline in SCr and eGFR Through Week 48



- **Changes in SCr and CrCl consistent with MATE-1 transporter inhibition by COBI**
  - **At baseline, there was inhibition of MATE-1 transporter by RTV**

Median change from baseline in SCr at Week 48: E/C/F/TDF, 6.19 µmol/L vs. PI + RTV + FTC/TDF, -0.88 µmol/L

Atazanavir Subgroup

Table 8. Change From Baseline in Fasting Lipids at Week 48

	Total-c	LDL-c	Triglycerides	HDL-c
Baseline, median, Q1, Q3 (mg/dL)				
E/C/F/TDF (n=116)	179 (152, 203)	115 (90, 138)	112 (84, 166)	48 (42, 59)
Atazanvir (n=50)	183 (161, 207)	118 (101, 140)	106 (80, 156)	46 (43, 59)
Change from baseline at Week 48: median, Q1, Q3 (mg/dL)				
E/C/F/TDF (n=110)	4 (-9, 24)	3 (-10, 17)	-12 (-40, 17)	0 (-5, 6)
Atazanvir (n=41)	-3 (-25, 18)	-2 (-13, 14)	15 (-23, 46)	-2 (-9, 4)
P value[a]	0.11	0.20	0.01	0.12

Darunavir Subgroup

Table 9. Change From Baseline in Fasting Lipids at Week 48

	Total-c	LDL-c	Triglycerides	HDL-c
Baseline, median, Q1, Q3 (mg/dL)				
E/C/F/TDF (n=107)	182 (160, 206)	115 (96, 139)	111 (89, 157)	48 (42, 56)
Darunavir (n=58)	193 (169, 219)	128 (105, 152)	112 (79, 180)	51 (43, 57)
Change at Week 48: median, Q1, Q3 (mg/dL)				
E/C/F/TDF (n=105)	0 (-13, 16)	0 (-13, 15)	-11 (-35, 16)	3 (-2, 9)
Darunavir (n=53)	0 (-20, 13)	0 (-14, 13)	-5 (-31, 26)	0 (-5, 5)
P value[a]	0.43	0.56	0.32	0.03

a. Comparison between treatment group using the Wilcoxon Rank Sum test. Changes from baseline in total cholesterol/HDL ratios were not statistically significant.

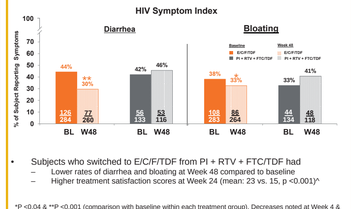
Lopinavir/Ritonavir Subgroup

Table 10. Change From Baseline in Fasting Lipids at Week 48

	Total-c	LDL-c	Triglycerides	HDL-c
Baseline, median, Q1, Q3 (mg/dL)				
E/C/F/TDF (n=44)	202 (183, 224)	133 (111, 151)	168 (120, 207)	50 (39, 60)
LPV/RTV (n=21)	197 (177, 224)	127 (115, 142)	170 (132, 205)	51 (43, 59)
Change from baseline at Week 48: median, Q1, Q3 (mg/dL)				
E/C/F/TDF (n=45)	-25 (-39, -2)	-13 (-27, 3)	-46 (-84, 25)	-2 (-5, 3)
LPV/RTV (n=19)	-1 (-18, 20)	-9 (-20, 24)	2 (-40, 44)	5 (-3, 11)
P value[a]	0.002	0.160	0.003	0.016

a. Comparison between treatment group using the Wilcoxon Rank Sum test. Changes from baseline in total cholesterol/HDL ratios were not statistically significant.

Figure 8. Patient Reported Outcomes



- Subjects who switched to E/C/F/TDF from PI + RTV + FTC/TDF had
  - Lower rates of diarrhea and bloating at Week 48 compared to baseline
  - Higher treatment satisfaction scores at Week 24 (mean: 23 vs. 15, p <0.001)^

*P <0.04 & **P <0.001 (comparison with baseline within each treatment group). Decreases noted at Week 4 & sustained to Week 48.
P <0.001, diarrhea & P=0.019, bloating (comparison of changes from baseline at week 48 between treatment group).
^ HIV Treatment Satisfaction questionnaire, score range: -30 to 30

Conclusions

- Switching to E/C/F/TDF from PI + RTV + FTC/TDF was noninferior in maintaining virologic suppression at Week 48
  - E/C/F/TDF compared to PI+RTV had significantly higher rates of virologic suppression
  - High rates of virologic efficacy across subgroups by age, gender, race, PI use, and number of prior regimens
  - No treatment-emergent resistance
- E/C/F/TDF was well tolerated with low rates of discontinuation due to adverse events
  - AE's reported were consistent with the known safety profile of E/C/F/TDF
  - Decrease in $eGFR_{CG}$ consistent with known COBI inhibition of Cr secretion
  - No cases of proximal renal tubulopathy
  - Decrease in triglycerides in PI + RTV + FTC/TDF to E/C/F/TDF switches
    - Decreases in total-c, triglycerides, and HDL-c in LPV/RTV switches
    - Decrease in triglycerides in ATV switches and increase in HDL-c in DRV switches
- Subjects switching to E/C/F/TDF reported lower rates of diarrhea and bloating

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