Changes in renal laboratory markers and bone mineral density in treatment-naïve HIV-1-infected adolescents initiating INSTI-based single-tablet regimens containing tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF)

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- Study 106 and 112 are Gilead Sciences sponsored Phase II studies
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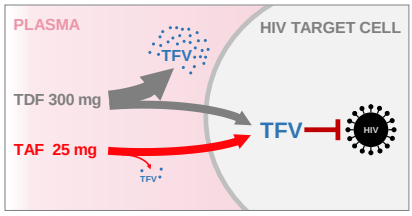
Tenofovir Alafenamide (TAF, GS-7340) Novel Prodrug of Tenofovir



- 90% lower TFV levels minimizes renal and bone effects while maintaining high potency for suppressing HIV

1. Lee W et. Antimicr Agents Chemo 2005;49:1898-906; 2. Birkus G et al. Antimicr Agents Chemo 2007;51:543-50; 3. Babusis D, et al. Mol Pharm 2013;10:459-66; 4. Ruane P, et al. J Acquir Immune Defic Syndr 2013;63:449-55;5. Sax P, et al. JAIDS 2014;2014;67:52-8.6. Sax P, et al. Lancet 2015;385:2606-15.

Background: E/C/F/TAF and E/C/F/TDF

- E/C/F/TDF (commercially available as Stribild) and E/C/F/TAF (not commercially available yet) are single pill formulations that both contain elvitegravir (EVG) 150 mg, cobicistat (COBI) 150 mg, and emtricitabine (FTC) 200 mg
  - E/C/F/TAF contains TAF 10 mg
  - E/C/F/TDF (Stribild) contains TDF 300 mg
- Two phase 3 double blind adult studies[1] comparing E/C/F/TAF to E/C/F/TDF demonstrated
  - Noninferior efficacy of E/C/F/TAF
  - Significantly reduced renal and bone effects with E/C/F/TAF
- Two single-arm open-label studies[2,3] of E/C/F/TAF and E/C/F/TDF conducted in treatment-naïve adolescents have shown
  - These STRs are well tolerated
  - Plasma levels of all components are similar to those in adults

1. Sax P, et al. Lancet 2015;385:2606-15; 2. Gaur A, et al. CROI 2014. Abstract 909; 3. Kizito H, et al. CROI 2015. Abstract 953.

Methods

- Cross-study comparison of 2 ongoing open-label, single-arm studies in treatment-naïve adolescents
  - Study 292-0106: E/C/F/TAF administered for 48 weeks (N=50)
  - Study 236-0112: E/C/F/TDF administered for 48 weeks (N=50)
- Primary endpoint: safety
- Secondary endpoint: viral suppression
- For both studies key inclusion/exclusion criteria:
  - Age ≥12 to < 18 years
  - Weight >35 kg
  - HIV-1 RNA >1000 copies/mL
  - No prior ARV therapy
  - CD4 count >100 cells/mm^3

Study Assessments and Analysis Methods

- Safety assessments
  - Adverse events and laboratory assessments: hematology, chemistry, renal tubular protein biomarkers
  - Dual X-ray absorptiometry (DXA) of spine and total body less head (TBLH) at baseline and every 24 weeks
- Efficacy assessments
  - HIV-1 RNA (TaqMan 2.0) and CD4 count at every visit
  - Resistance testing in cases of confirmed virologic failure (HIV-1 RNA >400 copies/mL)
- Statistical methods
  - Cross-calibration between DXA scanner types (Hologic and Lunar)
  - Calculation of standard and height-adjusted Z-scores and predicted BMD change
  - Snapshot algorithm for HIV-1 RNA < 50 copies/mL at Week 24

Demographics and Baseline Characteristics

		E/C/F/TAF n=50	E/C/F/TDF n=50	p-value
Age	Years, median (range)	15 (12-17)	16 (12-17)	**0.040**
Sex	Male, n (%)	22 (44)	35 (70)	**0.009**
Country of Origin	Uganda, n (%)	30 (60)	0	
	South Africa	3 (6)	22 (44)	
	Thailand	6 (12)	14 (28)	
	United States	11 (22)	14 (28)	
eGFR (Schwartz)	mL/min/1.73 m^2, median	156.0	139.5	0.082
Spine BMD	g/cm^2, median	0.78	0.93	0.027
	Standard Z-score	-1.30	-0.72	0.20
	Height-adjusted Z-score	-0.54	+0.09	**0.015**

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Baseline Disease Characteristics

		E/C/F/TAF n=50	E/C/F/TDF n=50	p value
HIV-1 RNA	Log_{10} copies/mL, mean (SD)	4.62 (0.59)	4.60 (0.55)	0.98
	>100,000 copies/mL, n (%)	11 (22)	10 (20)	0.81
CD4 Count	Cells/μL, median (Q1, Q3)	456 (332, 574)	402 (298, 486)	0.060
	<200 cells/μL, n (%)	4 (8)	2 (4)	
Mode of Infection	Vertical transmission, n (%)	32 (64)	17 (34)	
	Heterosexual sex	12 (24)	12 (24)	
	Homosexual sex	8 (16)	19 (38)	

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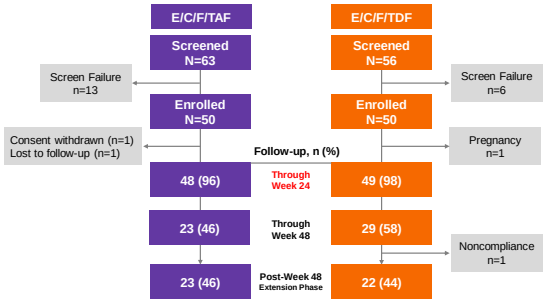
Patient Disposition



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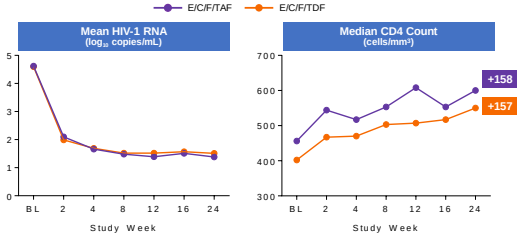
Efficacy: Overview



- All subjects achieved HIV-1 RNA < 50 copies/mL by Week 12
- Proportion with HIV-1 RNA < 50 copies/mL at Week 24: E/C/F/**TAF** 90% (45/50), E/C/F/**TDF** 88% (44/50)
- Most failures were associated with decreased adherence
- No emergent resistance

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Safety Overview

- No deaths or adverse events (AEs) leading to treatment discontinuation
- Most AEs mild or moderate and unrelated to study treatment
- No cases of proximal renal tubulopathy or Fanconi syndrome
- Serious adverse events:

E/C/F/TAF: 5 SAEs in 4 patients	E/C/F/TDF: 5 SAEs in 4 subjects
Urinary retention, neuropathic pain, constipation	1) Suicide gesture 2) Shigella dysentery, acute renal injury
Conduct disorder, polysubstance abuse, bipolar disorder	Pre-term labor
Intermediate uveitis, visual disorder*	Immune reconstitution inflammatory syndrome
1) Substance abuse 2) Suicidal ideation, suicide attempt	Acute asthma exacerbation

*Only treatment-related SAE and resolved without E/C/F/TAF interruption.

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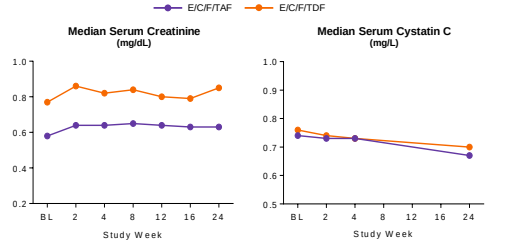
Creatinine and Cystatin C by Visit



- Median change in Cr (mg/dL) at Week 24: E/C/F/**TAF** **+0.08**, E/C/F/**TDF** **+0.08**
- Median change in eGFR (mL/min/1.73 m^2) at Week 24: E/C/F/**TAF** **-15.0**, E/C/F/**TDF** **-14.0**
- Slight decrease in Cystatin C (not affected by COBI) in both groups

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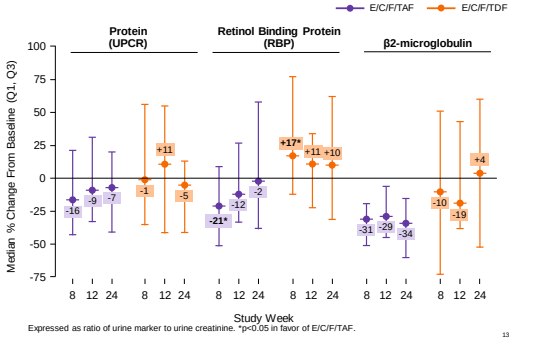
Changes in Renal Tubular Biomarkers Through Week 24



Expressed as ratio of urine marker to urine creatinine. *p<0.05 in favor of E/C/F/TAF.

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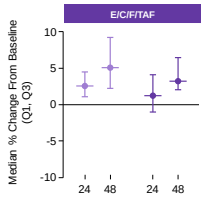
Changes in Spine Bone Mineral Density



		Predicted	Actual
Median (Q1, Q3) % Change	Week 24 (n=47)	+2.55 (+1.11, +4.54)	+1.25 (-0.96, +4.11)
	Week 48 (n=23)	+5.09 (+2.23, +9.23)	+3.25 (+2.07, +6.47)

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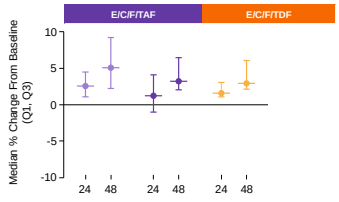
Changes in Spine Bone Mineral Density



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Median (Q1, Q3) % Change	Week 24 (n=47)	+2.55 (+1.11, +4.54)	+1.25 (-0.96, +4.11)	+1.55 (+1.11, +3.07)
	Week 48 (n=23)	+5.09 (+2.23, +9.23)	+3.25 (+2.07, +6.47)	+2.95 (+2.20, +6.08)

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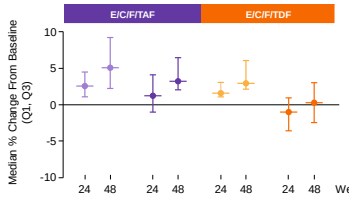
Changes in Spine Bone Mineral Density



		Predicted	Actual	Predicted	Actual	p-value
Median (Q1, Q3) % Change	Week 24 (n=47)	+2.55 (+1.11, +4.54)	+1.25 (-0.96, +4.11)	+1.55 (+1.11, +3.07)	-0.985 (-3.57, +0.95)	0.009
	Week 48 (n=23)	+5.09 (+2.23, +9.23)	+3.25 (+2.07, +6.47)	+2.95 (+2.20, +6.08)	+0.299 (-2.45, +3.04)	0.12

- At Week 24, compared to spine BMD at baseline a decrease of ≥4% was seen in:
  - 3/47 participants (6.7%) in the E/C/F/TAF cohort
  - 10/47 participants (21%) in the E/C/F/TDF cohort (p=0.070)

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Conclusions

While being cognizant that this was a cross-study comparison and there were differences (age, gender, geography, mode of transmission) at baseline, we note

- Both groups exhibited rapid virologic response and high rates of virologic success at Week 24, with no emergent resistance
- E/C/F/TAF and E/C/F/TDF generally well tolerated
- Small observed increases in serum Cr, consistent with known effect of cobicistat in adults
- E/C/F/TAF decreased renal biomarkers, similar to that observed in adult E/C/F/TAF phase 3 studies
- E/C/F/TAF group had increased median spine BMD at Week 24 (+1.3%) compared with a decrease (-1.0%) in E/C/F/TDF group
- These data support use of both regimens in treatment-naïve adolescents and suggest potential renal and bone safety advantages of TAF

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Acknowledgments

Principal Investigators:

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Our patients and their families

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QUESTIONS?