Phase 3b, Randomized, Open-Label Study to Evaluate Switching from a Tenofovir Disoproxil Fumarate (TDF) Containing Regimen to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) in Virologically-Suppressed, HIV-1 Infected ParticipantsAged > 60 Years: Week 48 Results of GS-US-292-1826

Poster P145

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
Tel: (650) 574-3000
Fax: (650) 578-9264

F Maggiolo[1], G Rizzardini[2], F Raffi[3], F Pulido[4], GM Mateo Garcia[5], JM Molina[6], E Ong[7], Y Shao[8], S Chuck[8], I McNicholl[8], D Piontkowsky[8], M Das[8], R Haubrich[8]

[1]Division of Infectious Diseases, ASST Papa Giovanni XXIII, Bergamo, Italy; [2]Division of Infectious Diseases, Luigi Sacco Hospital, ASST Fatebenefratelli Sacco, Milan, Italy; [3]Department of Infectious and Tropical Diseases and CIC 1413, INSERM, University Hospital, Nantes, France; [4]HIV Unit, Hospital 12 de Octubre, imas12, UCM, Madrid, Spain; [5]Infectious Diseases Unit, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; [6]Department of Infectious Diseases, Saint Louis Hospital, University Paris Diderot, France; [7]Victoria Royal Infirmary, Newcastle upon Tyne Hospitals NHS Trust, Newcastle, UK; [8]Gilead Sciences, Inc., Foster City, CA, USA

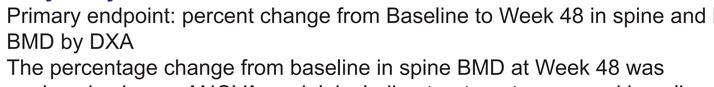
Background

- As almost 50% of people living with HIV are now >50 years old, long term safety is paramount.
- Older individuals are at increased risk of osteopenia and osteoporosis so ensuring the safety of ART in this population is critical.
- TAF is a tenofovir prodrug associated with 90% lower tenofovir plasma levels than TDF resulting in less renal and bone toxicity.
- We evaluated bone mineral density (BMD) changes after switching participants 60 years and older from a TDF- to a TAF-containing regimen.

Methods

Switch from TDF to E/C/F/TAF for Age ≥ 60
GS-US-292-1826

Multicenter, randomized, open-label, active control, 48-week study



- **Eligibility criteria**
  - HIV-1 RNA <50 c/mL for ≥6 months
  - ≥ 6 months on a TDF-containing 3 drug regimen
  - No known resistance for TDF or 3TC/FTC
  - No ongoing treatment for bone diseases
- **Primary Endpoint**
  - Mean percent change from Day 1 to Week 48 in spine and hip BMD by DXA
- **Secondary Endpoints**
  - Mean percent change from Day 1 to Week 24 in spine and hip BMD by DXA
  - Safety profile: adverse events, clinical laboratory tests
  - HIV RNA < 50 copies/ mL at Week 24 and 48 using FDA snapshot

Key Inclusion Criteria

- Age ≥ 60 years
- Currently receiving a TDF and FTC or 3TC-containing (maximum 2 NRTIs) regimen plus a third agent for ≥ 6 consecutive months prior to screening visit.
- HIV-1 RNA < 50 copies/mL at screening and for at least 6 months
- One blip (HIV-1 RNA ≥ 50 and < 400 copies/mL) was acceptable
- Historical or Monogram Archive genotype without resistance to TDF or FTC
- Estimated GFR ≥ 30 mL/min (Cockcroft-Gault formula) and are on ARVs that are appropriately dose adjusted for renal function per package insert

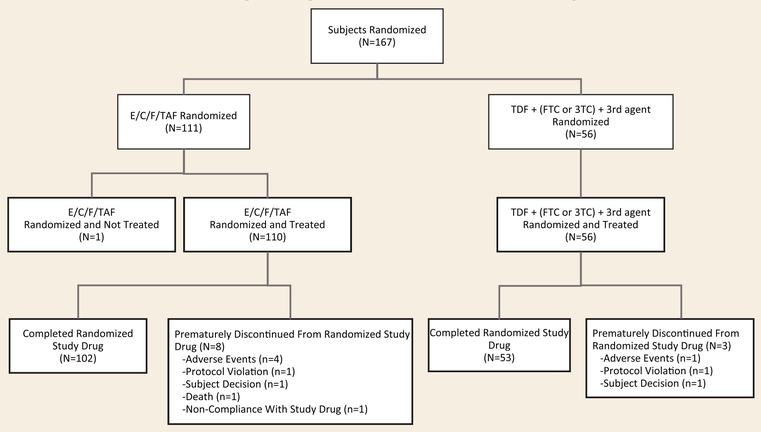
Key Exclusion Criteria

- Subjects receiving ongoing treatment for bone disease (e.g., osteoporosis), including bisphosphonates, denosumab, and strontium ranelate
- The following medications were not permitted:
  probenecid, calcium > 500 mg/day, vitamin D3 or D2 > 800 IU/day, TNF-alpha antagonists, (eg infliximab, etanercept, adlimumab, certolizumab, golimumab), teriparatide, denosumab, and strontium ranelate

Primary analysis

- Primary endpoint: percent change from Baseline to Week 48 in spine and hip BMD by DXA
- The percentage change from baseline in spine BMD at Week 48 was analyzed using an ANOVA model, including treatment group and baseline spine BMD T-score (< -1.00 vs ≥ -1.00) as a fixed effect in the model with baseline BMD and sex as covariates
- The spine and hip BMD were tested using the fallback procedure (to control for two primary endpoints). If spine BMD was statistically significant ($\alpha = 0.03$), then the hip BMD was tested at 0.05 alpha level; if no statistically significant difference was found, then the hip BMD was tested at a 0.02 alpha level
- If no W48 BMD value available, participant censored from primary analysis

Disposition of Study Subjects: All Screened Subjects

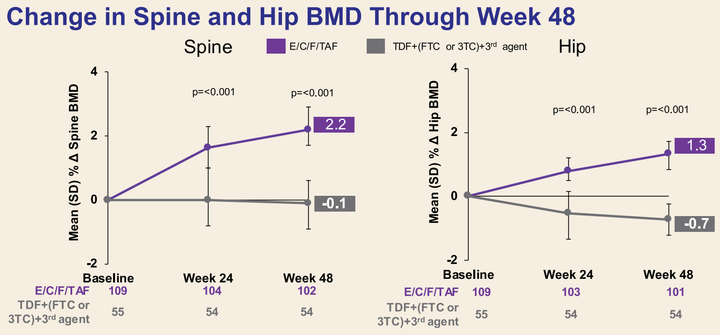


Results

Baseline Characteristics

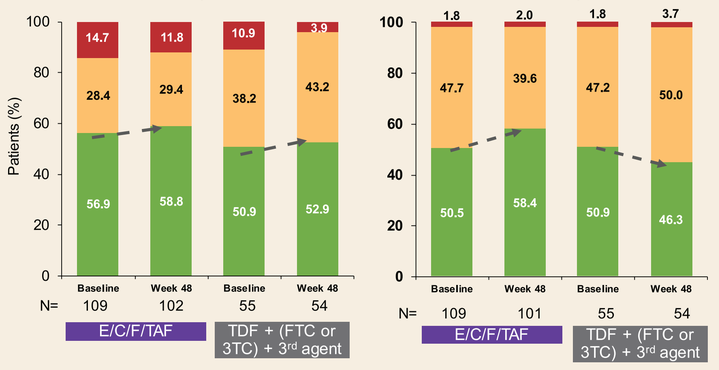
	E/C/F/TAF N=110	TDF + (FTC or 3TC) + 3rd agent N=56
Median age, years (range)	64 (60-80)	65 (60-80)
Female, % (n)	13% (14)	9% (5)
Race, %, (n)		
White	94% (103)	88% (49)
Black or African American	1.8% (2)	3.6% (2)
Median weight (kg) (range)	76 (52-111)	75 (51-105)
Median estimated GFR_{CG}, mL/min (range)	80 (46-165)	80 (46-124)
Mode of Infection		
MSM (n)	47% (52)	34% (19)
Heterosexual (n)	44% (48)	57% (32)
HIV RNA < 50 copies/mL at baseline	109 (99)	56 (100)
Median CD4 count, cells/mm^3, (range)	618 (231-1430)	667 (183-1516)
Baseline Regimen (n)		
NNRTI	73% (80)	73% (41)
INSTI	19% (21)	14% (8)
PI	8% (9)	12% (7)
Medical History (n)		
Diabetes	16% (17)	11% (6)
Hypertension	39% (43)	29% (16)
Hyperlipidemia	27% (30)	27% (15)
Cardiovascular Disease	4% (4)	2% (1)
Smoking, current	24% (27)	27% (15)
Screening Spine BMD T-score (n)		
< -1.00	44% (48)	48% (27)
≥ -1.00	56% (62)	52% (29)
Screening Hip BMD T-score (n)		
< -1.00	50% (55)	48% (27)
≥ -1.00	50% (55)	52% (29)

Change in Spine and Hip BMD Through Week 48

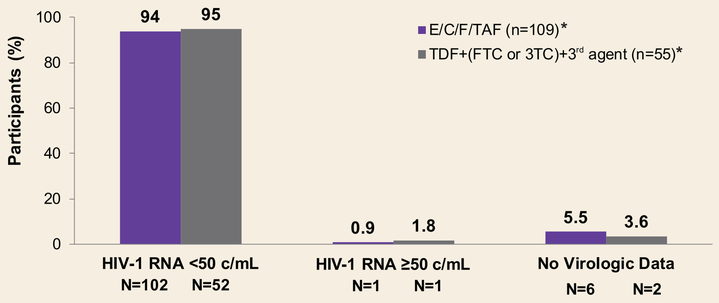


BMD=bone mineral density
P-values reflect comparison between treatment arms

Change in Diagnosis of Osteopenia or Osteoporosis Defined by T-Score



Virologic Outcomes at Week 48 (Snapshot Analysis)



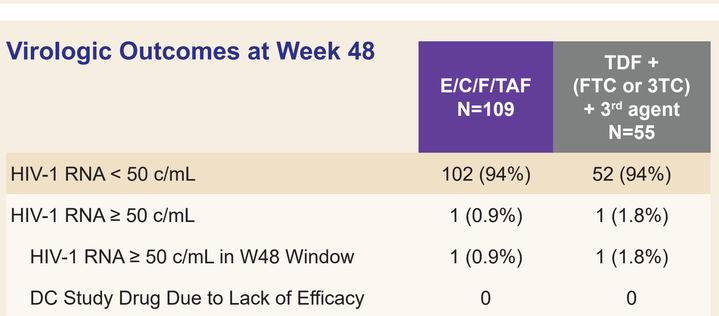
* One subject in each arm was excluded due to a disallowed regimen

Virologic Outcomes at Week 48

	E/C/F/TAF N=109	TDF + (FTC or 3TC) + 3rd agent N=55
HIV-1 RNA < 50 c/mL	102 (94%)	52 (94%)
HIV-1 RNA ≥ 50 c/mL	1 (0.9%)	1 (1.8%)
HIV-1 RNA ≥ 50 c/mL in W48 Window	1 (0.9%)	1 (1.8%)
DC Study Drug Due to Lack of Efficacy	0	0
DC Study Drug Due to AE/Death and Last Available HIV-1 RNA ≥ 50 c/mL	0	0
DC Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 c/mL	0	0
No Virologic Data in W48 Window	6 (5.5%)	2 (3.6%)
DC Study Drug Due to AE/Death and Last Available HIV-1 RNA < 50 c/mL	4 (3.7%)	1 (1.8%)
DC Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 c/mL	2 (1.8%)	1 (1.8%)
Missing Data During Window but on Study Drug	0	0

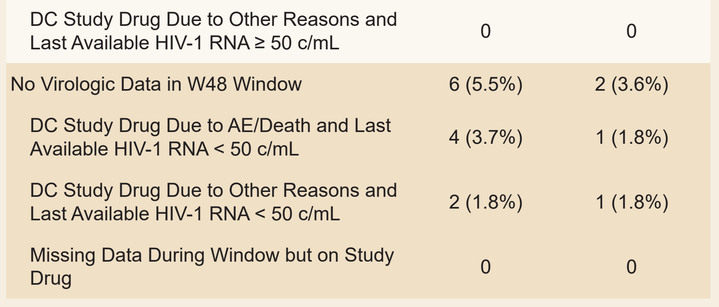
c/mL=copies/mL, DC=discontinued

Median Change in CD4 Count from Baseline through Week 48



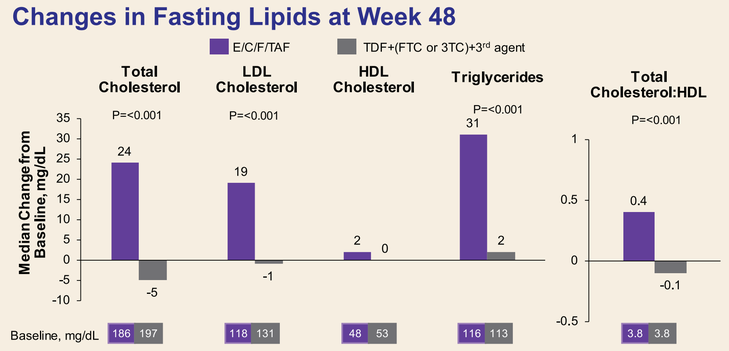
* One subject in each arm was excluded due to a disallowed regimen

Renal Biomarker Changes (%) at Week 48



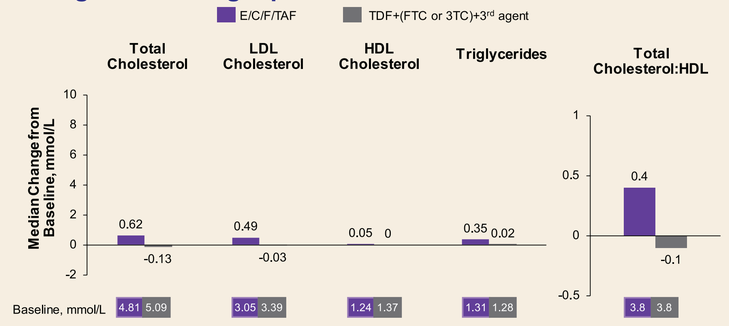
*Complete renal biomarker panel was collected up to Week 48
UACR, urine albumin/creatinine; RBP:Cr, retinol-binding protein/creatinine; β2m:Cr, urine beta-2-microglobulin/creatinine

Changes in Fasting Lipids at Week 48



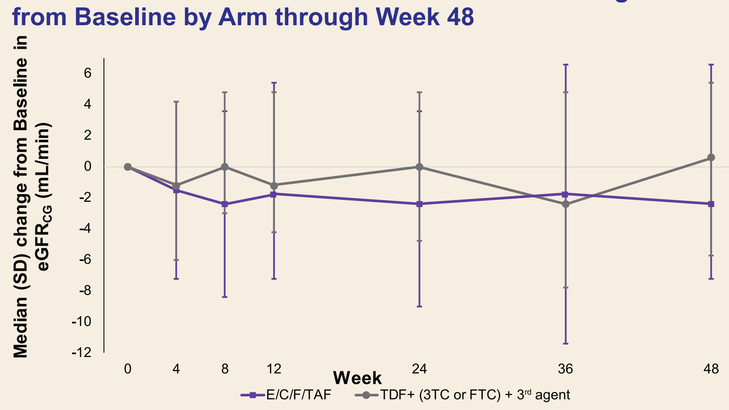
- Similar proportions of participants were on lipid-modifying medication
  - At baseline: E/C/F/TAF 37 (34%); TDF+ (FTC or 3TC) +3rd agent 18 (32%)
  - Initiated during study: E/C/F/TAF 3 (3%); TDF+ (FTC or 3TC) +3rd agent 1 (2%)

Changes in Fasting Lipids at Week 48



- Similar proportions of participants were on lipid-modifying medication
  - At baseline: E/C/F/TAF 37 (34%); TDF+ (FTC or 3TC) +3rd agent 18 (32%)
  - Initiated during study: E/C/F/TAF 3 (3%); TDF+ (FTC or 3TC) +3rd agent 1 (2%)

Estimated Glomerular Filtration Rate: Median Changes from Baseline by Arm through Week 48



$eGFR_{CG}$, estimated glomerular filtration rate calculated with Cockcroft-Gault equation

- 6% randomized to switch to E/C/F/TAF and 12% remaining on a TDF regimen switched from a boosted PI regimen

Virologic Outcomes at Week 48

	E/C/F/TAF N=109	TDF + (FTC or 3TC) + 3rd agent N=55
Any Grades 2, 3 and 4 Study Drug-Related AE (n)	6.4% (7)	0
Any Grades 3-4 Study Drug-Related AEs	0	0
Grades 3 or 4 Lab AEs (n)	12% (13)	12% (7)
Any Study Drug-Related Serious AE	0	0
AEs Leading to Study Drug Discontinuation (n)	3.6% (4)*	1.8% (1)
Renal AEs Leading to Study Drug Discontinuation	0	0
Treatment-Emergent Fractures	0	0
Death	1**	0

*1) diarrhea, headache; 2) diarrhea; 3) flatulence; 4) depression
**73 yo White male with a history of diabetes mellitus, colorectal cancer and pneumonia was hospitalized for dehydration. Participant died on D107 due to E. coli sepsis

Conclusions

- Through W48, spine and hip BMD significantly increased in older participants who switched to E/C/F/TAF compared to those who continued a TDF-containing regimen.
  - Spine: 2.2% gain with TAF vs 0.1% loss with continued TDF (P < 0.001)
  - Hip: 1.3% gain with TAF vs 0.7% loss with TDF (P < 0.001)
  - No treatment-emergent fracture events reported
- Through W48, rates of virologic suppression were high in both groups
- AEs leading to discontinuation were low in both arms
- Adverse events and tolerability were also comparable between groups.
- Concentrations of renal biomarkers decreased more in those receiving a TAF-based regimen
- The Week 48 BMD, safety and efficacy data support the switch from a TDF containing regimen to E/C/F/TAF in suppressed HIV-infected participants aged > 60 years.

Acknowledgments

We extend our thanks to the participants, their partners and families, and all GS-US-292-1826 Investigators
V Abril López de Medrano, F Ajana, A Antinori, R Cauda, E Cua, S de Wit, A Di Biagio, G Di Perri, C Duvivier, A Freedman, PM Girard, E Lazaro, G Madeddu, F Maggiolo, J Mallolas Masferrer, GM Mateo García, JM Molina, P Morlat, C Mussini, J Navarro, J Olalla Sierra, E Ong, G Parruti, P Philibert, L Piroth, F Pulido, T Quirino, S Quah, F Raffi, G Rizzardini, D Salmon-Ceron, L Vandekerckhove, L Waters
This study was funded by Gilead Sciences, Inc.