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%), had HIV-1 subtype B (85%), and had baseline median CD4 counts of 594 cells/mm³ 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, or N155S, or R263K, +/-secondary substitutions. All suppressed participants maintained virologic suppression throughout 48 weeks without any viral blips. One treatment-naïve participant had virus with Q148H+G140S that was fully sensitive to bictegravir but only 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 67% of those individuals, respectively.26

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

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 or elvitegravir (EVG)-based triple therapy, 21%–60% of participants with VF developed INSTI-R substitutions.16–18 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, E9Q, 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
with differences, because studies have found that BIC is more broadly active against INSTI-R variants than DTG. 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. 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. 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. This efficacy also extends to VS patients with certain nucleos(t)ide reverse transcriptase inhibitor (NRTI) substitutions, including M184V/I and thymidine analog substitutions. 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/NCT0260793018,19 and GS-US-380-1490/NCT0260795619,20) and ART-experienced VS participants (GS-US-380-1844/NCT0260312021; GS-US-380-1878/NCT0260310722; GS-US-380-4580/NCT0363173223; GS-US-380-4030/NCT03110380;24 and GS-US-380-4449/NCT0340593525).

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

Virologic 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/mm3 (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 suggested 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%), S119PR/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
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

| Participant ID | Study/Status | Age, y | Sex | Race | HIV Subtype | CD4 Count | Viral Load, Copies/mL | 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   | Black| 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      | <20          |
| 15             | 4030/VS      | 64     | M   | Black| B           | 547       | <20      | <20          |
| 16             | 4580/VS      | 44     | M   | Black| B           | 465       | <20      | <20          |
| 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.
| Participant ID | Primary INSTI-R | Secondary INSTI-R | NRTI-R | NNRTI-R | PI-R | Drug Class | Reported Drug Name | Start Date | End Date | Time on ART, y |
|----------------|----------------|------------------|--------|---------|------|------------|-------------------|------------|----------|---------------|
| 1              | Q148H          | M50I, G140S      | K70R   | K103N   | None | NRTI/PI    | TRUVADA (FTC + TDF) + DRV + RTV | 11/2008    | 5/22/2016 | 7.5           |
| 2              | E92G           | S119T            | None   | K103N   | None | NRTI/INSTI | GENVOYA (EVG + COBI + FTC + TAF) | 1/31/2017  | 10/4/2018 | 1.7           |
| 3              | E92G           | None             | K70R, M184V | None   | None | NRTI/NNRTI | COMPLERA/EVIPLERA (FTC + RPV + TDF) | 09/2013    | 10/25/2018 | 5.1           |
| 4              | E92G           | None             | None   | E138A   | None | NRTI/NNRTI | COMPLERA/EVIPLERA (FTC + RPV + TDF) | 03/2017    | 9/25/2018 | 1.5           |
| 5              | Y143C          | None             | None   | H221Y   | None | NRTI/INSTI | STRIBILD (EVG + COBI + FTC + TDF) | 12/11/2013 | 1/29/2015 | 1.0           |
| 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  |               |
| 9              | Y143H          | None             | D67N, K70E/G, 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) + DRV + RTV | 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    | TRIZIVIR (ABT + 3TC) + ATV + RTV | 4/4/2005   | 3/13/2006  |               |
|                |                |                  |        |         |      | NRTI/PI    | TRIZIVIR (ABC + AZT + 3TC) | 3/13/2006  | 10/7/2013  |               |
|                |                |                  |        |         |      | NRTI/NNRTI | COMPLERA/EVIPLERA (FTC + RPV + TDF) | 10/7/2013  | 5/12/2014  |               |
|                |                |                  |        |         |      | NRTI/PI    | TRUVADA (FTC + TDF) + DRV + 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 | COMBIVIR (AZT + 3TC) + KALETRA (LPV + RTV) | 11/14/2006 | 6/15/2007  | 9.6           |
|                |                |                  |        |         |      | NRTI/PI    | EPZICOM/KIVEXA (ABC + 3TC) + KALETRA (LPV + RTV) | 6/16/2007  | 3/30/2008  |               |
|                |                |                  |        |         |      | NRTI/INSTI | 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   |               |

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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 | Drug Class | Reported Drug Name | Start Date | End Date | Time on ART, y |
|----------------|----------------|------------------|--------|---------|------|------------|-------------------|------------|----------|--------------|
| 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 |
|                |                |                  |        |         |      | NRTI/INSTI | GENVOYA (EVG + COBI + FTC + TAF) | 01/2017    | 11/17/2018 | 1.8          |
| 16             | Q148K          | L74I/M, M50I, S119P | None | None | D30D/N | NRTI/INSTI | 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 |
| 17             | Q148R          | S119T            | None   | None | K103N G190E | NRTI/PI | TRUVADA (FTC + TDF) + KALETRA (LPV + RTV) | 2011       | 9/11/2016 | 6.6          |
|                |                |                  |        |         |      | NRTI/INSTI | DESCovy 200/25 MG (FTC + TAF) + DTG | 9/12/2016 | 8/4/2017 |
| 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 |

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change increases. In the 3 real-world cases, other INSTI-R substitutions were also noted, including L74I, E138K, M184V/I, and L90M in PR.

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. The requirement of a fully active agent in the optimized background regimen also potentially affected the VF among participants in the SWITCHMRK studies.

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**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 | Drug Class | Reported Drug Name | Start Date | End Date | Time on ART, y |
|---------------|-----------------|-------------------|-------|---------|-----|------------|-------------------|------------|----------|--------------|
| 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/K, 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, V188C/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/I, 50L/V, I54M/L, H100K/R, I50L/V, I54M/L, 55E, 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, nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

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=CIPrportion&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 amplicons, and removing hypermutated variants, which enhance the reporting of substitutions found on intact virus. 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 United 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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