HIV-1 Resistance Analysis of Treatment-Naïve People With HIV and HBV Receiving B/F/TAF or DTG + F/TDF

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ALLIANCE

Conclusions

- In people with HIV-1 and HBV receiving DTG + F/TDF or B/F/TAF, preexisting RAMs were uncommon and did not affect HIV-1 virologic suppression through EOS
- Among participants meeting criteria for inclusion in the final RAP, none developed resistance to the study drugs
- Two emergent RAMs occurred in one participant who experienced nonadherence while receiving DTG + F/TDF, highlighting the importance of adherence in suppressing viral load and preventing treatment-emergent resistance
- These results provide further evidence of the long-term efficacy and high barrier to resistance associated with B/F/TAF

Plain Language Summary

- The ALLIANCE study looked at how well two treatments called B/F/TAF and DTG + F/TDF work to treat adults who had both human immunodeficiency virus type 1 (HIV-1) and hepatitis B virus (HBV) infections
 - After 96 weeks, both treatments lowered the levels of HIV-1 and HBV in the blood
- This analysis of the ALLIANCE study looks at genetic changes in HIV. These changes occur by chance and some of them stop HIV medicines from working; these changes are called resistance mutations
- People were tested at the start of the study to see if they had HIV resistance mutations
 - The results showed that most people did not have resistance mutations
 - When resistance mutations were present, they did not affect the ability of the treatments to lower the level of HIV-1 in the blood
- Researchers wanted to see if people with increases of HIV-1 in their blood during the study had developed resistance mutations during the study
 - One person, taking DTG + F/TDF, developed resistance mutations

Introduction

- Globally, approximately 3.1 million people are living with both HIV-1 and hepatitis B virus (HBV)[1]
- Tenofovir alafenamide (TAF)– or tenofovir disoproxil fumarate (TDF)–based antiretroviral therapy is recommended as an initial treatment for most adults and adolescents with HIV-1 and HBV[2-4]
- The ALLIANCE study demonstrated that bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) was noninferior to dolutegravir (DTG) + F/TDF at achieving HIV-1 RNA suppression, and superior at achieving HBV DNA suppression, at Week 48 in treatment-naïve adults with both HIV-1 and HBV infections, with high rates of HIV-1 and HBV suppression also observed at Week 96[5]
- Resistance-associated mutations (RAMs) can reduce the effectiveness of HIV-1 treatments; guidelines recommend genotypic testing when starting treatment or during treatment failure, and that treatment options with a high barrier to resistance should be selected when possible[2,3,6,7]

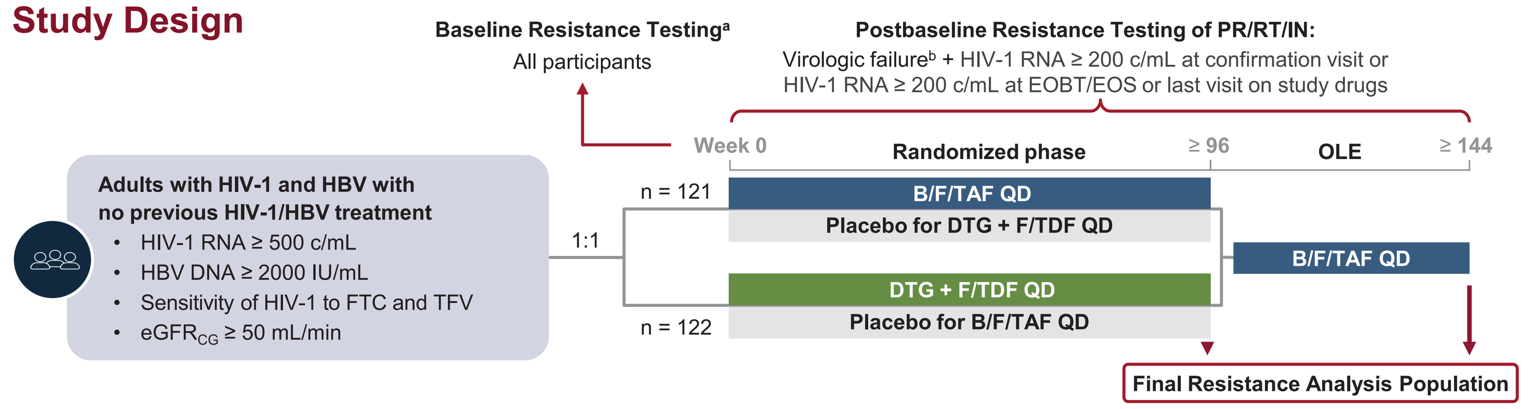
Objective

- To report HIV-1 resistance analyses to the end of the ALLIANCE study up to ≥ 144 weeks, including the 48-week open-label extension (OLE) phase in which participants received B/F/TAF

Methods

- ALLIANCE (NCT03547908) was a randomized, double-blind, active-controlled, Phase 3 clinical study, which included a 48-week OLE phase[1]

Study Design


Baseline Resistance Testing[a]
All participants
Postbaseline Resistance Testing of PR/RT/IN:
Virologic failure[b] + HIV-1 RNA ≥ 200 c/mL at confirmation visit or HIV-1 RNA ≥ 200 c/mL at EOBT/EOS or last visit on study drugs
Adults with HIV-1 and HBV with no previous HIV-1/HBV treatment
HIV-1 RNA ≥ 500 c/mL
HBV DNA ≥ 2000 IU/mL
Sensitivity of HIV-1 to FTC and TFV
eGFRCG ≥ 50 mL/min
1:1
Week 0
Randomized phase
≥ 96
OLE
≥ 144
n = 121
B/F/TAF QD
Placebo for DTG + F/TDF QD
n = 122
DTG + F/TDF QD
Placebo for B/F/TAF QD
B/F/TAF QD
Final Resistance Analysis Population

[a]Historical genotypes (PR/RT/IN) were collected if available, and PR/RT genotyping from screening plasma samples was aggregated to generate a composite baseline sequence. [b]Virologic failure was defined as virologic rebound (HIV-1 RNA ≥ 50 c/mL after achieving < 50 c/mL, subsequently confirmed at the following visit; > 1 $\log_{10}$ increase from nadir, subsequently confirmed at the following visit) or HIV-1 RNA ≥ 50 c/mL at last on-treatment visit.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; c, copies; DTG, dolutegravir; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation; EOBT, end of blinded treatment; EOS, end of study; F/TDF, emtricitabine/tenofovir disoproxil fumarate; FTC, emtricitabine; HBV, hepatitis B virus; IN, integrase; OLE, open-label extension; PR, protease; QD, once daily; RT, reverse transcriptase; TFV, tenofovir.

- Participants meeting the criteria for postbaseline resistance testing for protease (PR), reverse transcriptase (RT), and integrase (IN) who did not subsequently achieve resuppression (HIV-1 RNA < 50 copies [c]/mL) on study drugs were included in the final resistance analysis population (RAP) according to treatment group:
 1. **DTG + F/TDF group**: Participants who received DTG + F/TDF in the randomized phase, analyzed through end of blinded treatment
 2. **B/F/TAF group**: Participants who received B/F/TAF in the randomized phase, irrespective of receiving B/F/TAF in the OLE phase, analyzed through end of study (EOS)
 3. **DTG + F/TDF → B/F/TAF group**: Participants who received DTG + F/TDF in the randomized phase and then received ≥ 1 dose of B/F/TAF in the OLE phase, analyzed through EOS
- Virologic outcomes were assessed using the last-observation-carried-forward (LOCF) approach

Results

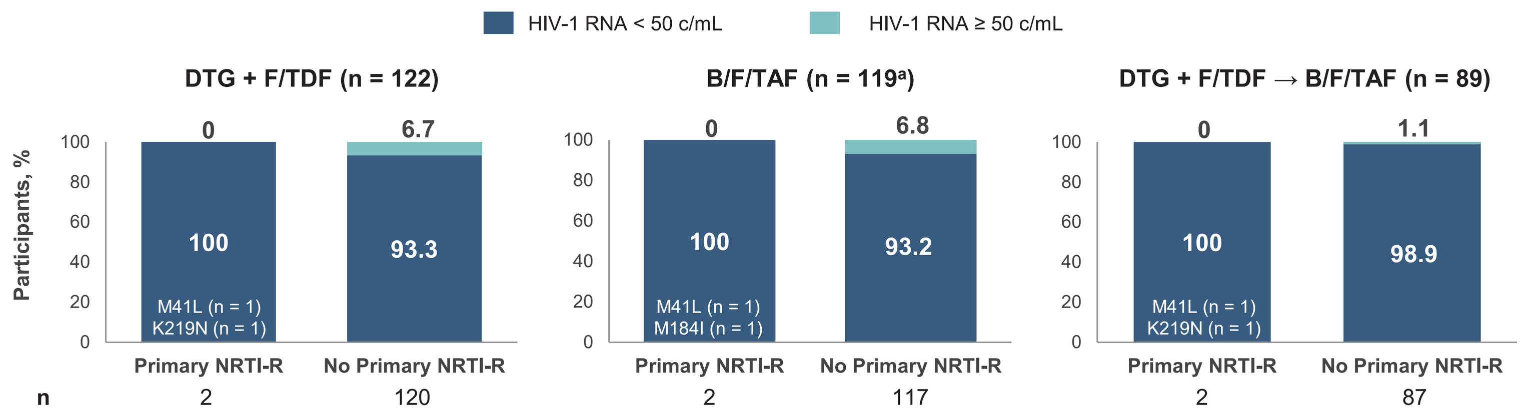
Baseline Demographic and Clinical Characteristics[5]

	DTG + F/TDF n = 122	B/F/TAF n = 121	DTG + F/TDF → B/F/TAF n = 89[a]
Age, years, median (Q1, Q3)	32 (25, 38)	31 (27, 39)	34 (28, 39)
Male sex at birth, n (%)	120 (98)	112 (93)	87 (98)
Asian race, n (%)	106 (87)	108 (89)	84 (94)
BMI, kg/m^2, median (Q1, Q3)	21.7 (19.3, 23.7)	22.2 (19.9, 24.7)	22.4 (20.4, 25.5)
$eGFR_{CG}$, mL/min, median (Q1, Q3)	104.7 (93.0, 124.2)	106.8 (94.8, 130.8)	94.2 (80.4, 112.8)
HIV-1 RNA, $\log_{10}$ c/mL, median (Q1, Q3)	4.69 (4.26, 5.04)	4.66 (4.22, 5.12)	1.28 (1.28, 1.28)
HIV-1 RNA > 100,000 c/mL, n (%)	34 (28)	38 (31)	0 (0)
HIV-1 subtype B, n (%)	33 (27)	24 (20)	11 (12)
HIV-1 non-B subtype, n (%)	59 (48)[b]	70 (59)[c]	49 (55)[d]
CD4 count, cells/μL, median (Q1, Q3)	236 (121, 380)	245 (127, 383)	497 (320, 617)
HIV-1 disease status: asymptomatic, n (%)	81 (66)	83 (69)	57 (64)
HBV DNA ≥ 8 $\log_{10}$ IU/mL, n (%)	66 (54)	60 (50)	0 (0)

[a]Data for this group refer to the baseline at entry to the OLE phase.
[b]Non-B subtypes: AB (3%), AE (35%), BF (2%), G (2%), complex (7%); there were 30 participants (25%) with unknown HIV-1 subtype.
[c]n = 119; non-B subtypes: A (1%), AB (1%), AE (39%), AG (3%), BC (1%), C (1%), G (3%), complex (10%); there were 25 participants (21%) with unknown HIV-1 subtype.
[d]Non-B subtypes: AB (3%), AE (45%), G (2%), complex (4%); there were 29 participants (33%) with unknown HIV-1 subtype.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BMI, body mass index; c, copies; CD4, cluster of differentiation 4; DTG, dolutegravir; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft-Gault equation; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HBV, hepatitis B virus; OLE, open-label extension; Q, quartile.

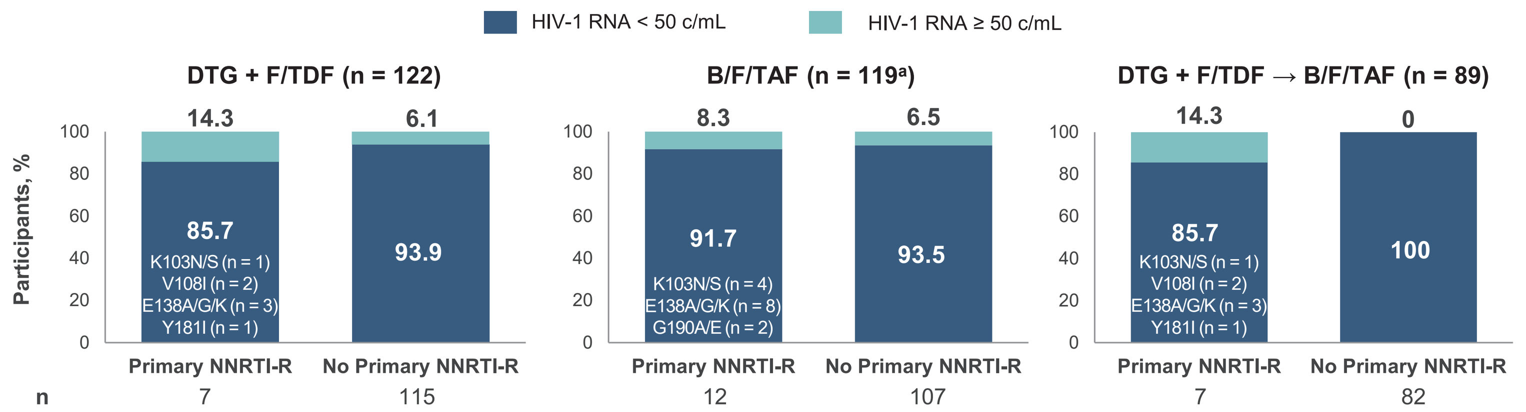
- The presence of primary RAMs affecting nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) had no significant effect on efficacy outcomes
 - NRTI primary RAMs: DTG + F/TDF n = 2, B/F/TAF n = 2, DTG + F/TDF → B/F/TAF n = 2
 - NNRTI primary RAMs: DTG + F/TDF n = 7, B/F/TAF n = 12, DTG + F/TDF → B/F/TAF n = 7

LOCF Efficacy by Baseline NRTI-R


HIV-1 RNA < 50 c/mL
HIV-1 RNA ≥ 50 c/mL
Participants, %
DTG + F/TDF (n = 122)
Primary NRTI-R: 100 / 0; M41L (n = 1), K219N (n = 1); n 2
No Primary NRTI-R: 93.3 / 6.7; n 120
B/F/TAF (n = 119[a])
Primary NRTI-R: 100 / 0; M41L (n = 1), M184I (n = 1); n 2
No Primary NRTI-R: 93.2 / 6.8; n 117
DTG + F/TDF → B/F/TAF (n = 89)
Primary NRTI-R: 100 / 0; M41L (n = 1), K219N (n = 1); n 2
No Primary NRTI-R: 98.9 / 1.1; n 87

[a]Two randomized and treated participants were excluded from the full analysis set due to having no postbaseline HIV-1 RNA or HBV DNA results while on study drug.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; c, copies; DTG, dolutegravir; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HBV, hepatitis B virus; LOCF, last observation carried forward; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; R, resistance.

LOCF Efficacy by Baseline NNRTI-R


HIV-1 RNA < 50 c/mL
HIV-1 RNA ≥ 50 c/mL
Participants, %
DTG + F/TDF (n = 122)
Primary NNRTI-R: 85.7 / 14.3; K103N/S (n = 1), V108I (n = 2), E138A/G/K (n = 3), Y181I (n = 1); n 7
No Primary NNRTI-R: 93.9 / 6.1; n 115
B/F/TAF (n = 119[a])
Primary NNRTI-R: 91.7 / 8.3; K103N/S (n = 4), E138A/G/K (n = 8), G190A/E (n = 2); n 12
No Primary NNRTI-R: 93.5 / 6.5; n 107
DTG + F/TDF → B/F/TAF (n = 89)
Primary NNRTI-R: 85.7 / 14.3; K103N/S (n = 1), V108I (n = 2), E138A/G/K (n = 3), Y181I (n = 1); n 7
No Primary NNRTI-R: 100 / 0; n 82

[a]Two randomized and treated participants were excluded from the full analysis set due to having no postbaseline HIV-1 RNA or HBV DNA results while on study drug.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; c, copies; DTG, dolutegravir; F/TDF, emtricitabine/tenofovir disoproxil fumarate; HBV, hepatitis B virus; LOCF, last observation carried forward; NNRTI, non-nucleoside reverse transcriptase inhibitor; R, resistance.

- Baseline primary RAMs affecting PR inhibitors were rare: DTG + F/TDF n = 4, B/F/TAF n = 1, DTG + F/TDF → B/F/TAF n = 1
 - All of these participants achieved virologic suppression (< 50 c/mL) at EOS
- Seven participants (5.7%) in the DTG + F/TDF group met the criteria for inclusion in the final RAP at the end of the randomized phase
 - No postbaseline primary RAMs were detected in the seven participants with IN data
 - Of the six participants with PR/RT data, none had treatment-emergent primary RAMs, although one had primary NNRTI RAMs at baseline (E138E/G) and at Week 156 (E138G)
 - Emergent secondary RAMs in IN and RT were not associated with genotypic or phenotypic changes to bictegravir, DTG, emtricitabine (FTC), or tenofovir (TFV)
- Six participants (5.0%) in the B/F/TAF group and one participant (1.1%) in the DTG + F/TDF → B/F/TAF group met the criteria for inclusion in the final RAP through EOS
 - Five participants had IN data; none had postbaseline primary RAMs
 - Five participants had postbaseline PR/RT data; none had postbaseline primary RAMs
 - Emergent secondary RAMs in RT were not associated with phenotypic changes to FTC or TFV

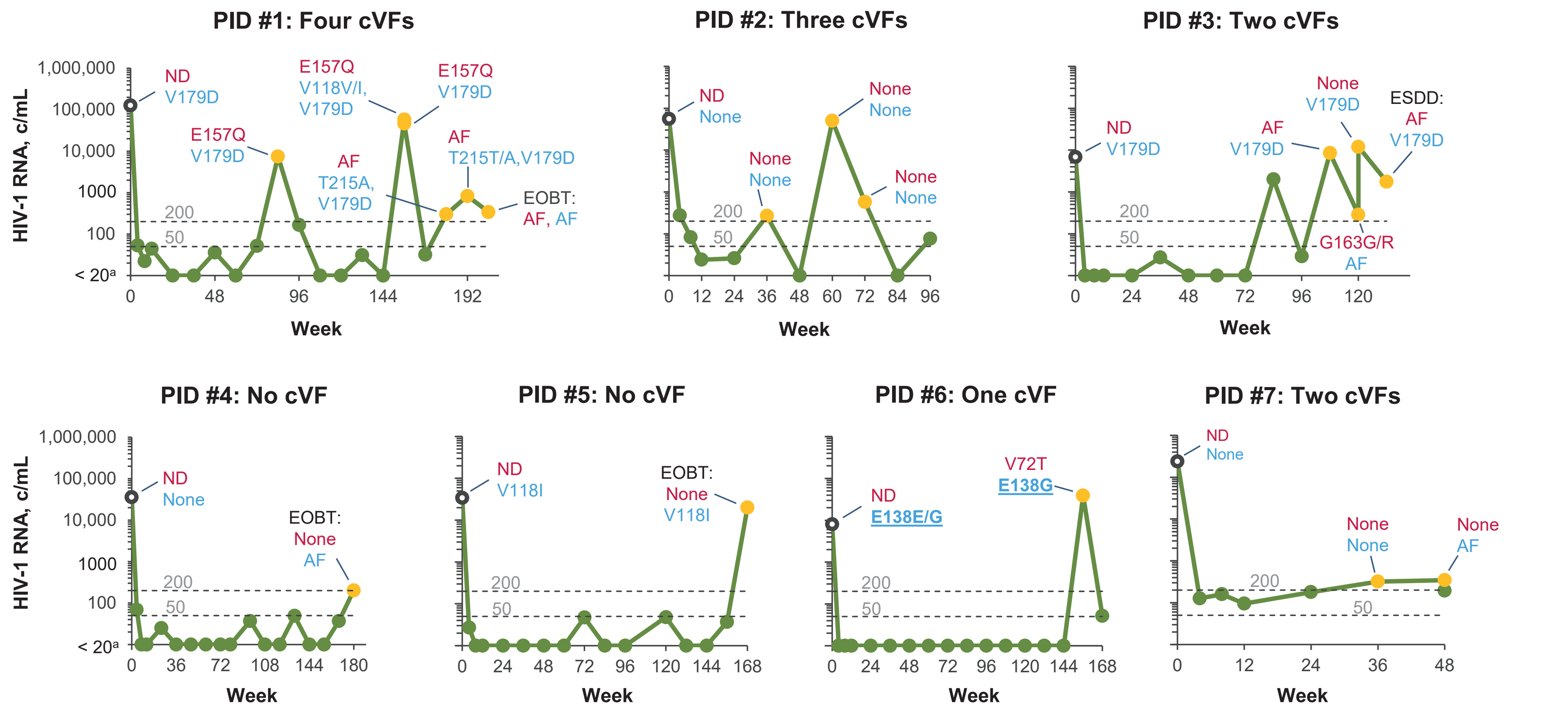
HIV-1 Drug RAMs (Based on IAS-USA List)[7]

	Primary RAMs	Secondary RAMs
NRTI-R	K65R/E/N, T69 insertions, K70E, L74V/I, Y115F, Q151M, M184V/I, TAMs (M41L, D67N, K70R, L210W, T215F/Y, K219E/N/Q/R)	E44D, A62V, T69D/N, V75I, F77L, F116Y, V118I, T215A/C/D/E/G/H/I/L/N/S/V
NNRTI-R	L100I, K101E/P, K103N/S, V106A/M, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C, M230I/L	V90I, A98G, K101H, V106I, V179D/F/T
PI-R	D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M	Not analyzed
INSTI-R	T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K	M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C, A128T, E138K/A, G140A/C/S, P145S, Q146R/I/K/L/P, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A

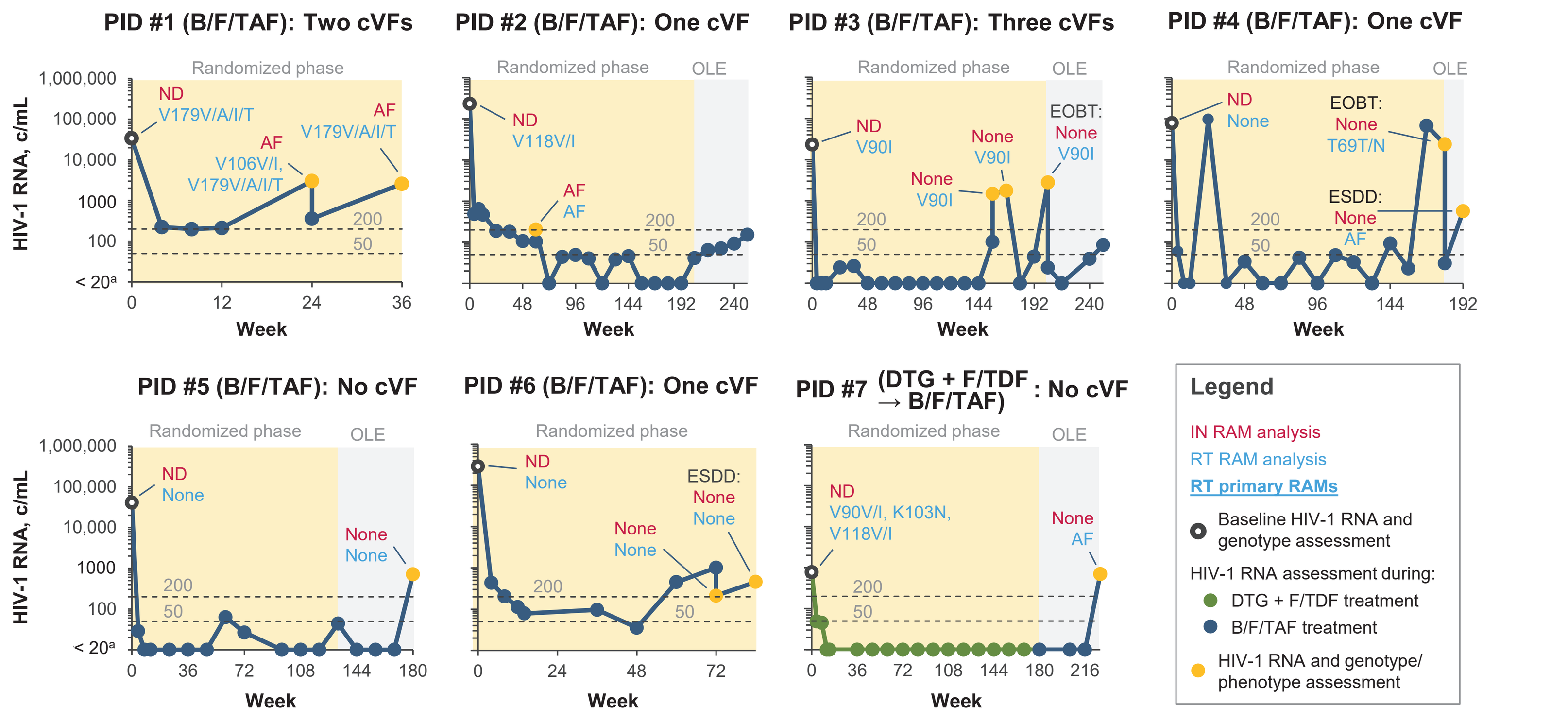
IAS-USA, International Antiviral Society–USA; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; R, resistance; RAM, resistance-associated mutation; TAM, thymidine analog mutation.

Virologic Profiles and RAMs

Participants Receiving DTG + F/TDF in the Final RAP Through EOBT


PID #1: Four cVFs
PID #2: Three cVFs
PID #3: Two cVFs
PID #4: No cVF
PID #5: No cVF
PID #6: One cVF
PID #7: Two cVFs
HIV-1 RNA, c/mL
Week

Participants Receiving B/F/TAF in the Final RAP Through EOS


PID #1 (B/F/TAF): Two cVFs
PID #2 (B/F/TAF): One cVF
PID #3 (B/F/TAF): Three cVFs
PID #4 (B/F/TAF): One cVF
PID #5 (B/F/TAF): No cVF
PID #6 (B/F/TAF): One cVF
PID #7 (DTG + F/TDF → B/F/TAF): No cVF
Randomized phase
OLE
HIV-1 RNA, c/mL
Week
Legend
IN RAM analysis
RT RAM analysis
RT primary RAMs
Baseline HIV-1 RNA and genotype assessment
HIV-1 RNA assessment during:
DTG + F/TDF treatment
B/F/TAF treatment
HIV-1 RNA and genotype/phenotype assessment

Week 0 (baseline) sequences are the composite of historical and screening genotyping data.
[a]Includes all readings where HIV-1 RNA was not detected.
AF, assay failure; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; c, copies; cVF, confirmed virologic failure; DTG, dolutegravir; EOBT, end of blinded treatment; EOS, end of study; ESDD, early study drug discontinuation; F/TDF, emtricitabine/tenofovir disoproxil fumarate; IN, integrase; ND, no data; OLE, open-label extension; PID, participant ID; RAM, resistance-associated mutation; RAP, resistance analysis population; RT, reverse transcriptase.

Additional Postbaseline Testing

- Another eight participants who did not qualify for the final RAPs had resistance testing during the study due to confirmed virologic failure(s) or having HIV-1 RNA ≥ 200 c/mL at key study endpoints (DTG + F/TDF n = 3, B/F/TAF n = 4, DTG + F/TDF → B/F/TAF n = 1)
- For participants with available IN postbaseline data (n = 5), no INSTI RAMs were detected
- For participants with available PR/RT postbaseline data (n = 4), emergent RAMs (K70E and M184V/I) in RT were detected in one participant receiving DTG + F/TDF
 - This participant had documented nonadherence to DTG + F/TDF throughout the study, experienced three confirmed virologic failures, and subsequently achieved HIV-1 RNA < 50 c/mL on study drugs

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