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Lack of Emergent Resistance in HIV-1-Infected Adolescents on Elvitegravir-Based STRs

DP Porter*, SR Bennett, E Quirk, MD Miller, KL White

Gilead Sciences, Inc., Foster City, CA

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

Background

- Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) and elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF) are integrase inhibitor-containing single-tablet regimens (STRs) under study for the treatment of HIV-1 infected adolescents
  - E/C/F/TDF was approved for adults in the US in 2012 and in the EU in 2013
  - E/C/F/TAF is currently under regulatory review in the US and EU
  - TAF is a new prodrug of tenofovir (TFV) with enhanced delivery to lymphoid cells, resulting in reduced circulating plasma TFV levels relative to TDF[1]
- E/C/F/TAF and E/C/F/TDF could provide additional treatment options for HIV-infected adolescents with potential benefits including:
  - Simplified once-daily dosing of STR formulations may help address the known challenge of adherence in this population[2]
  - Antiviral activity against pre-existing NNRTI and PI resistance[3,4]
  - Improved tolerability compared with efavirenz-containing regimens[5]
- Studies GS-US-292-0106 and GS-US-236-0112 are ongoing single-arm studies of E/C/F/TAF and E/C/F/TDF, respectively, in treatment-naive adolescents

Methods

- Genotyping was performed for all subjects enrolled in Studies 236-0112 and 292-0106 at study entry to confirm sensitivity to FTC and tenofovir; screening genotyping to confirm sensitivity to EVG was done in study GS-US-292-0106 only
- Criteria for inclusion in the protocol-defined resistance analysis populations:
  - Suboptimal virologic response
    - <1 $\log_{10}$ below baseline at Week 8 and HIV-1 RNA ≥400 c/mL, confirmed at the next scheduled or unscheduled visit
  - Virologic rebound: two consecutive visits with HIV-1 RNA
    - ≥400 c/mL after achieving HIV-1 RNA <50 c/mL OR
    - >1 $\log_{10}$ increase from nadir and HIV-1 RNA ≥400 c/mL
- Reverse transcriptase (RT), protease (PR), and integrase (IN) genotyping and phenotyping of virologic failures was done at the virologic failure confirmation visit (Monogram Biosciences)
- Subjects that had completed their Week 24 study visit at the time of the Week 24 interim analyses of each study are included in this analysis

Figure 1. GS-US-292-0106: E/C/F/TAF Adolescent Phase 2/3 Study Design

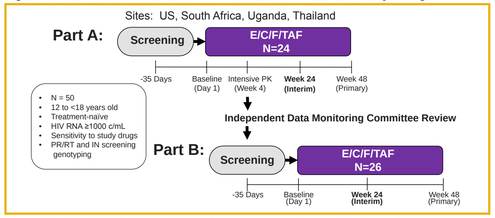
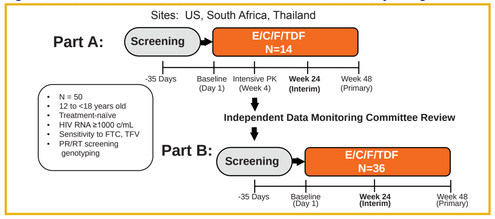


Figure 2. GS-US-236-0112: E/C/F/TDF Adolescent Phase 2/3 Study Design



Results

Table 1. Baseline Characteristics

Characteristics	E/C/F/TAF (N = 23)	E/C/F/TDF (N = 21)
Median age, years (IQR)	14 (12–16)	15 (14–17)
Male, n (%)	12 (52.2)	13 (61.9)
Black, n (%)	19 (82.6)	16 (76.2)
Asian, n (%)	4 (17.4)	4 (19.0)
White, n (%)	0	1 (4.8)
Hispanic or Latino, n (%)	0	1 (4.8)
Median weight, kg	47.9	52.1
Mean baseline HIV-1 RNA, $\log_{10}$ copies/mL (SD)	4.8 (0.5)	4.8 (0.5)
≤ 100,000 copies/mL, n (%)	15 (65.2)	15 (71.4)
> 100,000 copies/L, n (%)	8 (34.8)	6 (28.6)
Mean baseline CD4 count, cells/μL (SD)	426 (173.4)	443 (126.9)
Median time since diagnosis, years (IQR)	1.0 (0–5.0)	1.0 (0–2.0)

Table 2. Efficacy by Snapshot Algorithm at Week 24

Characteristics	E/C/F/TAF (N = 23)	E/C/F/TDF (N = 21)
Virologic Success at Week 24, % (n)	91.3 (21)	85.7 (18)
HIV-1 RNA <50 copies/mL	91.3 (21)	85.7 (18)
Virologic Failure at Week 24, % (n)	8.7 (2)	9.5 (2)
HIV-1 RNA ≥ 50 copies/mL	8.7 (2)[a]	9.5 (2)[b]
Discontinued due to lack of efficacy	0	0
Discontinued due to other reasons and last available HIV-1 RNA ≥ 50 copies/mL	0	0
No Virologic Data in Week 24 Window, % (n)	0	4.8 (1)
Discontinued due to AE/death	0	0
Discontinued due to other reasons and last available HIV-1 RNA <50 copies/mL	0	4.8 (1)
Missing data during window but on drug	0	0

[a] Two subjects had HIV-1 RNA of 56 and 1010 copies/mL at Week 24; both resuppressed to <50 copies/mL at a later time point on study without a change in regimen.
[b] Two subjects had HIV-1 RNA of 54 and 51 copies/mL at Week 24; both resuppressed to <50 copies/mL at a later time point on study without a change in regimen.

Figure 3. Subjects Achieving HIV-1 RNA <50 copies/mL

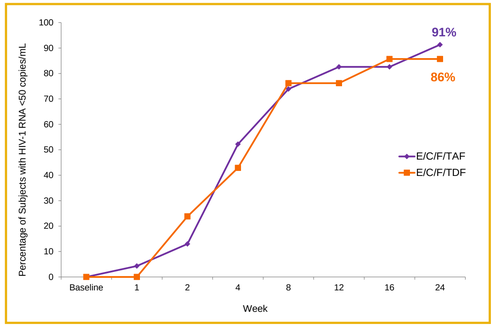


Figure 4. HIV-1 Subtype Distribution by Geography for E/C/F/TAF Subjects (n=23)

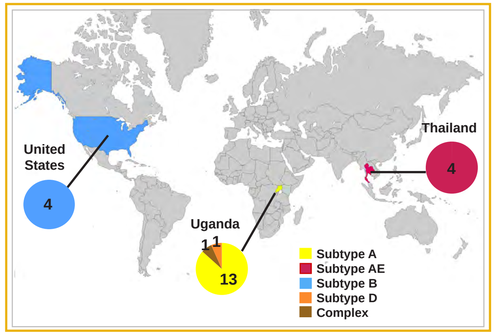


Figure 5. HIV-1 Subtype Distribution by Geography for E/C/F/TDF Subjects (n=21)

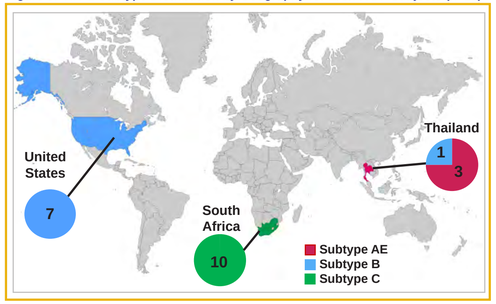


Table 3. Virologic Succes at Week 24 by HIV-1 Subtype

HIV-1 Subtype	E/C/F/TAF (n = 23)		E/C/F/TDF (n = 21)	
	Subjects, n	Subjects with Virologic Success at Week 24	Subjects, n	Subjects with Virologic Success at Week 24
Subtype A1	13	12/13 (92.3%)[a]	0	n/a
Subtype AE	4	4/4 (100%)	3	2/3 (66.7%)[a]
Subtype B	4	3/4 (75%)[a]	8	8/8 (100%)
Subtype C	0	n/a	10	8/10 (80%)[a,b]
Subtype D	1	1/1 (100%)	0	n/a
Complex	1	1/1 (100%)	0	n/a

n/a = not applicable
[a] All subjects with HIV-1 RNA ≥50 copies/mL at Week 24 subsequently suppressed to HIV-1 <50 copies/mL at a later time point on study without a change in regimen
[b] One subject had no data in the Week 24 window (discontinued E/C/F/TDF due to pregnancy prior to Week 24) but was suppressed at Week 12 (last visit on study drug)

- Virologic response rates were similar across HIV-1 subtypes

Table 4. Baseline Resistance Mutations

Mutation Class	E/C/F/TAF (n = 23)	E/C/F/TDF (n = 21)
NRTI-Associated[a], n (%)	4 (17.4)	0
Average Number of NRTI-R Mutations	1.25	n/a
TAMs	1 (4.3)	
E44D	1 (4.3)	
T69N	2 (8.7)	
V118I	1 (4.3)	
K219Q	1 (4.3)	
Primary INSTI-Associated[b], n (%)	0	ND
Secondary INSTI-Associated[c], n (%)	5 (21.7)	ND
Average Number of Secondary INSTI-R Mutations	1	n/a
M501	3 (13.0)	
S119P	2 (8.7)	
NNRTI-Associated[d], n (%)	2 (8.7)	3 (14.3)
Average Number of NNRTI-R Mutations	2	2
V90I	0	1 (4.8)
K103N	2 (8.7)	2 (9.5)
V106I	1 (4.3)	1 (4.8)
E138A	1 (4.3)	1 (4.8)
V179T	0	1 (4.8)
Primary PI-Associated[e], n (%)	0	0
Secondary PI-Associated[f], n (%)	23 (100)	20 (95.2)

n/a = not applicable; ND = no data
[a] Nucleoside reverse transcriptase inhibitor (NRTI)-associated resistance mutations are M41L, E44D, A62V, K65R, D67N, T69 insertion, T69D/N, K70E/R, L74V/I, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R
[b] Primary integrase strand transfer inhibitor (INSTI)-associated resistance mutations are T66I/A/K, E92Q/G, T97A, Y143R/H/C, S147G, Q148H/K/R, N155H/S
[c] Secondary integrase strand transfer inhibitor (INSTI)-associated resistance mutations are M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C/Y, A128T, E138K/A, G140A/C/S, P145S, Q146R/I/K/L/P, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A, R263K
[d] Non-nucleoside reverse transcriptase inhibitor (NNRTI)-associated resistance mutations are V90I, A98G, L100I, K101E/H/P, K103N/S, V106M/A/I, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230L/I
[e] Primary protease inhibitor (PI)-associated resistance mutations are D30N, V32I, L33F, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, I84V, N88S, L90M
[f] Secondary protease inhibitor (PI)-associated resistance mutations are L10I/F/R/V/C, V11I, I13V, G16E, K20I/M/R/T/V, L24I, L33I/V, E34Q, E35G, M36I/L/V, K43T, F53L/Y, I54A/S/T/V, D60E, I62V, L63P, I64L/M/V, H69K, A71V/T/I/L, G73A/C/S/T, V77I, V82I, N83D, I85V, N88D, L89V, I93L/M

Table 5. Baseline Resistance and Virologic Success at Week 24

Resistance Mutations at Baseline	E/C/F/TAF (n = 23)		E/C/F/TDF (n = 21)	
	Subjects with Mutations, n	Subjects with Virologic Success at Week 24	Subjects with Mutations, n	Subjects with Virologic Success at Week 24
NRTI-Associated	4	4/4 (100%)	0	n/a
Primary INSTI-Associated	0	n/a	ND	n/a
Secondary INSTI-Associated	5	4/5 (80%)[a]	ND	n/a
NNRTI-Associated	2	2/2 (100%)	3	2/3 (66.7%)[a]
Primary PI-Associated	0	n/a	0	n/a
Secondary PI-Associated	23	21/23 (91.3%)[a]	20	17/20 (85%)[a,b]

n/a = not applicable; ND = no data
[a] All subjects with HIV-1 RNA ≥50 copies/mL at Week 24 subsequently suppressed to HIV-1 <50 copies/mL at a later time point on study without a change in regimen
[b] One subject had no data in the Week 24 window (discontinued due to pregnancy prior to Week 24) but was suppressed at her last visit on study drug

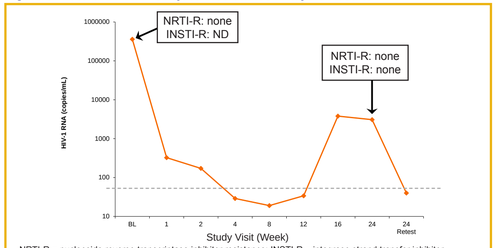
- Virologic response rates were similar regardless of baseline resistance mutations

Table 6. Resistance Analysis Population (RAP) at Week 24

Resistance Category	E/C/F/TAF (n = 23)	E/C/F/TDF (n = 21)
RAP, n (%)	1 (4.3)	1 (4.8)
Subjects with Data, n	0	1
Subjects who Resuppressed HIV-1 RNA <50 c/mL, n (%)	1 (4.3)	0
Final RAP, n (%)	0	1 (4.8)
Final RAP with Resistance, n (%)	0	0

- One subject on E/C/F/TAF had unconfirmed virologic rebound at Week 24 (1010 copies/mL) but resuppressed at the next study visit without a change in regimen and therefore their virus was not analyzed for resistance development
- One subject on E/C/F/TDF had confirmed virologic rebound at Week 24 and their virus was analyzed for resistance development; no emergent resistance was detected and the subject subsequently resuppressed at the next study visit without a change in regimen
- No subjects met the criteria for suboptimal virologic response in either study

Figure 6. E/C/F/TDF RAP Subject: Resistance Analysis Results



NRTI-R = nucleoside reverse transcriptase inhibitor resistance; INSTI-R = integrase strand transfer inhibitor resistance; ND = no data

Conclusions

- **E/C/F/TAF and E/C/F/TDF had similarly high efficacy rates at Week 24**
- **E/C/F/TAF and E/C/F/TDF demonstrated efficacy against diverse HIV-1 subtypes**
  - **HIV-1 subtype distribution correlated with geography**
- **Pre-existing NNRTI, NRTI, secondary PI, or secondary INSTI resistance mutations present at baseline did not impact virologic response rates**
- **No emergent drug resistance was detected in either study**
- **Both studies are ongoing through 48 weeks of treatment**
- **Continued study of E/C/F/TAF and E/C/F/TDF as potentially effective treatment options for HIV-1-infected adolescent populations globally is warranted**

References

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3. K White et al, HIV Clinical Trials, 2014
4. K White et al, Antiviral Therapy, 2014
5. Stribild US Prescribing Information, December 2014