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Bictegravir/Emtricitabine/Tenofovir Alafenamide Efficacy in Participants With Preexisting Primary Integrase Inhibitor Resistance Through 48 Weeks of Phase 3 Clinical Trials

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Background: Preexisting drug resistance limits the utility of HIV antiretroviral therapy. Studies have demonstrated safety and efficacy of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF), including in patients with M184V/I substitutions.

Setting: We investigated virologic outcomes through 48 weeks of B/F/TAF treatment in individuals with preexisting primary integrase strand transfer inhibitor resistance (INSTI-R).

Methods: Preexisting INSTI-R was retrospectively evaluated from 7 B/F/TAF studies. INSTI-R was assessed by historical genotypes and/or baseline RNA or DNA sequencing. Viral loads were measured at all visits.

Results: Preexisting primary INSTI-R substitutions were detected in 20 of the 1907 participants (1.0%). The 20 participants were predominantly male (75%), were Black (65%), had HIV-1 subtype B (85%), and had baseline median CD4 counts of 594 cells/mm^3 and median age of 52 years. Most of the participants (n = 19) were virologically suppressed at baseline and had one primary INSTI-R substitution, E92G, Y143C/H, S147G, Q148H/K/R, N155S, or R263K, +/−secondary substitutions. All suppressed participants maintained virologic suppression throughout 48 weeks without any viral blips. One treatment-naive participant had virus with Q148H+G140S that was fully sensitive to bictegravir but only partially to dolutegravir (phenotype <2.5-fold change and >4-fold change, respectively). With a baseline viral load of 30,000 copies/mL, this participant was virologically suppressed by week 4 and maintained <50 copies/mL through week 48.

Conclusions: This small cohort with primary INSTI-R achieved and/or maintained virologic suppression through 48 weeks of B/F/TAF treatment. Consistent with the potent in vitro activity of bictegravir against most INSTI-R patterns, B/F/TAF may be a potential treatment option for patients with select preexisting INSTI-R, if confirmed by further studies.

Key Words: preexisting resistance, primary integrase strand transfer inhibitor, bictegravir/emtricitabine/tenofovir alafenamide, DNA genotyping, virologic suppression

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INTRODUCTION

Because preexisting drug resistance can limit the use of antiretroviral drugs and render them less effective, genotypic drug resistance testing is recommended before initiating treatment or when switching regimens in a person with a history of virologic failure (VF).[1,2] Integrase strand transfer inhibitor resistance (INSTI-R) testing is not recommended unless there is suspicion of transmitted INSTI-R because the prevalence of resistance in this drug class is low (approximately 1%).[3–10] Although high efficacy is observed for INSTI-based triple therapy in clinical trials,[11–15] differences exist among the various regimens, including dosing intervals, boosting requirements, and the risk of emergent resistance in the setting of VF. In clinical trials of raltegravir (RAL)-based and elvitegravir (EVG)-based triple therapy, 21%–60% of participants with VF developed INSTI-R substitutions.[11–15] With dolutegravir (DTG) triple therapy, treatment-emergent INSTI-R in clinical trials was rare.[16,17] By contrast, no treatment-emergent INSTI-R has been documented in clinical studies of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF).[17–25] Cabotegravir, a long-acting injectable INSTI used as a single agent for PrEP or in combination with rilpivirine for HIV treatment, has demonstrated high efficacy in trials, but INSTI-R substitutions were observed in those with HIV acquisition or treatment failure, occurring in 33% and 67% of those individuals, respectively.[26–30]

Although INSTI-R is rare, studying resistance in this drug class remains important and relevant because INSTIs are the backbone of initial regimens for most people with HIV.[1,31] Primary INSTI drug resistance reported in surveillance studies are mainly substitutions that cause resistance to RAL and EVG (T66A/I, E92Q, Y143C/H/R, S147G, Q148H/K/R, and N155H pathways) and R263K, which confers low-level reduced susceptibility to EVG, DTG, and bictegravir (BIC).[4,6,8,10,32–34] BIC and DTG generally have good activity against many RAL-resistant and EVG-resistant variants, but

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with differences, because studies have found that BIC is more broadly active against INSTI-R variants than DTG.[35] Specifically, compared with DTG, BIC has greater in vitro activity against variants with G140/Q148 mutations accompanied by 1–2 additional substitutions and variants with the E92Q/N155H combination.[36] DTG dosed twice daily has been shown to provide viral suppression in individuals with primary EVG and RAL substitutions, although virologic response has been poor with certain INSTI-R patterns.[37–39] Clinical trials of BIC in viremic individuals failing therapy with INSTI-R have not been conducted.

Studies in both treatment-naive and virologically suppressed (VS) participants have demonstrated the safety and efficacy of B/F/TAF, a potent, once-daily, single-tablet regimen for treatment of HIV-1 infection.[22,40–42] This efficacy also extends to VS patients with certain nucleos(t)ide reverse transcriptase inhibitor (NRTI) substitutions, including M184V/I and thymidine analog substitutions.[43] However, the impact of INSTI-R substitutions on B/F/TAF efficacy has not been well-documented. The objective of this study was to investigate virologic outcomes after 48 weeks of B/F/TAF treatment in a pooled analysis of individuals with preexisting INSTI-R from clinical trials.

MATERIALS AND METHODS

Pooled Analysis Participants

Preexisting INSTI-R was determined in adults with a least one visit on study drug from B/F/TAF clinical trials conducted in antiretroviral therapy (ART)-naive (GS-US-380-1489/NCT02607930[18,19] and GS-US-380-1490/NCT02607956[19,20]) and ART-experienced VS participants (GS-US-380-1844/NCT02603120[21]; GS-US-380-1878/NCT02603107[22]; GS-US-380-4580/NCT03631732[23]; GS-US-380-4030/NCT03110380;[24] and GS-US-380-4449/NCT03405935[25]).

Baseline Genotypic Analysis

The presence of preexisting resistance-associated substitutions in the protease (PR), reverse transcriptase (RT), and integrase (IN) genes were evaluated by historical genotypes, if available, at or after enrollment and/or by plasma or proviral DNA genotyping of baseline samples using Genosure MG, GenoSure Archive (Monogram Biosciences, South San Francisco, CA) or deepType HIV assay (frequency cutoff ≥15%, Seq-IT GmbH & Co, KG, Kaiserslautern, Germany). Of note, GenoSure Archive analysis uses bioinformatic filters to remove APOBEC-mediated, hypermutated deep-sequence reads and reports consensus sequences based on cutoffs similar to population sequencing. Drug resistance substitutions were adapted from the IAS-USA guidelines.[44]

B/F/TAF Efficacy Analysis

Viral loads were measured using TaqMan v2.0 at all visits. Virologic outcomes were defined by the last on-treatment observation carried forward (LOCF) method with HIV-1 RNA <50 copies/mL (success) or ≥50 copies/mL (failure).

RESULTS

Demographics and Patient Characteristics

Although known primary INSTI-R was exclusionary per study entry criteria if known before randomization, participants with preexisting INSTI-R identified after enrollment remained on study. This pooled analysis included 1906 B/F/TAF participants from studies 380–1489 (n = 315), 380–1490 (n = 320), 380–1844 (n = 282), 380–1878 (n = 290), 380–4580 (n = 330), 380–4030 (n = 284), and 380–4449 (n = 86). Preexisting primary INSTI-R substitutions were detected in 20 (1%) individuals.

Of the 20 participants, 15 were male, 11 were Black, and 17 had HIV-1 subtype B. Median baseline CD4 count was 641 cells/mm^3 (interquartile range [IQR] 527, 771), and median age was 52 years (IQR 43, 59) (Table 1). Nineteen participants were VS, with a median time on ART of 6.6 years (range 0.4-15.7 years), and prior use of NRTI- (100%), non-NRTI (NNRTI)- (42%), and/or PR-inhibitor (PI)- (47%) based regimens (Tables 1 and 2). Prior INSTI use was allowed in studies 1844, 4030, and 4580 if there had been no VF on the INSTI-based regimen; 14 participants (74%) had prior use of EVG (n = 5), RAL (n = 2), and DTG (n = 9) (Table 2). Inclusion criteria specified that confirmed VF while on an INSTI-containing regimen was not allowed; therefore, preexisting INSTI-R was most likely partly due to transmission. However, lack of full clinical history and of potential documentation of VF for participants who were INSTI-experienced suggests some INSTI-R could have been treatment emergent. One participant was enrolled in the treatment-naive study 1489.

Resistance Profile of Participants With Preexisting INSTI-R

Of the 8 amino acid positions listed with primary INSTI-R substitutions, 6 were detected in these participants: E92G (n = 3; 15%), Y143C/H (n = 6; 30%), S147G (n = 2; 10%), Q148H/K/R (n = 6; 30%), N155S (n = 1; 5%), and R263K (n = 2; 10%) (Table 2). Secondary INSTI-R substitutions included M50I (n = 4; 20%), L68V (n = 1; 5%), L74I/M (n = 1; 5%), S119P/R/T (n = 6; 30%), and G140S (n = 2; 10%). Additional NRTI-R, NNRTI-R, and PI-R substitutions were detected in 4 (20%), 8 (40%), and 5 (25%) participants, respectively (Table 2). All substitutions were present at baseline (n = 1, RNA, and n = 18, proviral DNA) except for participant #5, who had Y143C detected historically in plasma only. Of the 18 with baseline proviral DNA genotyping, 15 had no historical data, and for participants with multiple reports, substitutions were detected in both RNA and DNA (n = 1) or DNA only (n = 2). Drug resistance substitutions in multiple drug classes were observed in some participants. Notably, 4 had INSTI-R combined with NRTI-R substitutions relevant to the emtricitabine (FTC) or TAF components of the B/F/TAF regimen (M184V and/or K70E). The treatment-naive participant had K103N and K70R

TABLE 1. Baseline Clinical and Demographic Characteristics and Virologic Outcomes of Participants With Preexisting INSTI-R

							Viral Load, Copies/mL	
Participant ID	Study*/Status	Age, y	Sex	Race	HIV Subtype	CD4 Count	Baseline	Week 48 LOCF
1	1489/Naive	58	M	Black	B	722	30,000	<20
2	1878/VS	44	M	White	B	187	No HIV-1 RNA	No HIV-1 RNA
3	4580/VS	71	M	Black	B	464	No HIV-1 RNA	<20
4	4580/VS	37	M	Black	B	701	No HIV-1 RNA	No HIV-1 RNA
5	4580/VS	52	M	Other	B	74	No HIV-1 RNA	<20
6	4580/VS	48	M	Black	B	777	No HIV-1 RNA	No HIV-1 RNA
7	1844/VS	59	M	White	B	941	No HIV-1 RNA	No HIV-1 RNA
8	4580/VS	63	F	Black	B	895	No HIV-1 RNA	No HIV-1 RNA
9	4030/VS	51	M	White	B	507	No HIV-1 RNA	No HIV-1 RNA
10	4030/VS	35	M	White	B	722	<20	No HIV-1 RNA
11	1878/VS	20	M	Black	B	552	<20	<20
12	4030/VS	59	M	White	B	641	No HIV-1 RNA	No HIV-1 RNA†
13	1844/VS	41	F	Black	AG	124	<20	<20
14	4580/VS	60	F	Black	B	1394	<20	No HIV-1 RNA
15	4030/VS	64	M	Black	B	547	<20	<20
16	4580/VS	44	M	Black	B	465	<20	No HIV-1 RNA
17	4580/VS	57	F	Black	B	921	No HIV-1 RNA	No HIV-1 RNA
18	4030/VS	31	M	White	B	820	No HIV-1 RNA	No HIV-1 RNA
19	4030/VS	48	M	Black	C	188	No HIV-1 RNA	No HIV-1 RNA
20	4030/VS	53	F	Black	C	588	No HIV-1 RNA	No HIV-1 RNA

*Participants were required to have been suppressed for a minimum of 3–6 months depending on the study.
†Participant 12 had viral load measurements until week 12 when they decided to withdraw.

in RT and Q148H and G140S in IN genes. This clinical isolate with Q148H+G140S was phenotypically susceptible to BIC (2.14-fold change, less than the cutoff of 2.5-fold), partially susceptible to DTG (4.45-fold change, greater than the cutoff of 4-fold), and resistant to EVG and RAL (PhenoSense® Integrase assay, Monogram Biosciences).[45]

Viral Loads and Virologic Outcome of Participants With Preexisting INSTI-R

The treatment-naive participant with preexisting Q148H and G140S had a viral load of 30,000 copies/mL at baseline and was suppressed by week 4, maintaining viral loads of <50 copies/mL through week 48, and even week 216, without blips. The ART-experienced participants (n = 19) maintained HIV-1 RNA <50 copies/mL at all study visits through week 48 without blips. All study participants achieved virologic success by week 48 (Table 1), which was similar to that observed in the overall study population from the 7 clinical trials.[18,20–25]

DISCUSSION

In this pooled analysis, high rates of virologic suppression without VF or treatment-emergent resistance were achieved/maintained in both ART-naive and ART-experienced individuals with a broad range of primary INSTI-R, demonstrating the efficacy of B/F/TAF. Successful virologic outcomes in the presence of select INSTI-R substitution patterns conferring predominantly RAL and/or EVG resistance are consistent with previous phenotypic analyses of clinical isolates demonstrating the activity of BIC against virus with primary INSTI-R substitutions, such as E92Q, Y143C/H, S147G, N155H, and Q148H/K/R.[36,46–48] In addition, virologic suppression was attained in one treatment-naive individual with Q148H and G140S IN substitutions, demonstrating BIC's favorable resistance profile. As observed in the viremic individual in this study, BIC has broader phenotypic activity than other INSTIs, including DTG, against clinical isolates with Q148H + G140S combinations.[36,47,48]

Substitutions associated with BIC, which have been selected in vivo and in vitro, can lead to a range of phenotypic changes. For example, the combination of Q148H/K/R and G140A/C/S in the presence of additional substitutions can cause high-level resistance to BIC (>10-fold change in phenotype compared with wild type) but as was seen with the naive case presented in this study, the Q148H+G140S pattern can also be susceptible to BIC.[36,46–48] Examining the 3 real-world cases in which treatment-emergent resistance on B/F/TAF occurred can also help in understanding the activity of BIC against INSTI-R virus. Potential causes of VF in those cases included advanced disease (high viral load and low CD4 count), previous failure on an INSTI-based regimen, poor adherence, and nonstandard administration of B/F/TAF. All 3 individuals developed the R263K substitution.[49–51] R263K on its own causes small increases in fold change that may not be clinically relevant, but when it is selected in vitro along with secondary mutations such as M50I, the fold

TABLE 2. Resistance Profiles and ART History of Participants With Preexisting INSTI-R

Participant ID	Primary INSTI-R	Secondary INSTI-R	NRTI-R	NNRTI-R	PI-R	ART History				Time on ART, y
						Drug Class	Reported Drug Name	Start Date	End Date	
1	Q148H	M50I, G140S	K70R	K103N	None		N/A			
2	E92G	S119T	None	K103N	None	NRTI/PI	TRUVADA (FTC + TDF) + DRV + RTV	11/2008	5/22/2016	7.5
3	E92G	None	K70R, M184V	None	None	NRTI/INSTI	GENVOYA (EVG + COBI + FTC + TAF)	1/31/2017	10/4/2018	1.7
4	E92G	None	None	E138A	None	NRTI/NNRTI	COMPLERA/EVIPLERA (FTC + RPV + TDF)	09/2013	10/25/2018	5.1
5	Y143C	None	None	H221Y	None	NRTI/NNRTI	COMPLERA/EVIPLERA (FTC + RPV + TDF)	03/2017	9/25/2018	1.5
6	Y143C	M50I	None	None	None	NRTI/NNRTI	TRUVADA (FTC + TDF) + EFV	1/17/2005	8/6/2006	13.7
						NRTI/NNRTI	ATRIPLA (EFV + FTC + TDF)	8/7/2006	10/14/2017	
						NRTI/NNRTI	ODEFSEY (FTC + RPV + TAF)	10/15/2017	10/9/2018	
7	Y143H	S119R	None	None	None	NRTI/INSTI	STRIBILD (EVG + COBI + FTC + TDF)	12/11/2013	1/29/2015	2.0
						NRTI/INSTI	TRIUMEQ (ABC + DTG + 3TC)	1/30/2015	12/28/2015	
8	Y143H	None	None	None	None	NRTI/INSTI	GENVOYA (EVG + COBI + FTC + TAF)	11/28/2017	12/7/2018	1.0
9	Y143H	None	D67N, K70E/G/R, L74V, M184V, K219Q	L100I, K103N	M46I, N88S	NRTI/NNRTI	COMPLERA/EVIPLERA (FTC + RPV + TDF)	2011	02/2014	6.6
						NRTI/INSTI	TRUVADA (FTC + TDF) + DTG	02/2014	8/14/2017	
10	Y143H	None	None	K103N	None	NRTI/INSTI	TRUVADA (FTC + TDF) + DTG	4/20/2017	10/16/2017	0.4
11	S147G	None	None	None	V82A	NRTI/PI	TRUVADA (FTC + TDF) + DRV + RTV	5/9/2015	5/4/2016	0.9
12	S147G	None	None	None	M46I	NRTI	TRIZIVIR (ABC + AZT + 3TC)	1/17/2005	1/29/2005	12.6
						NRTI/PI	3TC + TDF + ATV + RTV	4/4/2005	3/13/2006	
						NRTI/PI	TRUVADA (FTC + TDF) + ATV + RTV	3/13/2006	10/7/2013	
						NRTI/NNRTI	COMPLERA/EVIPLERA (FTC + RPV + TDF)	10/7/2013	5/12/2014	
						NRTI/PI	TRUVADA (FTC + TDF) + ATV + RTV	5/12/2014	10/5/2015	
						NRTI/INSTI	TRUVADA (FTC + TDF) + DTG	10/5/2015	11/5/2017	
13	Q148H	None	None	None	None	NRTI/NNRTI	3TC + TDF + EFV	11/14/2006	6/15/2007	9.6
						NRTI/PI	COMBIVIR (AZT + 3TC) + KALETRA (LPV + RTV)	6/16/2007	3/30/2008	
						NRTI/PI	EPZICOM/KIVEXA (ABC + 3TC) + KALETRA (LPV + RTV)	4/1/2008	11/17/2015	
						NRTI/INSTI	TRIUMEQ (ABC + DTG + 3TC)	11/18/2015	7/4/2016	

TABLE 2. (*Continued*) Resistance Profiles and ART History of Participants With Preexisting INSTI-R

Participant ID	Primary INSTI-R	Secondary INSTI-R	NRTI-R	NNRTI-R	PI-R	ART History				Time on ART, y
						Drug Class	Reported Drug Name	Start Date	End Date	
14	Q148H	S119P	None	None	None	NRTI/NNRTI	ATRIPLA (EFV + FTC + TDF)	2007	11/17/2009	8.9
						NRTI/PI/INSTI	TDF + RAL + ATV+RTV	11/18/2009	12/2/2009	
						NRTI/PI/INSTI	TDF + RAL + KALETRA (LPV + RTV)	12/3/2009	12/27/2015	
						NRTI/INSTI	STRIBILD (EVG + COBI + FTC + TDF)	12/28/2015	9/4/2016	
						NRTI/INSTI	GENVOYA (EVG + COBI + FTC + TAF)	9/5/2016	9/30/2018	
15	Q148H	G140S	M184V	K101P/Q/T, Y181C, H221Y	None	NRTI/INSTI	COMBIVIR (AZT + 3TC) + RAL	2009	2011	8.1
						NRTI/PI	TRUVADA (FTC + TDF) + RTV + DRV	2011	2/13/2017	
						NRTI/INSTI	DESCOVY 200/25 MG (FTC + TAF) + DTG	2/13/2017	9/6/2017	
16	Q148K	L74I/M, M50I, S119P	None	None	D30D/N	NRTI/INSTI	GENVOYA (EVG + COBI + FTC + TAF)	01/2017	11/17/2018	1.8
17	Q148R	S119T	None	K103N G190E	Q58E	NRTI/PI	TRUVADA (FTC + TDF) + KALETRA (LPV + RTV)	2003	2/24/2013	15.7
						NRTI/INSTI	STRIBILD (EVG + COBI + FTC + TDF)	2/25/2013	2/26/2017	
						OTHER	PRO 140 (LERONLIMAB)	2/20/2017	4/28/2017	
						NRTI/INSTI	GENVOYA (EVG + COBI + FTC + TAF)	5/1/2017	9/24/2018	
18	N155S	S119R	None	None	None	NRTI/INSTI	TRUVADA (FTC + TDF) + DTG	2011	9/11/2016	6.6
						NRTI/INSTI	DESCOVY 200/25 MG (FTC + TAF) + DTG	9/12/2016	8/4/2017	
19	R263K	M50I L68V	None	None	None	NRTI/NNRTI	3TC + TDF + EFV	7/8/2003	4/11/2004	14.2
						NRTI	TRIZIVIR (ABC + AZT + 3TC)	4/12/2004	9/19/2004	
						NRTI/NNRTI	3TC + ABC + EFV	9/20/2004	1/23/2005	
						NRTI/NNRTI	EPZICOM/KIVEXA (ABC + 3TC) + EFV	1/24/2005	10/30/2005	
						NRTI/PI	EPZICOM/KIVEXA (ABC + 3TC) + ATV + RTV	10/31/2005	10/8/2007	
						NRTI/NNRTI	EPZICOM/KIVEXA (ABC + 3TC) + EFV	10/9/2007	11/9/2008	
						NRTI/NNRTI	ATRIPLA (EFV + FTC + TDF)	11/10/2008	2/13/2014	
						NRTI/INSTI	TRUVADA (FTC + TDF) + DTG	2/14/2014	10/5/2016	
						NRTI/INSTI	DESCOVY 200/25 MG (FTC + TAF) + DTG	10/6/2016	9/13/2017	

(*continued on next page*)

TABLE 2. (*Continued*) Resistance Profiles and ART History of Participants With Preexisting INSTI-R

Participant ID	Primary INSTI-R	Secondary INSTI-R	NRTI-R	NNRTI-R	PI-R	ART History				Time on ART, y
						Drug Class	Reported Drug Name	Start Date	End Date	
20	R263K	None	None	None	None	NRTI/PI	TRUVADA (FTC + TDF) + KALETRA (LPV + RTV)	1/6/2009	8/6/2014	8.7
						NRTI/INSTI	EPZICOM/KIVEXA (ABC + 3TC) + DTG	8/6/2014	10/27/2016	
						NRTI/INSTI	TRIUMEQ (ABC + DTG + 3TC)	10/28/2016	3/1/2017	
						NRTI/INSTI	DESCOVY 200/25 MG (FTC + TAF) + DTG	3/1/2017	10/3/2017	

Primary INSTI-R substitutions were T66I/A/K, E92Q/G, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, and R263K in IN. Secondary INSTI-R substitutions were M50I, H51Y, L68V/I, V72A/N/T, L74M, Q95K/R, T97A, 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, and E170A in IN. Primary nucleos(t)ide RT inhibitor (NRTI)-R substitutions were K65R/E/N, T69 insertions, K70E, L74V/I, Y115F, Q151M, M184V/I, and TAMs (M41L, D67N, K70R, L210W, T215F/Y, K219E/N/Q/R) in RT. Primary non-NRTI (NNRTI)-R substitutions were 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. Primary PR inhibitor (PI)-R substitutions were 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.

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; COBI, cobicistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; LPV, lopinavir; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-NRTI; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

change increases.[36] In the 3 real-world cases, other INSTI-R substitutions were also noted, including L74I, E138K, S147G, and H51Y, along with M184V in RT.[49–51] The accumulation of multiple INSTI-R mutations, along with M184V, which confers resistance to FTC, may have contributed to VF. Interestingly, in this study, suppressed participants with R263K (alone or in combination with M50I and L68V) maintained viral loads of <50 copies/mL.

In B/F/TAF study participants, preexisting primary INSTI-R was rare (1%) and reflects real-world surveillance data. Demonstrating viral suppression in the presence of single INSTI-R substitutions in predominantly VS individuals is a step toward determining the ability of BIC to inhibit viral replication in persons with INSTI-R substitutions and understanding who can be treated with B/F/TAF. Along with resistance profile, other factors should be considered when choosing treatment regimens. In the VIKING trial, treatment-emergent resistance occurred as early as 11 days after DTG initiation, perhaps indicating the presence of additional preexisting resistance mutations below population sequencing thresholds that rapidly predominated with selective pressure by DTG.[39] The requirement of a fully active agent in the optimized background regimen also potentially affected the VIKING study outcomes.[37] History of ART failure was hypothesized to be a contributing factor to the increased risk of VF among participants in the SWITCHMRK studies.[52] Moreover, resistance to the nucleoside components of the regimen and the lower barrier to resistance of RAL versus lopinavir/ritonavir may have influenced virologic suppression in the SWITCHMRK studies.[52] Taken together, these data highlight the complexity of evaluating the impact of INSTI-R substitutions on treatment efficacy, where resistance patterns have a range of phenotypic resistance, some substitutions may be present below the detection limit, and drug resistance from other regimen components may also contribute to loss of susceptibility to the regimen.

Limitations of this study include that in B/F/TAF clinical trials, INSTI-R was exclusionary and allowed only if identified after enrollment; therefore, the number of participants was low. As a result, this analysis had only statistical power to detect a VF rate of ≥16% (https://epitools.ausvet.com.au/ciproportion?page=CIProportion&SampleSize=21&Positive=1&Conf=0.95&method=2&Digits=4). In addition, our population consisted primarily of stably suppressed clinical trial participants. Most INSTI-R substitutions were detected by proviral DNA genotyping, which is unable to determine whether reported drug resistance substitutions occur on intact, potentially reactivatable HIV genomes. This is partially mitigated by the GenoSure Archive assay, amplifying a large portion of the polymerase gene, sequencing full-length amplification products, and removing hypermutated variants, which enhance the reporting of substitutions found on intact virus.[53] In addition, phenotypes of proviral HIV DNA cannot be determined.

Resistance guidance in the prescribing information for B/F/TAF differs by geographical location. Currently, in the Unites States, there can be no known substitutions associated with resistance to the individual components of B/F/TAF, whereas in Europe, B/F/TAF is indicated for patients who have no resistance to INSTIs. Although the use of BIC in individuals with INSTI-R is off-label in some regions, the results presented in this study are reassuring for situations where patients with unmeasured or undetected resistance are treated with B/F/TAF. Although patients with complex patterns of INSTI-R substitutions and predicted high-level resistance should be treated with multiple fully active agents, these results support further study of B/F/TAF in those who have INSTI-R virus predicted to be susceptible to BIC.

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