Preexisting and Post-Baseline Resistance Analyses in Pooled Pediatric Studies of Emtricitabine/Tenofovir Alafenamide (F/TAF)–Based Antiretroviral Therapy

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Key Findings

- Durable virologic suppression regardless of preexisting resistance was observed in this pooled analysis of four studies evaluating the efficacy, safety and PK of F/TAF-based ART in pediatric participants
- There was no treatment-emergent resistance to B/F/TAF or E/C/F/TAF

Conclusions

- In total, 341 pediatric participants across four studies received F/TAF-based regimens for a median treatment duration of 157 weeks
- 31% (47/152) of participants with BL genotypic data had ≥ 1 preexisting resistance-associated substitution
- Durable virologic suppression was observed across all treatment regimens, including in participants with preexisting resistance
- Four participants without BL resistance data who were receiving F/TAF + efavirenz experienced virologic failure with presumed treatment-emergent resistance
  - All had NNRTI resistance substitutions and two had K65R ± M184V
  - All switched third agents and were able to achieve HIV-1 RNA < 50 c/mL at subsequent timepoints
- High levels of virologic suppression, regardless of preexisting resistance, through long-term follow-up demonstrate the efficacy of F/TAF-based ART in pediatric populations

Introduction

- TAF results in 91% lower plasma TFV exposure than TDF, and is associated with improved renal and bone safety in adults and adolescents[1,2]
- F/TAF is a guideline-recommended NRTI backbone for HIV treatment,[3–5] with two fixed-dose combinations approved in the U.S.A. for use in adolescents and children (as part of a regimen that does not include a boosted PI)[4]
  - 200/25 mg for adults and children weighing ≥ 25 to < 35 kg
  - 120/15 mg for children weighing ≥ 14 to < 25 kg
- F/TAF is also coformulated as a complete single tablet regimen with cobicistat-boosted elvitegravir (E/C/F/TAF) or bictegravir (B/F/TAF); low-dose formulations of E/C/F/TAF and B/F/TAF are approved for use in children in the EU and/or U.S.[6–9]
  - E/C/F/TAF: 90/90/120/6 mg for children aged ≥ 2 years and weighing ≥ 14 to < 25 kg (EU only)[6]; 150/150/200/10 mg for children ≥ 25 kg and adults[6,9]
  - B/F/TAF: 30/120/15 mg for children weighing ≥ 14 to < 25 kg; 50/200/25 mg for children ≥ 25 kg and adults[7,8]

Objective

- To assess **preexisting drug resistance**, **treatment-emergent resistance** and the **effect of resistance on long-term efficacy** in four studies evaluating the efficacy, safety and PK of F/TAF-based ART in pediatric populations

Methods

Study Designs

VS Virologically suppressed; TN Treatment naïve

B/F/TAF		
GS-US-380-1474[10,*]	VS Cohort 1: **12 to < 18 years; ≥ 35 kg**	B/F/TAF (50/200/25 mg); n = 50
	VS Cohort 2: **6 to < 12 years; ≥ 25 kg**	B/F/TAF (50/200/25 mg); n = 50
	VS Cohort 3: **≥ 2 years; ≥ 14 to < 25 kg**	B/F/TAF (30/120/15 mg); n = 22
E/C/F/TAF		
	TN Cohort 1: **12 to < 18 years; ≥ 35 kg**	E/C/F/TAF (150/150/200/10 mg); n = 50
GS-US-292-0106[11]	VS Cohort 2: **6 to < 12 years; ≥ 25 kg**	E/C/F/TAF (150/150/200/10 mg); n = 52
	VS Cohort 3: **≥ 2 years; ≥ 14 to < 25 kg**	E/C/F/TAF (90/90/120/6 mg); n = 27
GS-US-292-1515[12]	VS **12 to < 18 years; ≥ 35 kg**	E/C/F/TAF (150/150/200/10 mg); n = 50
F/TAF + 3rd agent		
GS-US-311-1269[13]	VS Cohort 1: **12 to < 18 years; ≥ 35 kg**	F/TAF + 3rd agent (200/25 mg/unboosted and 200/10 mg/boosted); n = 28
	VS Cohort 2, Group 1: **6 to < 12 years; ≥ 25 kg**	F/TAF + 3rd agent (200/25 mg/boosted or unboosted); n = 9
	VS Cohort 2, Group 2: **2 to < 12 years; 17 to < 25 kg**	F/TAF + 3rd agent (120/15 mg/boosted or unboosted); n = 3

*Data cutoffs – GS-US-380-1474: 10 May 2021; GS-US-292-0106: September 2020 (Cohorts 1 and 2), December 2020 (Cohort 3); GS-US-292-1515: end of study; GS-US-311-1269: 1 October 2020.

BL Genotypic Analyses
- Prospective HIV-1 plasma RNA genotyping (participants who were treatment naïve)
- Historical HIV-1 genotypes, if available, and retrospective HIV-1 proviral DNA genotyping (participants with suppressed HIV-1 RNA)

Resistance Analysis Population
- Participants with HIV-1 RNA ≥ 200 c/mL (B/F/TAF) or ≥ 400 c/mL (E/C/F/TAF and F/TAF + 3rd agent) at confirmed virologic failure (HIV-1 RNA ≥ 50 c/mL at two consecutive visits) or last on-treatment visit

Efficacy Analysis Population
- Participants with ≥ 1 on-treatment HIV-1 RNA measurement
- Virologic outcomes based on last available on-treatment HIV-1 RNA (LOCF imputation)
  - < 50 c/mL (suppression) or ≥ 50 c/mL (no suppression)

Results

Demographics and BL Characteristics

Characteristic	F/TAF pooled pediatric participants N = 341
Age, years, median (Q1, Q3)	12 (9, 15)
12 to < 18 years, n (%)	178 (52)
6 to < 12 years, n (%)	143 (42)
2 to < 6 years, n (%)	20 (6)
Female sex at birth, n (%)	196 (58)
Black race, n (%)	256 (75)
Treatment naïve,* n (%)	50 (15)
Receiving ART, n (%)	291 (85)
With virologic suppression	289 (85)[†]

Participants were from South Africa (n = 121), Uganda (n = 81), U.S.A. (n = 71), Thailand (n = 47), Panama (n = 19) and Zimbabwe (n = 2). *All participants who were treatment naïve were enrolled in Cohort 1 of Study 292-0106 and received E/C/F/TAF; [†]In two participants, HIV was not suppressed at BL after VL < 50 c/mL at screening: one in Study 292-1515 had VL 3,850 c/mL and one in Study 311-1269 had VL 159 c/mL.

For further information on study regimens, please scan the QR code

Results

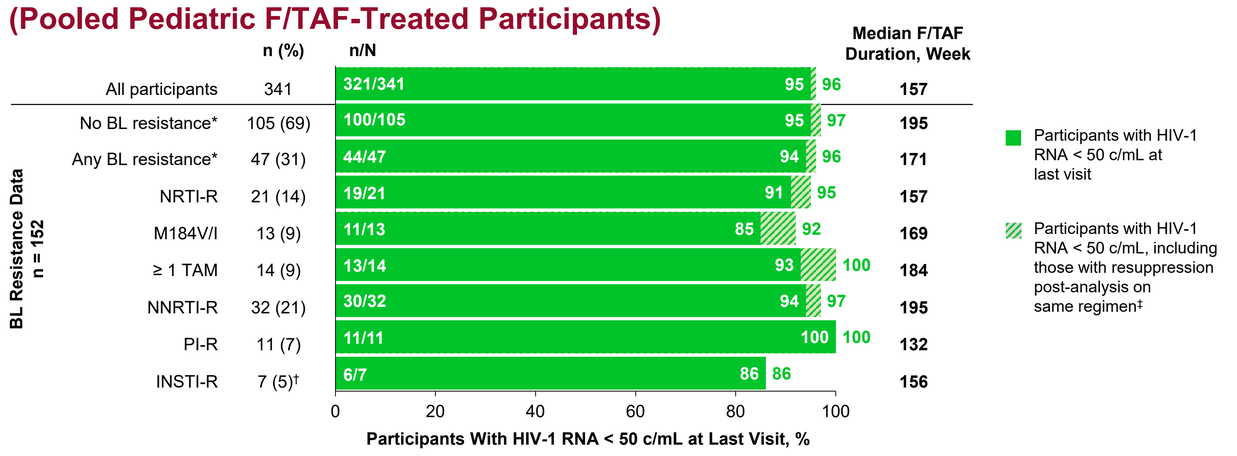
BL Genotypic Data

Participants, n (%)	F/TAF pooled N = 341	B/F/TAF (VS) n = 122	E/C/F/TAF (TN) n = 50	E/C/F/TAF (VS) n = 129	F/TAF + 3rd agent (VS) n = 40
PR/RT ± IN data at BL	152 (45)	95 (78)	50 (100)	7 (5)	0
PR/RT	152 (45)	95 (78)*	50 (100)	7 (5)[†]	0
IN	141 (41)	92 (75)[‡]	49 (98)	0	0

*n = 93 from BL proviral DNA genotypes and n = 22 from historical genotype (some participants had > 1 BL/pretreatment genotype); [†]n = 7 from historical genotype; [‡]n = 93 from BL proviral DNA genotypes and n = 1 from historical genotype (some participants had > 1 BL/pretreatment genotype).

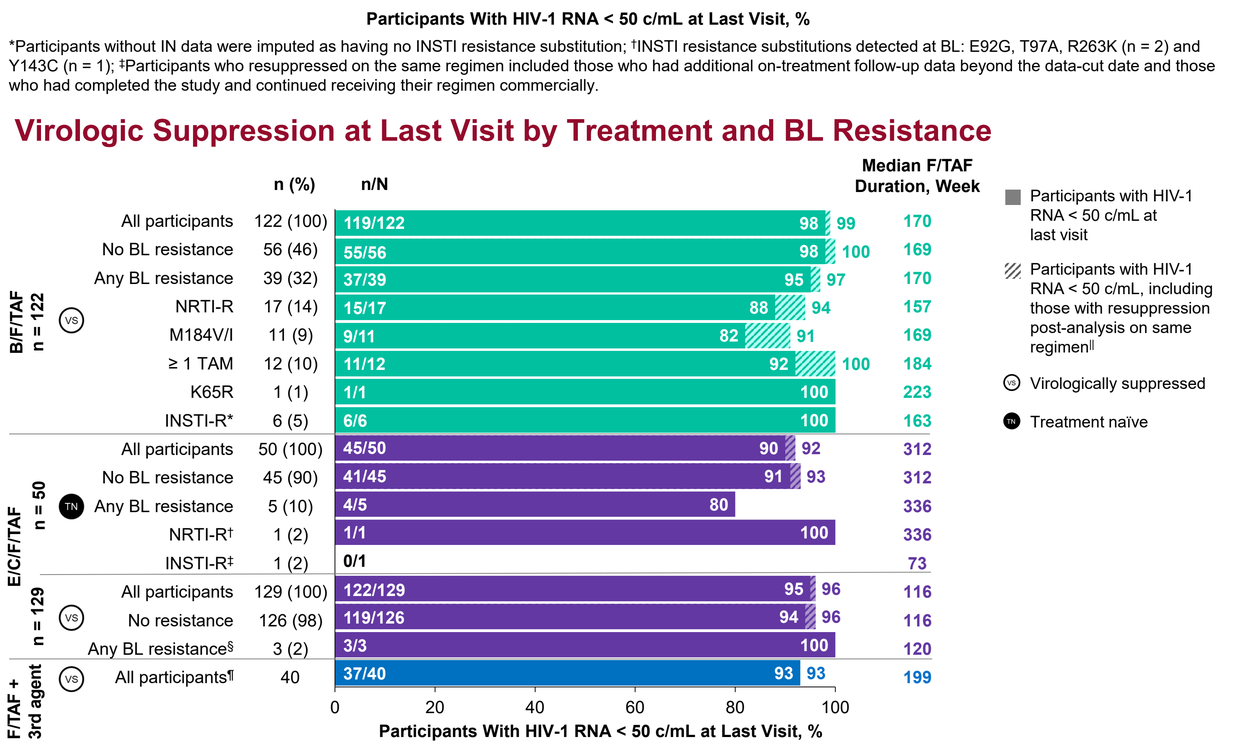
For further information on baseline resistance, please scan the QR code

BL Resistance and Virologic Suppression at Last Visit (Pooled Pediatric F/TAF-Treated Participants)



*Participants without IN data were imputed as having no INSTI resistance substitution; [†]INSTI resistance substitutions detected at BL: E92G, T97A, R263K (n = 2) and Y143C (n = 1); [‡]Participants who resuppressed on the same regimen included those who had additional on-treatment follow-up data beyond the data-cut date and those who had completed the study and continued receiving their regimen commercially.

Virologic Suppression at Last Visit by Treatment and BL Resistance



*E92G, T97A (n = 2 each); R263K, Y143C (n = 1 each); [†]K219Q; [‡]R263K; [§]M184V (n = 2), T215F (n = 1); [¶]No BL data available; [‖]Participants who resuppressed on the same regimen included those who had additional on-treatment follow-up data beyond the data-cut date and those who had completed the study and continued receiving their regimen commercially.

Post-BL Resistance Analyses

Participants, n (%)	B/F/TAF (VS) n = 122	E/C/F/TAF (TN) n = 50	E/C/F/TAF (VS) n = 129	F/TAF + 3rd agent (VS) n = 40
Participants analyzed for resistance development	8/122 (7)	9/50 (18)	10/129 (8)	4/40 (10)
Treatment-emergent resistance substitutions	0	0	0	4/4 (100)
Emergent NRTI-R	0	0	0	2/4 (50)
K65R	–	–	–	2/4 (50)
M184V/I	–	–	–	1/4 (25)
1 TAM (D67N or K219N)	–	–	–	2/4 (50)
Emergent NNRTI-R	0	0	0	4/4 (100)
K101E	–	–	–	1/4 (25)
K103N	–	–	–	4/4 (100)
V106M	–	–	–	1/4 (25)
Y181C	–	–	–	1/4 (25)
Y188C/H/L	–	–	–	2/4 (50)
Emergent PI-R	0	0	0	0
Emergent INSTI-R	0	0	0	1/4 (25)
T97A	–	–	–	1/4 (25)
Resuppressed without change in study regimen	7/8 (88)	6/9 (67)	7/10 (70)	0

- Four participants without BL genotypic data receiving F/TAF + efavirenz experienced confirmed virologic failure with (presumed) treatment-emergent resistance
  - All had samples from multiple timepoints analyzed with NNRTI resistance substitutions detected; K65R ± M184V was later detected in two participants
  - All switched their third agent and achieved HIV-1 RNA < 50 c/mL at subsequent timepoints, but three of the four participants had additional virologic rebounds
  - One participant with K65R maintained virologic suppression through study discontinuation at Week 264
  - One participant with K65R + M184V had virologic rebound again at Week 334 with no K65R or M184V detected
  - Adherence by pill count for these four participants was < 95%

For the virologic profiles of these individuals, please scan the QR code

References: **1.** Sax PE, et al. Lancet 2015;385:2606-2615. **2.** Sharma S, et al. Intl Workshop HIV Pediatr 2021; Poster 23. **3.** DHHS. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/pediatric-arv/guidelines-pediatric-arv.pdf (accessed May 16, 2023). **4.** Descovy USPI, Gilead Sciences, January 2022. **5.** EACS. https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf (accessed May 16, 2023). **6.** Genvoya EU SmPC, Gilead Sciences, September 2020. **7.** Biktarvy USPI, Gilead Sciences, October 2022. **8.** Biktarvy EU SmPC, Gilead Sciences, April 2023. **9.** Genvoya USPI, Gilead Sciences, January 2022. **10.** NCT02881320. https://clinicaltrials.gov/ct2/show/NCT02881320 (accessed April 28, 2023). **11.** NCT01854775. https://clinicaltrials.gov/ct2/show/NCT01854775 (accessed April 28, 2023). **12.** NCT02276612. https://clinicaltrials.gov/ct2/show/NCT02276612 (accessed April 28, 2023). **13.** NCT02285114. https://clinicaltrials.gov/ct2/show/NCT02285114 (accessed April 28, 2023).

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Abbreviations: ART, antiretroviral therapy; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BL, baseline; c, copies; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; EU, European Union; F/TAF, emtricitabine/tenofovir alafenamide; IN, integrase; INSTI, integrase strand transfer inhibitor; LOCF, last observation carried forward; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PI, protease inhibitor; PK, pharmacokinetics; PR, protease; Q, quartile; R, resistance; RT, reverse transcriptase; TAF, tenofovir alafenamide; TAM, thymidine analog mutation; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; TN, treatment-naïve; VL, viral load; VS, virologically suppressed.

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