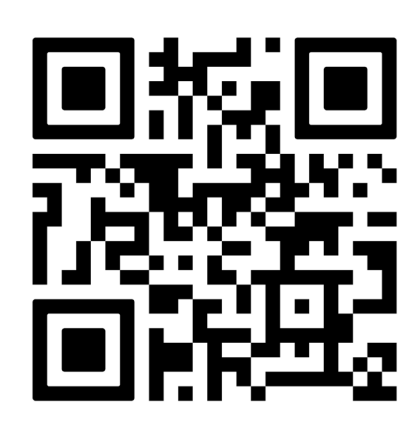


Preexisting and Post-Baseline Resistance Analyses in Pooled Pediatric Studies of Emtricitabine/Tenofovir Alafenamide (F/TAF)–Based Antiretroviral Therapy

Scan for more information



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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

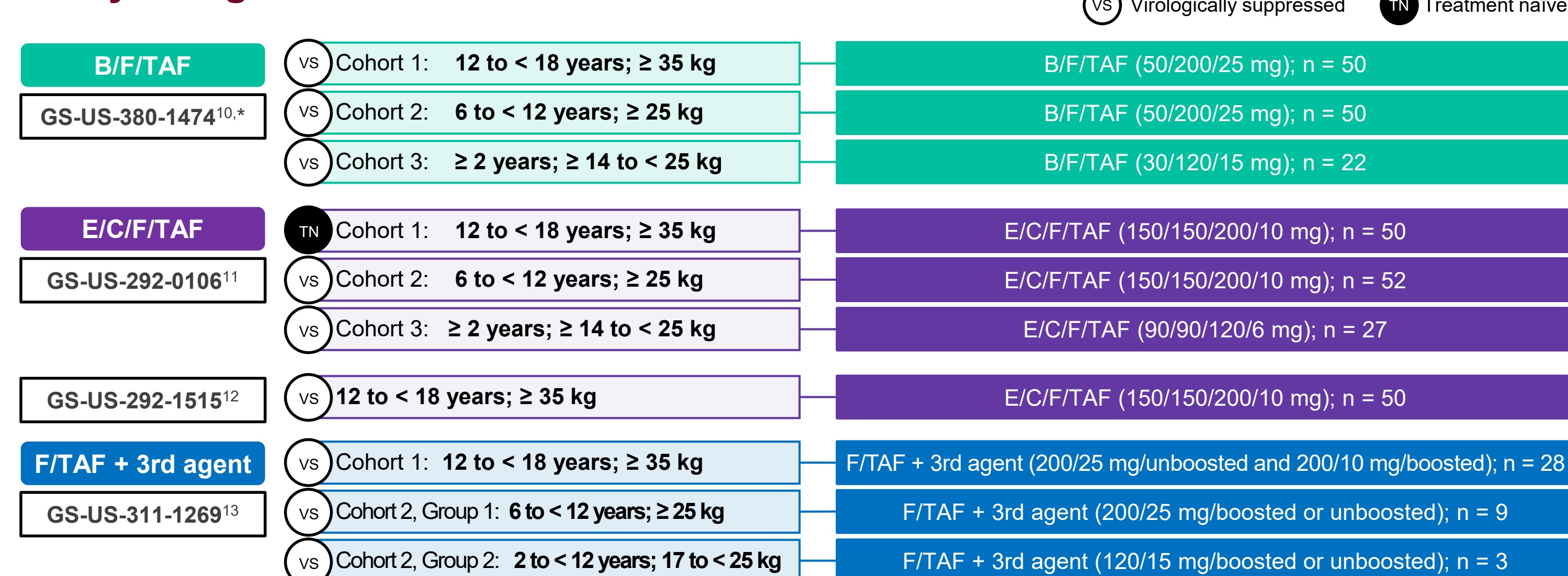
- TAF results in 91% lower plasma TFV exposure than TDF, and is associated with improved renal and bone safety in adults and adolescents^{1,2}
- F/TAF is a guideline-recommended NRTI backbone for HIV treatment,^{3–5} with two fixed-dose combinations approved in the U.S.A. for use in adolescents and children (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 adults⁹
 - 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



*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 = 120), Uganda (n = 81), U.S.A. (n = 70), 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

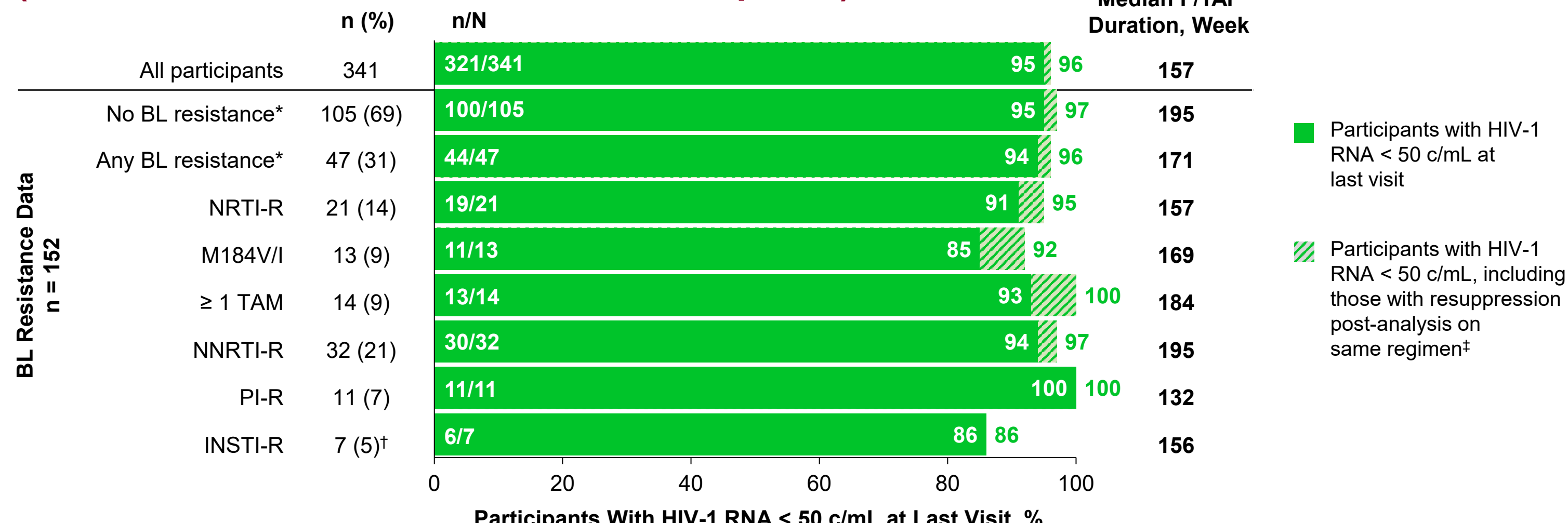
Participants, n (%)	F/TAF pooled N = 341	B/F/TAF (VS) n = 122	E/C/F/TAF (TN) n = 50	E/C/F/TAF (VS) n = 129	F/TAF + 3rd agent (VS) n = 40
PR/RT ± IN data at BL	152 (45)	95 (78)	50 (100)	7 (5)	0
PR/RT	152 (45)	95 (78)*	50 (100)	7 (5) [†]	0
IN	141 (41)	92 (75) [‡]	49 (98)	0	0

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

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

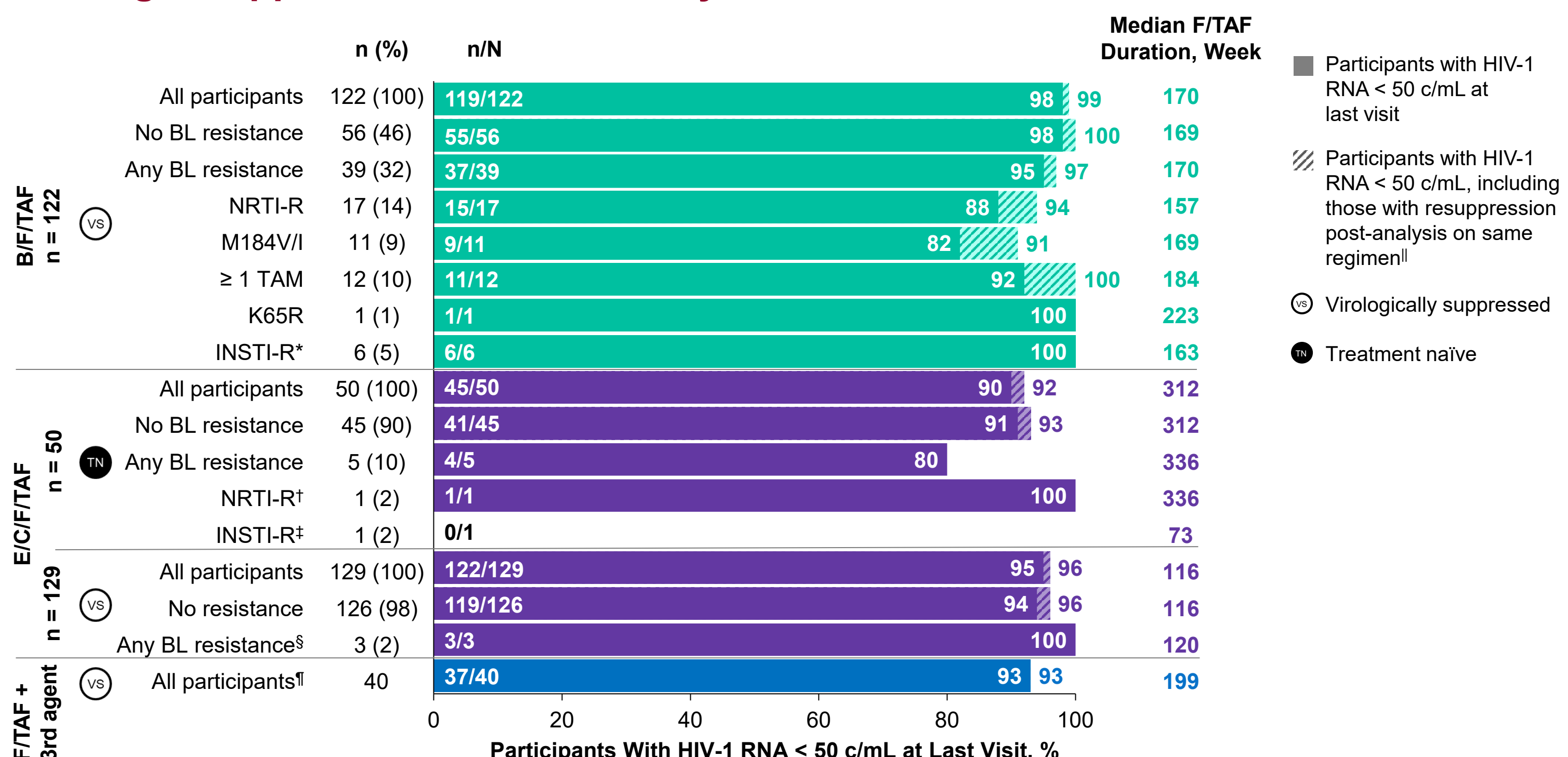


BL Resistance and Virologic Suppression at Last Visit (Pooled Pediatric F/TAF-Treated Participants)



*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



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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.