Poster 506

Resistance Analyses of Bictegravir/Emtricitabine/Tenofovir Alafenamide Switch Studies

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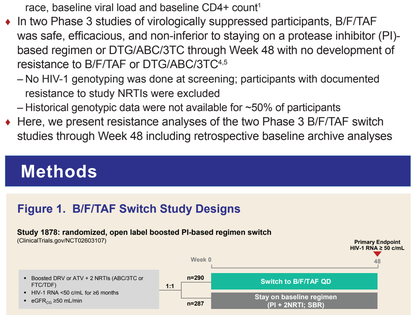
Background

- Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a single table regimen recently approved by the US FDA for treatment of HIV-1 infection in treatment-naïve and virologically suppressed adults without resistance to its components[1]
- In two Phase 3 studies of treatment-naïve participants, B/F/TAF was safe, efficacious, and non-inferior to either dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) or dolutegravir + F/TAF through Week 48 with no development of resistance to study medications[2,3]
  - Treatment outcomes were similar across subgroups, regardless of age, sex, race, baseline viral load and baseline CD4+ count[1]
- In two Phase 3 studies of virologically suppressed participants, B/F/TAF was safe, efficacious, and non-inferior to staying on a protease inhibitor (PI)-based regimen or DTG/ABC/3TC through Week 48 with no development of resistance to B/F/TAF or DTG/ABC/3TC[4,5]
  - No HIV-1 genotyping was done at screening; participants with documented resistance to study NRTIs were excluded
  - Historical genotypic data were not available for ~50% of participants
- Here, we present resistance analyses of the two Phase 3 B/F/TAF switch studies through Week 48 including retrospective baseline archive analyses

Methods

Figure 1. B/F/TAF Switch Study Designs



- Historical plasma RNA genotypes were collected if available but were not required for study entry
- Eligible participants had no documented or suspected resistance to FTC, TFV, DTG, ABC, or 3TC, including but not limited to K65R and M184V/I in reverse transcriptase (RT)
- Plasma viral RNA genotyping and phenotyping of protease (PR), RT, and integrase (IN) (PhenoSenseGT, GeneSeq IN, and PhenoSense IN, Monogram Biosciences) were attempted for all participants in the resistance analysis population (RAP):
  - Confirmed virologic failure (two consecutive visits with HIV-1 RNA ≥ 50 c/mL) and HIV-1 RNA ≥ 200 c/mL at the confirmation visit
  - HIV-1 RNA ≥ 200 c/mL at Week 48 or last visit on study drug
- Baseline proviral DNA genotyping (GenoSure Archive, Monogram Biosciences) was conducted retrospectively on select participants:
  - Participants included in the RAP
  - Participants who switched to B/F/TAF with ≥ 10 years prior antiretroviral (ARV) treatment or unknown ARV initiation date
- Drug resistance substitutions were defined according to the IAS-USA list[6] with some modifications
  - **Primary INSTI-R:** T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K in IN
  - **Secondary INSTI-R:** M50I, H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, G118R, S119P/R/T, F121C, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151A/L, S153A/F/Y, E157K/Q, G163K/R, and E170A in IN
  - **NRTI-R:** M41L, K65E/N/R, D67N, T69 insertions, K70E/R, L74I/V, Y115F, Q151M, M184I/V, L210W, T215F/Y, and K219E/N/Q/R in RT
  - **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, and M230I/L in RT
  - **PI-R:** D30N, V32I, M46I/L, I47A/V, G48V, I50L/V, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, and L90M in PR

INSTI = IN strand transfer inhibitor; NRTI = nucleos(t)ide RT inhibitor; NNRTI = nonnucleoside RT inhibitor; PI = protease inhibitor; R = resistance

Results

Figure 2. Virologic Outcome at Week 48 by FDA Snapshot

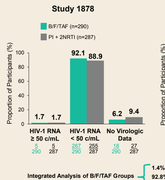


Table 1. Baseline Genotypic Data Sources (Integrated Analysis of B/F/TAF Groups)

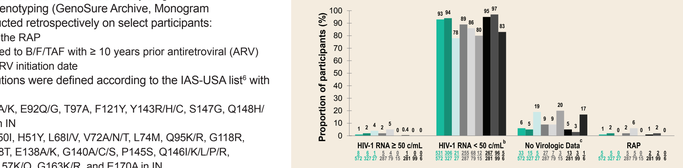
	Number of Participants, n (%)		
	B/F/TAF n=572	PI + 2NRTI n=287	ABC/DTG/3TC n=281
IN Baseline Data Available	170 (30%)	16 (6%)	14 (5%)
Historical Genotype	23 (4%)	11 (4%)	12 (4%)
Baseline Proviral Genotype	149 (26%)	7 (2%)	2 (1%)
PR/RT Baseline Data Available	405 (71%)	125 (44%)	138 (49%)
Historical Genotype	280 (49%)	122 (43%)	137 (49%)
Baseline Proviral Genotype	149 (26%)	7 (2%)	2 (1%)

IN = integrase; PR = protease; RT = reverse transcriptase

Table 2. Distribution of Baseline HIV-1 Subtypes

	Number of Participants, n (%)		
HIV-1 Subtype	B/F/TAF n=405	PI + 2NRTI n=125	ABC/DTG/3TC n=138
B	327 (81%)	79 (63%)	99 (72%)
Non-B	27 (7%)	15 (12%)	6 (4%)
A	2 (<1%)	0	0
A1	2 (<1%)	0	0
AE	3 (<1%)	0	3
AG	5 (1%)	5 (4%)	0
C	4 (1%)	6 (5%)	1 (<1%)
Complex	9 (2%)	3 (2%)	2 (1%)
D	1 (<1%)	0	0
F	1 (<1%)	0	0
H	0	1 (<1%)	0
Undetermined	51 (13%)	31 (25%)	33 (24%)

Fiugre 3. Virologic Outcome at Week 48 Stratified by HIV-1 Subtype



a. Participants with no baseline genotypic data are excluded from the subtype analysis.
b. Differences between subtype B and non-B Week 48 outcomes were assessed by Fisher's exact test. For the HIV-1 RNA < 50 c/mL category, p values for the B/F/TAF, PI + 2NRTI, and ABC/DTG/3TC groups were 0.01, 0.69, and 0.21, respectively.
c. For the No Virologic Data category, p values for the B/F/TAF, PI + 2NRTI, and ABC/DTG/3TC groups were 0.01, 0.20, and 0.21, respectively.

RAP = resistance analysis population

Among all treatment groups, a higher proportion of participants with non-B subtypes were missing virologic data at Week 48 compared to the proportion of participants with subtype B. In the B/F/TAF group (n=5), 3 of 5 had HIV-1 RNA < 50 c/mL at their subsequent Week 48 visits and 2 of 5 discontinued early with HIV-1 RNA < 50 c/mL. In the PI + 2NRTI group (n=3), 2 of 3 had HIV-1 RNA < 50 c/mL at their subsequent Week 48 visits and 1 of 3 had HIV-1 RNA > 50 c/mL at Week 48. In the ABC/DTG/3TC group (n=1), this participant had HIV-1 RNA < 50 c/mL at their subsequent Week 48 visit.

Table 3. Frequency of Baseline INSTI Resistance-Associated Substitutions

	Number of Participants, n (%)		
Resistance Class	B/F/TAF n=170	PI + 2NRTI n=16	ABC/DTG/3TC n=14
Primary INSTI-R	1 (0%)	0	2 (14%)
T66I	0	0	1 (7%)
T97A	1 (1%)	0	1 (7%)
Secondary INSTI-R	86 (51%)	6 (38%)	6 (43%)
M50I	30 (18%)	2 (13%)	4 (29%)
L68I/V	4 (2%)	0	0
L74M	5 (3%)	0	0
S119P/R/T	54 (32%)	4 (25%)	3 (21%)
A128T	1 (1%)	0	0
E157K/Q	8 (5%)	0	2 (14%)
G163K/R	2 (1%)	1 (6%)	0

INSTI = integrase strand transfer inhibitor; R = resistance

Table 4. Frequency of Baseline NRTI Resistance-Associated Substitutions

	Number of Participants, n (%)		
Resistance Class	B/F/TAF n=405	PI + 2NRTI n=125	ABC/DTG/3TC n=138
NRTI-R	52 (13%)	10 (8%)	4 (3%)
K65N/R	5 (1%)	1 (1%)	0
M184I/V	30 (7%)	2 (2%)	0
L74V	2 (1%)	1 (1%)	0
Y115F	2 (1%)	1 (1%)	0
Q151M	2 (1%)	0	0
Any TAM[a]	29 (7%)	8 (6%)	4 (3%)
1 TAM[a]	16 (4%)	2 (2%)	3 (2%)
≥2 TAMs[a]	13 (3%)	6 (5%)	1 (1%)
M41L	14 (4%)	2 (2%)	2 (1%)
D67N	7 (2%)	6 (5%)	0
K70R	11 (3%)	5 (4%)	0
L210W	4 (1%)	0	1 (1%)
T215F/Y	9 (2%)	4 (3%)	0
K219E/N/Q/R	8 (2%)	6 (5%)	2 (1%)

a.TAMs are M41L, D67N, K70R, L210W, T215F/Y, and K219E/N/Q/R in RT

NRTI = nucleos(t)ide reverse transcriptase inhibitor; R = resistance; RT = reverse transcriptase; TAMs = thymidine analog mutations

Table 5. Frequency of Baseline NNRTI Resistance-Associated Substitutions

	Number of Participants, n (%)		
Resistance Class	B/F/TAF n=405	PI + 2NRTI n=125	ABC/DTG/3TC n=138
NNRTI-R	73 (18%)	25 (20%)	13 (9%)
K101E/P	6 (2%)	1 (1%)	0
K103N/S	46 (11%)	14 (11%)	5 (4%)
V108I	6 (2%)	2 (2%)	2 (1%)
E138A/K/Q	12 (3%)	2 (2%)	5 (4%)
V179L	0	1 (1%)	0
Y181C/I	13 (3%)	5 (4%)	0
Y188H/L	3 (1%)	0	0
G190A/E	5 (1%)	4 (3%)	0
H221Y	3 (1%)	3 (2%)	3 (2%)
P225H	3 (1%)	0	0
F227C	1 (<1%)	0	0
M230I	0	0	1 (1%)

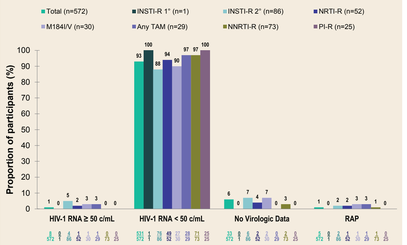
NNRTI = nonnucleoside reverse transcriptase inhibitor; R = resistance

Table 6. Frequency of Baseline PI Resistance-Associated Substitutions

	Number of Participants, n (%)		
Resistance Class	B/F/TAF n=405	PI + 2NRTI n=125	ABC/DTG/3TC n=138
PI-R	25 (6%)	5 (4%)	5 (4%)
D30N	3 (1%)	1 (1%)	0
M46I/L	8 (2%)	2 (2%)	3 (2%)
Q58E	1 (<1%)	0	1 (1%)
V82A/L/T	5 (1%)	1 (1%)	0
I84V	3 (1%)	0	0
L90M	9 (2%)	1 (1%)	2 (1%)

PI-R = protease inhibitor resistance

Figure 4. Week 48 Virologic Outcome of B/F/TAF-treated Participants Stratified by Baseline Resistance Category



1° = primary; 2° = secondary; RAP = resistance analysis population

No significant differences in virologic outcome by presence or absence of baseline resistance in the B/F/TAF group were observed.

Table 7. Profiles of Participants in Resistance Analysis Population

Patient #	Treatment Group	USPI RAP[a]	Virologic Outcome	Visit	HIV-1 RNA (c/mL)	Resistance Substitutions[a] IN	Resistance Substitutions[a] RT	Drug Susceptibility (Fold Change from WT)[b] BIC	DTG	ABC	3TC	FTC	TFV	ATV	DRV
1	B/F/TAF	No	ESDD ≥200 c/mL	Baseline	<20	S119T	none	ND	ND	ND	ND	ND	ND	ND	ND
				Week 24	499	ND[c]	AF	ND	ND	AF	AF	AF	AF	AF	AF
2	B/F/TAF	Yes	cVF; W48 <50 c/mL	Baseline	159	none	V106I/I	ND	ND	ND	ND	ND	ND	ND	ND
				Week 4	206	AF	V106I	AF	AF	0.75	1.09	0.98	0.75	0.83	0.80
				Week 8	117	AF	V106I	AF	AF	0.94	1.22	0.96	0.84	0.94	0.55
3	B/F/TAF	No	ESDD ≥200 c/mL	Baseline	<20	M50I	none	ND	ND	ND	ND	ND	ND	ND	ND
				Week 12	928	AF	AF	AF	AF	AF	AF	AF	AF	AF	AF
4	B/F/TAF	Yes	ESDD ≥200 c/mL	Baseline	28	none	K70K/R M184M/V	ND	ND	ND	ND	ND	ND	ND	ND
				Week 12*	2,860	none	M184V	0.78	0.99	3.51	>141	>95	0.54	1.01	0.79
5	B/F/TAF	No	cVF; W48 <50 c/mL	Baseline	<20	S119P	K103N	ND	ND	ND	ND	ND	ND	ND	ND
				Week 36	1,500	AF	AF	AF	AF	AF	AF	AF	AF	AF	AF
6	PI + 2NRTI (DRV/ COBI + FTC/TDF)	NA	cVF; W48 <50 c/mL	Baseline	TND	none	V106V/I	ND	ND	ND	ND	ND	ND	ND	ND
				Week 8	384	AF	none	AF	AF	0.79	1.14	1.03	0.86	0.97	0.49
7	PI + 2NRTI (DRV/ COBI + FTC/TDF)	NA	cVF; W48 <50 c/mL	Baseline	<20	M50M/I	none	ND	ND	ND	ND	ND	ND	ND	ND
				Week 12	357	AF	none	AF	AF	1.00	1.30	1.26	0.82	0.72	0.56
8	PI + 2NRTI (ATV + RTV + FTC/TDF)	NA	cVF; W48 ≥200 c/mL	Baseline	TND	S119S/ A/G/T	K103N	ND	ND	ND	ND	ND	ND	ND	ND
				Week 36	1580	none	K103N E138E/K	0.84	0.78	1.01	1.05	1.23	0.85	0.51	0.33
				Week 48	982	ND	K103N E138E/K	ND	ND	0.81	1.06	0.98	0.85	0.54	0.41
9	PI + 2NRTI (DRV/ COBI + FTC/TDF)	NA	cVF; ESDD ≥50 c/mL	Baseline	99,900	none	V90I M184I	0.89	0.98	2.17	>141	>95	0.50	0.64	0.47
				Week 8	1,060	none	V90I M184I	0.84	0.88	2.31	>127	>94	0.50	0.69	0.43
10	PI + 2NRTI (DRV + RTV + ABC/3TC)	NA	ESDD ≥200 c/mL	Baseline	6,980	none	V118I M230M/I	AF	AF	0.94	1.02	1.09	0.92	0.97	0.64
				Week 4	874	AF	L74L/V V118I	AF	AF	1.22	1.17	1.35	0.85	0.86	0.80
11	ABC/ DTG/3TC	NA	cVF; W48 <50 c/mL	Baseline	TND	M50I S119R E157Q	none	ND	ND	ND	ND	ND	ND	ND	ND
				Week 12	1,200	M150I S119R E157Q	none	0.54	0.64	0.68	0.84	0.96	0.62	0.73	0.4
12	ABC/ DTG/3TC	NA	ESDD ≥200 c/mL	Baseline	TND	ND[c]	ND[c]	ND	ND	ND	ND	ND	ND	ND	ND
				Week 8	12,600	none	none	0.80	0.97	0.88	1.09	1.09	0.81	0.77	0.74

a. Participants described in the US Prescribing Information.1
b. Resistance substitutions that emerged on study drugs are in bold.
c. Clinical cutoffs: BIC = 2.5, DTG = 4.0, ABC = 4.5, 3TC = 3.5, FTC = 3.5, TFV = 1.4, ATV = 5.2, DRV = 10.
d. Insufficient sample volume for testing.
e. Plasma concentrations of bictegravir were undetectable (BLQ) and adherence by pill count was 76%.

AF = assay failure; ATV = atazanavir; cVF = confirmed virologic failure; COBI = cobicistat; DRV = darunavir; ESDD = early study drug discontinuation; FTC = emtricitabine; NA = not applicable; ND = not determined; RAP = resistance analysis population; RTV = ritonavir; TFV = tenofovir, prodrug of TAF ; TND = target not detected; W48 = Week 48

Table 8. B/F/TAF Treatment Responses for Participants with Preexisting F/TAF Resistance

Resistance Category	Patient #	Baseline NRTI-R Substitutions	Genotypic Assessment INSTI	FTC	TFV	HIV-1 RNA (c/mL)[a] D1	W4	W8	W12	W24	W36	W48
K65N/R ± other NRTI	1	K65K/N	S	S	R	<20	<20	<20	<20	25	<20	<20
	2	K65K/R	S	R	R	<20	TND	TND	TND	TND	TND	<20
	3	K65K/R	S	R	R	TND	TND	TND	TND	TND	TND	TND
	4	K65K/R, D67D/G, K70K/R, K219K/Q	S	R	R	<20	TND	<20	<20	TND	TND	TND
	5	K65K/R, Q151G/K/L/M	S	R	R	<20	TND	29	TND	TND	TND	<20
M184V/I	6	M184M/T	S	R	S	<20	<20	TND	TND	TND	TND	TND
	7	M184M/I/V	S	R	S	TND	<20	22	TND	<20	TND	TND
	8	M184M/V	S	R	S	24	TND	TND	TND	TND	<20	TND
	9	M184M/V	S	R	S	TND	53, TND	<20	TND	TND	TND	TND
	10	M184M/V	S	R	S	TND	TND	TND	TND	TND	TND	TND
	11	M184M/V	S	R	S	30	<20	22	<20	<20	TND	25
	12	M184M/V	S	R	S	TND	TND	TND	TND	TND	25	<20
	13	M184M/V	S	R	S	TND	TND	TND	TND	TND	<20	TND
	14	M184M/V	S	R	S	<20	<20	<20	23	<20	<20	TND
	15	M184V	S	R	S	TND	TND	TND	TND	TND	TND	TND
	16	M184M/V	S	R	S	<20	TND	TND	<20	TND	TND	TND
	17	M184M/V	S	R	S	TND	<20	TND	<20	TND	<20	TND
	18	M184V	S	R	S	TND	TND	TND	<20	TND	TND	TND
	19	M184M/V	S	R	S	<20	<20	<20	TND	<20	TND	<20
	20	M184V	S	R	S	TND	TND	TND	TND	TND	TND	TND
	21	M184V	S	R	S	TND	TND	TND	TND	31	TND	TND
	22	M184M/V	S	R	S	<20	<20	TND	TND	TND	TND	TND
	23	M184V	S	R	S	270	TND	(lost to follow-up)				
M184V/I + other NRTI-R	24	M184M/V, A62A/V, L74L/V	S	R	S	TND	TND	TND	<20	TND	TND	TND
	25	M184M/V, A62A/V, Y115Y/F, F116F/Y, Q151Q/M	S	R	S	TND	TND	TND	TND	TND	TND	TND
	26	M184M/V, K70K/R	S	R	S	TND	28	TND	<20	<20	<20	<20
	27[b]	M184M/V, K70K/R	S	R	S	28	<20	71, 170	2860, 1510	54[c]	38[b]	26[b]
	28	M184M/V, M41M/L, T215T/Y	S	R	RP	TND	TND	TND	TND	TND	TND	TND
	29	M184V, M41L, T215Y	S	R	RP	TND	TND	TND	TND	TND	TND	TND
	30	M184M/V, M41L, T215D/Y	S	R	RP	<20	TND	TND	TND	<20	TND	<20
	31	M184M/V, M41M/L, A62A/V, Y115Y/F	S	R	RP	TND	<20	TND	<20	<20	<20	TND
	32	M184M/V, D67D/N, K70K/R, T215T/F/I/S	S	R	RP	TND	TND	TND	TND	TND	TND	TND
	33	M184M/V, M41M/L, L210L/W, T215Y	S	R	R	<20	<20	TND	<20	42	TND	TND
	34	M184M/V, M41M/L, L210L/W, T215T/C/Y	S	R	R	<20	<20	TND	<20	53, 21	<20	24
	35	M184M/V, M41M/L, D67D/N, K70K/R, L210L/W, T215T/N/S/Y	S	R	R	TND	TND	TND	TND	TND	TND	TND
	36	M184M/V, M41M/L, E44E/D, D67D/N, L210L/R/W, T215T/N/S/Y	S	R	R	TND	<20	TND	20	TND	<20	<20
≥2 TAMs (no K65N/R or M184V/I)	37	D67N, K219Q	S	S	S	TND	TND	<20	<20	TND	TND	TND
	38	D67N, T69D/N, V118I/I, T215S, K219Q	S	S	S	<20	TND	TND	<20	TND	36	27
	39	D67N, T215V, K219Q	S	S	S	TND	<20	TND	<20	27	<20	<20
	40	D67D/N, T69T/N, K70R, T215T/F, K219K/Q	S	R	R	62	73, 42	50, 77	55, 33	42	<20	45

a. HIV-1 RNA color coding: no shading = HIV-1 RNA <50 c/mL; orange = HIV-1 RNA ≥50 -199 c/mL; red = HIV-1 RNA ≥200 c/mL
b. Testing of W12 plasma samples with HIV-1 RNA < 2860 c/mL showed no new resistance development and undetectable levels (BLQ) of bictegravir. This participant discontinued B/F/TAF after W12 and resuppressed on DRV/RTV+RPV (indicated by grey shading). See Table 7 for more details
c. Insufficient sample volume for testing.

D1 = day 1; DRV = darunavir; FTC = emtricitabine; NRTI-R = nucleos(t)ide reverse transcriptase inhibitor resistance; PI = protease inhibitor; R = resistance; RP = resistance possible; RPV = rilpivirine; RTV = ritonavir; S = sensitive; TAMs = thymidine analog mutations; TFV = tenofovir, prodrug of TAF ; TND = target not detected; W = week

Table 9. Resistance Development through Week 48

Resistance Category	Number of Participants, n (%) B/F/TAF n=572	PI + 2NRTI n=287	ABC/DTG/3TC n=281
Resistance Analysis Population (RAP)	5 (0.9%)	5 (1.7%)	2 (0.7%)
Data Available for Any Gene (% of RAP)	2 (40%)	5 (100%)	2 (100%)
PR/RT Data Available (% of RAP)	2 (100%)	5 (100%)	2 (100%)
IN Data Available (% of RAP)	1 (20%)	2 (40%)	2 (100%)
Resuppressed HIV-1 RNA <50 c/mL (% of RAP)	2 (40%)	2 (40%)	1 (50%)
Developed Resistance to Study Drugs	**0**	**1 (0.3%)**	**0**
NRTI-R Substitutions Acquired	-	L74V	-

Conclusions

- At Week 48, switching to B/F/TAF was noninferior to staying on a boosted PI-based regimen or ABC/DTG/3TC[3,4]
  - No participants in the B/F/TAF or ABC/DTG/3TC groups developed resistance
  - One participant in the PI + 2NRTI group on boosted DRV + ABC/3TC had virologic failure with treatment-emergent L74V in RT
- High rates of virologic suppression were maintained among participants who switched to B/F/TAF (93% overall), regardless of preexisting resistance substitutions
  - Lower subtype non-B response rate in B/F/TAF group was driven by participants who had no data at Week 48 but had HIV-1 RNA <50 c/mL at visit prior to and after Week 48
- Most B/F/TAF-treated participants with archived F/TAF resistance substitutions maintained HIV-1 RNA suppression through Week 48 (97%; 35/36)
  - 100% with K65R/N (5/5)
  - 100% with singleton M184V/I/T (18/18) and 92% with M184V + other NRTI-R (12/13)
  - 100% with ≥2 TAMs (4/4)
- These studies suggest that B/F/TAF may be an effective treatment in some suppressed patients with archived NRTI-R or INSTI-R substitutions and support future studies of bictegravir and B/F/TAF in INSTI- and NRTI- resistant populations

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