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Switching to bictegravir/emtricitabine/tenofovir alafenamide maintained HIV-1 RNA suppression in participants with archived antiretroviral resistance including M184V/I

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Objectives: Studies 1878 and 1844 demonstrated non-inferior efficacy of switching suppressed HIV-1-infected adults to bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) versus continuing boosted PI-based triple regimens or dolutegravir/abacavir/lamivudine (DTG/ABC/3TC). Here, detailed analyses of pre-existing resistance in the two BIC/FTC/TAF switch studies and efficacy at week 48 are described.

Methods: Pre-existing resistance was assessed from historical genotypes (documented resistance to study drugs was excluded) and by retrospective baseline proviral archive DNA genotyping from whole blood. Outcomes were based on HIV-1 RNA at week 48 with missing values imputed using the last on-treatment observation carried forward method.

Results: Cumulative pre-existing resistance data from historical and proviral genotypes were obtained for 95% (543/570) of participants who switched to BIC/FTC/TAF. Altogether, 40% (217/543) had one or more pre-existing primary resistance substitutions in protease, reverse transcriptase and/or integrase. Pre-switch NRTI resistance was detected in 16% (89/543) of BIC/FTC/TAF-treated participants, with M184V or M184I detected by proviral genotyping in 10% (54/543). At week 48, 98% (561/570) of all BIC/FTC/TAF-treated participants versus 98% (213/217) with pre-existing resistance and 96% (52/54) with archived M184V/I had HIV-1 RNA <50 copies/mL. No BIC/FTC/TAF-treated participants developed treatment-emergent resistance to study drugs.

Conclusions: Pre-existing resistance substitutions, notably M184V/I, were unexpectedly common among suppressed participants who switched to BIC/FTC/TAF. High rates of virological suppression were maintained in the overall study population and in those with pre-existing resistance, including M184V/I, for up to 48 weeks of BIC/FTC/TAF treatment with no resistance development. These results indicate that BIC/FTC/TAF is an effective treatment option for suppressed patients, including those with evidence of archived NRTI resistance.

Introduction

Modern ART achieves high rates of HIV suppression, enabling longer life expectancy and improved quality of life for people living with the disease. Once virologically suppressed, therapy changes are sometimes considered for tolerability, safety concerns or regimen simplification.[1,2] However, drug resistance continues to threaten long-term treatment success and should be taken into consideration before switching ART regimens. Furthermore, increases in global ART usage, in alignment with WHO recommendations, will likely yield increased acquired drug resistance among treated patients and transmitted drug resistance among those newly infected. Thus, developing regimens with improved genetic and pharmacological resistance barriers as well as reduced pill burden, fewer drug–drug interactions, fewer dosing requirements and reduced side effects is critical to accomplish real-world HIV treatment goals.

Bictegravir (BIC), a novel, unboosted, potent integrase strand transfer inhibitor (INSTI) with a high genetic and pharmacological barrier to resistance and low potential for drug–drug interactions,[3–5] has been coformulated with the guideline-recommended NRTIs emtricitabine (FTC) and tenofovir alafenamide (TAF) into the single-tablet regimen BIC/FTC/TAF. In 2018, the US FDA and the EMA approved BIC/FTC/TAF for the treatment of HIV-1 in treatment-naive and virologically suppressed patients based on 48 week safety and efficacy data from four Phase 3 clinical studies. In two studies

of ART-naive HIV-1-infected adults, BIC/FTC/TAF was well tolerated, demonstrated high rates of HIV-1 suppression with no resistance, and was non-inferior to dolutegravir-based triple regimens up to week 96.[6–9] In two studies of virologically suppressed HIV-1-infected adults, switching to BIC/FTC/TAF from regimens of two NRTIs plus a boosted PI or dolutegravir was well tolerated, maintained high rates of HIV-1 suppression with low rates of virological failure up to week 48, and was non-inferior to staying on baseline regimens.[10,11]

Determining the effects of archived pre-existing resistance on treatment outcomes is vital for understanding how to safely switch regimens in suppressed patients. In the BIC/FTC/TAF switch studies, historical HIV-1 genotype records were assessed for baseline resistance substitutions. Documented resistance to study drugs or evidence of previous virological failure led to exclusion from the trials if identified prior to randomization, but historical genotypic data were available for only half of all enrolled participants. Retrospective genotyping of proviral DNA from samples drawn at the baseline visit was performed to provide a more complete understanding of pre-existing drug resistance prior to study enrolment and the impact of baseline resistance on treatment efficacy after switching to BIC/FTC/TAF.

Patients and methods

Study design

Studies 1878 and 1844 are multicentre, randomized, non-inferiority trials that enrolled HIV-1-infected adults at 152 outpatient centres in Australia, Europe and North America. In the open-label study 1878, participants had been treated with PI-based therapy for a median duration of 5.5 years and were virologically suppressed (plasma HIV-1 RNA levels <50 copies/mL) for ≥6 months before screening on a regimen consisting of a ritonavir- or cobicistat-boosted PI (either atazanavir or darunavir) plus either the NRTI combination emtricitabine/tenofovir disoproxil fumarate or abacavir/lamivudine (ClinicalTrials.gov NCT02603107). In the double-blinded, placebo-controlled study 1844, participants were on a regimen of the INSTI dolutegravir plus abacavir/lamivudine (DTG/ABC/3TC) for a median duration of 1.2 years with HIV-1 RNA suppression for ≥3 months before screening (ClinicialTrials.gov NCT02603120). In both studies, eligibility criteria allowed prior regimen changes only for tolerability issues or simplification; participants with known or suspected previous confirmed virological failure or resistance to study drugs were excluded from enrolment. Participants were randomly assigned (1:1) to switch to BIC/FTC/TAF or remain on their baseline regimens for 48 weeks. Plasma HIV-1 RNA levels were measured at each study visit using Roche TaqMan 2.0 (Roche Diagnostics, Rotkreuz, Switzerland). Efficacy at the primary week 48 endpoint was assessed for all participants with at least one on-treatment post-baseline HIV-1 RNA measurement. Outcomes were reported as the proportions of participants with plasma HIV-1 RNA <50 copies/mL (virological suppression) or ≥50 copies/mL (virological failure) at week 48 using last observation carried forward (LOCF) imputation. Using this analysis, for example, the week 48 outcome for a participant who discontinued at week 36 with HIV-1 RNA <50 copies/mL would be imputed as <50 copies/mL.

Resistance analyses

Baseline resistance was assessed via two methods. First, for all participants, available historical genotype reports were collected. Historical genotypic data were derived from Sanger sequencing of plasma HIV-1 RNA (n=609) or deep sequencing of proviral DNA (n=7). Pre-existing resistance-associated and polymorphic substitutions in protease (PR), reverse transcriptase (RT) and integrase (IN), if applicable, were tabulated from historical reports. Second, retrospective analyses of HIV-1 proviral DNA from baseline whole-blood samples were attempted for all BIC/FTC/TAF-treated participants and a limited number of participants in the comparator groups (who qualified for post-baseline resistance testing as described below) using the GenoSure Archive® assay (Monogram Biosciences). GenoSure Archive® is a deep sequencing-based assay for genotyping PR, RT and IN from cell-associated HIV-1 DNA, which we refer to as proviral DNA (but could include other cell-associated HIV-1 DNA). As part of the assay analysis, deep-sequence reads with APOBEC-induced hypermutations were removed by bioinformatics filters and consensus sequences were generated based on Sanger sequencing-like mutation cut-offs. Data from historical and proviral genotypes were aggregated, and composite baseline sequences were derived from cumulative data for participants with multiple pretreatment genotypes. Virological outcome comparisons by resistance category were analysed by Fisher's exact test.

Confirmed virological failure was defined as HIV-1 RNA ≥50 copies/mL on two consecutive post-baseline visits. The resistance analysis population (RAP) included any participant with HIV-1 RNA ≥200 copies/mL at the virological failure confirmation (second) visit, last visit in the week 48 analysis window, or last visit on study drug. HIV-1 RNA from corresponding plasma samples was analysed for PR/RT and IN genotype and phenotype using the PhenoSense® GT, GeneSeq® Integrase and PhenoSense® Integrase assays (Monogram Biosciences, South San Francisco, CA, USA).

Drug resistance substitutions were adapted from the IAS-USA Guidelines.[12] Primary INSTI resistance (-R) substitutions were T66I/A/K, E92Q/G, T97A, 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, 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 NRTI-R substitutions were M41L, K65R/E/N, D67N, T69 insertions, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F and K219E/Q/N/R in RT. Primary NNRTI-R substitutions were L100I, K101E/P, K103N/S, V106M/A, V108I, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188C/H/L, G190A/E/Q/S, H221Y, P225H, F227C and M230L/I in RT. Primary PI-R substitutions were D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S and L90M in PR.

Results

Study population and baseline genotypic data

Altogether, 1136 participants were randomized across both studies and had at least one on-treatment post-baseline HIV-1 RNA measurement: 570 participants switched to BIC/FTC/TAF (289 in study 1878 and 281 in study 1844), 285 participants maintained boosted PI-based therapy (study 1878) and 281 participants maintained DTG/ABC/3TC (study 1844). The rates of virological suppression at week 48 using LOCF imputation for missing data were as follows: 98% (561/570) for the pooled BIC/FTC/TAF group, 98% (280/285) for the boosted PI group and >99% (280/281) for the DTG/ABC/3TC group (Table 1). Conversely, the rates of virological failure at week 48 were low, and consistent with previously published snapshot analyses.[10,11]

Pre-switch HIV-1 genotypes were derived from all available historical genotypic data and/or retrospective baseline testing of archived proviral DNA. Historical genotypes were collected from 49% (280/570) of participants in the BIC/FTC/TAF group, 43% (122/285) in the boosted PI group and 49% (137/281) in the DTG/ABC/3TC group (Table 2). The mean time between historical genotyping and study baseline was 5.0 years (range 34 days to 16.4 years). No participant had exclusionary substitutions such as K65R or M184V/I by historical genotypic data. To probe for drug resistance in the

Table 1. HIV-1 pre-existing resistance by drug class and virological suppression rate at week 48 (LOCF)

	Percentage of participants (*n* or *n*/*N*)					
	BIC/FTC/TAF		boosted PI+2 NRTIs		DTG/ABC/3TC	
Resistance category	total	HIV-1 RNA <50 copies/mL	total	HIV-1 RNA <50 copies/mL	total	HIV-1 RNA <50 copies/mL
All treated participants	570	98.4% (561/570)	285	98.2% (280/285)	281	99.6% (280/281)
Baseline PR/RT data available	95.3% (543)	98.3% (534/543)	43.9% (125)	96.8% (121/125)	49.1% (138)	100% (138/138)
no PR/RT primary resistance substitutions	61.7% (335)	98.5% (330/335)	74.4% (93)	97.8% (91/93)	85.5% (118)	100% (118/118)
any PR/RT primary resistance substitutions	38.3% (208)	98.1% (204/208)	25.6% (32)	93.8% (30/32)	14.5% (20)	100% (20/20)
any RT primary resistance substitutions	32.8% (178)	97.8% (174/178)	22.4% (28)	92.9% (26/28)	11.6% (16)	100% (16/16)
NRTI-R	16.4% (89)	96.6% (86/89)	8.0% (10)	90.0% (9/10)	2.9% (4)	100% (4/4)
NNRTI-R	22.8% (124)	99.2% (123/124)	20% (25)	96.0% (24/25)	9.4% (13)	100% (13/13)
PI-R	10.1% (55)	100% (55/55)	4.0% (5)	100% (5/5)	3.6% (5)	100% (5/5)
Baseline IN data available	91.1% (519)	98.3% (510/519)	5.3% (15)	80.0% (12/15)	5.0% (14)	100% (14/14)
no IN resistance substitutions	47.4% (246)	98.0% (241/246)	60.0% (9)	77.8% (7/9)	42.9% (6)	100% (6/6)
any IN resistance substitutions	52.6% (273)	98.5% (269/273)	40.0% (6)	83.3% (5/6)	57.1% (8)	100% (8/8)
primary INSTI-R	2.5% (13)	100% (13/13)	0	–	14.3% (2)	100% (2/2)
secondary INSTI-R	51.3% (266)	98.5% (262/266)	40.0% (6)	83.3% (5/6)	42.9% (6)	100% (6/6)

Table 2. Data sources for baseline genotypes

	Percentage of participants (*n*/*N*)		
Data sources	BIC/FTC/TAF (*n*=570)	boosted PI+2 NRTIs (*n*=285)	DTG/ABC/3TC (*n*=281)
Baseline data available (any gene)	95.3% (543/570)	43.9% (125/285)	49.1% (138/281)
historical genotype	49.1% (280/570)	42.8% (122/285)	48.8% (137/281)
proviral genotype	90.5% (516/570)	2.1% (6/285)	0.7% (2/281)
historical genotype only	5.0% (27/543)	95.2% (119/125)	98.6% (136/138)
proviral genotype only	48.4% (263/543)	2.4% (3/125)	0.7% (1/138)
both historical and proviral genotype	46.6% (253/543)	2.4% (3/125)	0.7% (1/138)

latent viral archive of these virologically suppressed participants, HIV-1 proviral DNA was genotyped from whole blood collected at the baseline visit. Proviral genotypes were obtained from 91% (516/570) in the BIC/FTC/TAF group, 2.1% (6/285) in the boosted PI group and 0.7% (2/281) in the DTG/ABC/3TC group, and some participants had both historical and proviral genotypes. Altogether, cumulative baseline PR/RT data (historical and/or proviral) were available for 95% (543/570) in the BIC/FTC/TAF group, 44% (125/285) in the boosted PI group and 49% (138/281) in the DTG/ABC/3TC group. Cumulative baseline IN data were available for 91% (519/570) in the BIC/FTC/TAF group, 5.3% (15/285) in the boosted PI group and 5.0% (14/281) in the DTG/ABC/3TC group.

Pre-existing resistance in HIV-1 RNA-suppressed participants

Utilizing all available pre-switch genotypic data, we detected pre-existing primary drug resistance in RT in 33% (178/543) of participants in the BIC/FTC/TAF group (Table 1). NNRTI-R substitutions were observed in 23% (124/543) of participants; the most frequently detected substitutions were K103N/S in 12% (64/543) and rilpivirine-associated resistance substitutions (L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C or M320I/L) in 10% (53/543) (Table 3). Pre-existing NRTI-R substitutions were observed in 16% (89/543) of BIC/FTC/TAF-treated participants; the most frequently detected substitutions were M184V/I in 10% (54/543) and thymidine analogue mutations (TAMs; M41L, D67N, K70R, L210W, T215Y/F and K219Q/N/E/R) in 8.8% (48/543). PI-R substitutions were observed in 10% (55/543), with M46I/L (4.1%, 22/543) and L90M (2.4%, 13/543) most frequently detected. Additionally, 53% (273/519) of participants in the BIC/FTC/TAF group had at least one pre-existing INSTI-R substitution, the majority of which were polymorphic secondary (accessory) INSTI-R substitutions, with S119P/R/T (32%, 164/519), M50I (22%, 114/519) and E157K/Q (4.4%, 23/519) most frequently observed. Primary INSTI-R substitutions were infrequent (2.5%, 13/519) and consisted of T97A (1.7%, 9/519) and E92G, Q148H, S147G or Y143H (0.2%, 1/519 each).

Table 3. Pre-existing resistance substitutions at baseline and virological outcomes at week 48 (LOCF) in the BIC/FTC/TAF treatment group

	Percentage of participants in the BIC/FTC/TAF group (*n* or *n*/*N*)			
		outcomes at week 48 (LOCF)		
Pre-existing resistance substitutions	total	HIV-1 RNA <50 copies/mL	HIV-1 RNA ≥50 copies/mL	resistance analysis population
All BIC/FTC/TAF-treated participants	570	98.4% (561/570)	1.6% (9/570)	0.9% (5/570)
Baseline PR/RT data available	95.3% (543)	98.3% (534/543)	1.7% (9/543)	0.9% (5/443)
NRTI-R	16.4% (89)	96.6% (86/89)	3.4% (3/89)	1.1% (1/89)
K65R/N	1.3% (7)	100% (7/7)	0	0
M184V/I	9.9% (54)	96.3% (52/54)	3.7% (2/54)[a]	1.9% (1/54)
V only	8.5% (46)	97.8% (45/46)	2.2% (1/46)[a]	2.2% (1/46)
I only	0.9% (5)	100% (5/5)	0	0
V/I mixture	0.6% (3)	66.7% (2/3)	33.3% (1/3)[a]	0
L74I/V	0.7% (4)	100% (4/4)	0	0
Y115F	0.6% (3)	100% (3/3)	0	0
Q151M	0.4% (2)	100% (2/2)	0	0
any TAM[b]	8.8% (48)	95.8% (46/48)	4.2% (2/48)	2.1% (1/48)
1 or 2 TAMs[b]	6.4% (35)	94.3% (33/35)	5.7% (2/35)	2.9% (1/35)
≥3 TAMs[b]	2.4% (13)	100% (13/13)	0	0
NNRTI-R	22.8% (124)	99.2% (123/124)	0.8% (1/124)	0.8% (1/124)
rilpivirine associated[c]	9.8% (53)	98.1% (52/53)	1.9% (1/52)	0
K101E/P	1.8% (10)	100% (10/10)	0	0
K103N/S	11.8% (64)	98.4% (63/64)	1.6% (1/64)	1.6% (1/64)
V108I	2.8% (15)	100% (15/15)	0	0
E138A/K/Q	4.6% (25)	100% (25/25)	0	0
Y181C/I	3.1% (17)	94.1% (16/17)	5.9% (1/17)	0
Y188C/H/L	1.1% (6)	100% (6/6)	0	0
G190A/E	1.5% (8)	100% (8/8)	0	0
H221Y	0.7% (4)	100% (4/4)	0	0
P225H	1.3% (7)	100% (7/7)	0	0
F227C or M230I	0.4% (2)	100% (2/2)	0	0
PI-R[d]	10.1% (55)	100% (55/55)	0	0
Baseline IN data available	91.1% (519)	98.3% (510/519)	1.7% (9/519)	1.0% (5/519)
primary INSTI-R	2.5% (13)	100% (13/13)	0	0
T97A	1.7% (9)	100% (9/9)	0	0
E92G or Y143H or S147G or Q148H	0.8% (4)	100% (4/4)	0	0
secondary INSTI-R	51.3% (266)	98.5% (262/266)	1.5% (4/266)	1.1% (3/266)
M50I	22.0% (114)	98.2% (112/114)	1.8% (2/114)	0.9% (1/114)
L68I/V	1.3% (7)	100% (7/7)	0	0
V72N/T	0.8% (4)	100% (4/4)	0	0
L74M	1.7% (9)	88.9% (8/9)	11.1% (1/9)	0
S119P/R/T	31.6% (164)	99.4% (163/164)	0.6% (1/164)	1.2% (2/164)
E138A/K	0.6% (3)	100% (3/3)	0	0
E157K/Q	4.4% (23)	100% (23/23)	0	0
G163K/R	0.6% (3)	100% (3/3)	0	0
other secondary INSTI-R[e]	1.3% (7)	100% (7/7)	0	0

[a]One participant with pre-existing M184V experienced confirmed virological failure coincident with poor BIC/FTC/TAF adherence (76% by pill count and undetectable plasma bictegravir levels) and did not develop any additional resistance substitutions (Participant 2 in Table 4). Another participant with pre-existing M184V/I discontinued the study early with poor BIC/FTC/TAF adherence (71% by pill count) and last available HIV-1 RNA 61 copies/mL, which did not qualify for post-baseline resistance testing.

[b]TAMs were defined as: M41L, D67N, K70R, L210W, T215Y/F and K219E/Q/R in RT. TAMs observed were: M41L (*n*=23), D67N (*n*=13), K70R (*n*=20), L210W (*n*=9), T215F/Y (*n*=16) and K219E/N/Q/R (*n*=13).

[c]Rilpivirine-associated resistance was defined as having one or more of the following substitutions: L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C or M320I/L.

[d]Primary PI-R substitutions observed were: M46I/L (*n*=22), L90M (*n*=13), D30N (*n*=9), V82A/L/T (*n*=7), I84V (*n*=5), I47V, N83D and N88S (*n*=2 each), and V32I, I50V, I54L, Q58E and L76V (*n*=1 each).

[e]Other secondary INSTI-R substitutions observed were: F121C, A128T and G140S (*n*=2 each), and S153A (*n*=1).

At week 48, rates of virological suppression among BIC/FTC/TAF-treated participants with and without pre-existing resistance substitutions were similar, and not significantly different from that of the overall study population: 97% (86/89) for those with NRTI-R, 99% (123/124) with NNRTI-R, 100% (55/55) with PI-R, 100% (13/13) with primary INSTI-R and 98% (262/266) with secondary INSTI-R versus 98% (561/570) for all BIC/FTC/TAF-treated participants ($P > 0.05$ for all comparisons).

In the comparator groups, baseline resistance data were more limited, consisting primarily of historical genotypic data, and are outlined in Table 1. Similar to the BIC/FTC/TAF group, there were no significant differences between the proportions of participants with and without pre-existing resistance who had virological suppression at week 48 ($P > 0.05$).

Pre-existing substitutions associated with emtricitabine and/or tenofovir resistance discovered by retrospective proviral archive genotyping

At the start of the studies, pre-existing resistance was assessed using historical genotypes collected from ∼50% of enrolled participants. Participants with documented resistance to emtricitabine or tenofovir or any evidence of prior confirmed virological failure were not eligible to switch to BIC/FTC/TAF; therefore, no participants in the BIC/FTC/TAF group had K65R, M184V/I, or three or more TAMs by historical genotype analysis (Table S1, available as Supplementary data at *JAC* Online). Retrospective proviral archive genotyping, however, detected previously undocumented emtricitabine/tenofovir resistance-associated substitutions in the baseline samples of 11% (62/543) of participants in the BIC/FTC/TAF treatment group (Table S2). These participants continued on study at the investigator's discretion and were included in all efficacy analyses.

As previously mentioned, pre-existing M184V or M184I substitutions, associated with resistance to emtricitabine and lamivudine, were found in 10% (54/543) of participants (46 had a V substitution only, 5 had an I substitution only, and 3 had a mixture of V and I). Pre-existing M184V/I was more frequently observed in participants switching from boosted PI-based regimens than from DTG/ABC/3TC (44 versus 10, respectively, $P < 0.0001$). Furthermore, pre-existing M184V/I was associated with longer duration of ART treatment: the mean time between ART initiation and BIC/FTC/TAF switch was 14.9 years (range 2.5–28.8 years) for participants with pre-existing M184V/I versus 7.7 years (range 0.3–31.8 years) for participants with WT M184 ($P < 0.0001$ by Student's *t*-test). The majority of those with pre-existing M184V/I did not have historical genotypic data available (83%, 45/54); however, 17% (9/54) had historical genotypes that did not report M184V at the time of sampling. For these nine participants, the mean time between most recent historical genotype and BIC/FTC/TAF switch was 6.0 years (range 3.3–10.6 years). M184V/I was present with other primary NRTI-R or NNRTI-R substitutions in 72% (39/54) of participants; other primary NRTI-R substitutions (mainly TAMs) were detected in 41% (22/54), while primary NNRTI-R substitutions were observed in 52% (28/54).

Most participants with baseline M184V/I were suppressed at week 48 or their last study visit (96%, 52/54). Two participants with pre-existing M184V/I discontinued early after poor BIC/FTC/TAF adherence and subsequent virological failure. The first participant had 71% adherence by pill count and HIV-1 RNA 61 copies/mL at their last visit at week 8, which did not qualify for resistance testing. The second was included in the RAP (Participant 2 in Table 4) with 76% adherence by pill count and undetectable bictegravir plasma concentrations at the time of resistance testing at week 12, indicating that they had not taken bictegravir for at least 8 days consecutively prior to resistance testing (data on file), and had M184V detected in plasma HIV-1 RNA but no *de novo* resistance development. Virological suppression rates at week 48 were similar among participants with and without M184V/I and not significantly different from that of the overall BIC/FTC/TAF-treated population: 96% (52/54) with M184V/I and 99% (482/489) with WT M184 versus 98% (561/570) for all BIC/FTC/TAF-treated participants ($P > 0.05$ for all comparisons). Similarly, the presence of additional NRTI-R or NNRTI-R substitutions with M184V/I did not affect virological suppression rates at week 48: 97% (38/39) with M184V/I plus other NRTI-R or NNRTI-R versus 93% (14/15) with M184V/I as the only RT substitution ($P = 0.5$).

Complex patterns of TAMs and other emtricitabine/tenofovir resistance-associated substitutions were infrequently detected at baseline by retrospective archive genotyping. Pre-existing K65R/N substitutions were found in 1.3% (7/543) of participants in the BIC/FTC/TAF treatment group. While TAMs were the second most frequent pre-existing NRTI-R substitutions observed (8.8%, 48/543), most of these participants had one or two TAMs detected in their baseline samples (6.4%, 35/543), which maintain phenotypic susceptibility to emtricitabine and tenofovir. Few participants had three or more TAMs detected (2.4%, 13/543), and only 8 of these participants (1.5%, 8/543) had three or more TAMs that included M41L or L210W, which is the pattern of TAMs associated with clinically significant tenofovir resistance.[13] All participants with pre-existing K65R/N or three or more TAMs had virological suppression at week 48, and none qualified for inclusion in the RAP.

Baseline multi-class drug resistance in the BIC/FTC/TAF treatment group

HIV-1 with pre-existing resistance to multiple ART drug classes was observed in a subset of participants in the BIC/FTC/TAF treatment group. Altogether, 40% (217/543) of BIC/FTC/TAF-treated participants with baseline genotypic data had at least one primary resistance substitution in PR/RT and/or IN at baseline, and 35% (188/543) had primary RT and/or IN resistance (Table 5). The majority of these participants with any pre-existing resistance had substitutions to one drug class only (30%, 163/543), consisting mostly of NNRTI-R substitutions (14%, 78/543). Two-class drug resistance was observed in 8.1% (44/543) of participants, consisting mostly of NNRTI-R and NRTI-R substitutions (4.8%, 26/543). Three-class drug resistance was observed in 1.8% (10/543) of participants, and consisted mostly of NNRTI-R, NRTI-R and PI-R substitutions (1.7%, 9/543). The proportion of participants with one-class drug resistance who had virological suppression at week 48 was 98% (159/163), including 95% (53/56) who had primary NRTI-R or INSTI-R substitutions. These rates of virological suppression were comparable to the rates of virological suppression in the overall study population (98%, 561/570, $P > 0.05$). Among BIC/FTC/TAF-treated participants with multi-class drug resistance, 100% (54/54) had virological suppression at week 48.

Resistance analysis population

Up to 48 weeks, 12 participants qualified for inclusion in the RAP and had samples analysed for post-baseline genotypic and

Table 4. Genotypic and phenotypic profiles of participants in the RAP

					Resistance substitutions[a]		Drug susceptibility (fold change from WT)[b]							
							INSTI		NRTI				PI	
No.	Treatment group	Visit name	Visit type	HIV-1 RNA (copies/mL)	IN	RT	BIC	DTG	ABC	3TC	FTC	TFV	ATV	DRV
1	BIC/FTC/TAF	baseline	first	<50	M50I	none	–	–	–	–	–	–	–	–
		week 12	last[c]	928	AF	AF	AF	AF	AF	AF	AF	AF	AF	AF
2	BIC/FTC/TAF	baseline	first	28	none	K70K/R, M184M/V	–	–	–	–	–	–	–	–
		week 12[d]	last[c]	2860	none	M184V	0.78	0.99	3.51	>141	>95	0.54	1.01	0.79
3	BIC/FTC/TAF	baseline	first	<50	S119T	none	–	–	–	–	–	–	–	–
		week 24	last[c]	499	AF	AF	AF	AF	AF	AF	AF	AF	AF	AF
4	BIC/FTC/TAF	baseline	first	159	none	V106V/I	–	–	–	–	–	–	–	–
		week 4	cVF	206	AF	V106I	AF	AF	0.75	1.09	0.98	0.75	0.83	0.80
		week 8	cVF	117	AF	V106I	AF	AF	0.94	1.22	0.96	0.84	0.94	0.55
		week 48	last	<50	ND	ND	–	–	–	–	–	–	–	–
5	BIC/FTC/TAF	baseline	first	<50	S119P	K103N	–	–	–	–	–	–	–	–
		week 36	cVF	1500	AF	AF	AF	AF	AF	AF	AF	AF	AF	AF
		week 48	last	<50	ND	ND	–	–	–	–	–	–	–	–
6	Boosted PI (DRV + RTV + ABC/3TC)	baseline	first	6980	none	V118I	AF	AF	0.94	1.02	1.09	0.92	0.97	0.64
		week 4	last[c]	874	AF	**L74L/V**, V118I	AF	AF	1.22	1.17	1.35	0.85	0.86	0.80
7	Boosted PI (DRV/COBI + FTC/TDF)	baseline	first	99900	none	V90I, M184I	0.89	0.98	2.17	>141	>95	0.50	0.64	0.47
		week 8	cVF	1060	none	V90I, M184I	0.84	0.88	2.31	>127	>94	0.50	0.69	0.43
		week 36	last[c]	171	ND	ND	–	–	–	–	–	–	–	–
8	Boosted PI (ATV + RTV + FTC/TDF)	baseline	first	<50	S119S/A/G/T	K103N	–	–	–	–	–	–	–	–
		week 36	cVF	1580	none	K103N, **E138E/K**[e]	0.84	0.78	1.01	1.05	1.23	0.85	0.51	0.33
		week 48	cVF	982	S119S/A/G/T	K103N, **E138E/K**[e]	0.98	1.01	0.81	1.06	0.98	0.85	0.54	0.41
		week 48	last	621	ND	ND	–	–	–	–	–	–	–	–
9	Boosted PI (DRV/COBI + FTC/TDF)	baseline	first	<50	none	V106V/I	–	–	–	–	–	–	–	–
		week 8	cVF	384	AF	none	AF	AF	0.79	1.14	1.03	0.86	0.97	0.49
		week 48	last	40	ND	ND	–	–	–	–	–	–	–	–
10	Boosted PI (DRV/COBI + FTC/TDF)	baseline	first	<50	M50M/I	none	–	–	–	–	–	–	–	–
		week 12	cVF	357	AF	none	AF	AF	1.00	1.30	1.26	0.82	0.72	0.56
		week 48	last	47	ND	ND	–	–	–	–	–	–	–	–
11	DTG/ABC/3TC	baseline	first	<50	AF	AF	AF	AF	AF	AF	AF	AF	AF	AF
		week 8	last[c]	12600	none	none	0.80	0.97	0.88	1.09	1.09	0.81	0.77	0.74
12	DTG/ABC/3TC	baseline	first	<50	M50I S119R E157Q	none	–	–	–	–	–	–	–	–
		week 12	cVF	1200	M50I S119R E157Q	none	0.54	0.64	0.68	0.84	0.96	0.62	0.73	0.40
		week 48	last	<50	ND	ND	–	–	–	–	–	–	–	–

AF, assay failure; ATV, atazanavir; cVF, confirmed virological failure; COBI, cobicistat; ND, not determined; RTV, ritonavir; TFV, tenofovir; –, phenotypic testing not performed.

[a]Resistance substitutions that emerged on study drugs are shown in bold.

[b]Phenotypic fold change represents the half-maximal inhibitory concentration compared with that of the intra-assay WT control. Fold change values greater than or equal to the assay cut-off indicate resistance. Phenotypic cut-offs are 2.5 for bictegravir, 4.0 for dolutegravir, 4.5 for abacavir, 3.5 for lamivudine, 3.5 for emtricitabine, 1.4 for tenofovir (parent compound of tenofovir alafenamide), 5.2 for boosted atazanavir and 10 for boosted darunavir.

[c]Early study drug discontinuation due to participant decision (1, 2, 7 and 11), adverse event (3) or non-compliance (6).

[d]Bictegravir plasma concentrations were undetectable at this study visit and BIC/FTC/TAF adherence was 76% by pill count up to week 12.

[e]The NNRTI resistance substitution E138K emerged at week 36, but was not associated with resistance to the current regimen.

Table 5. Pre-existing multi-class drug resistance and virological outcomes at week 48 (LOCF) in the BIC/FTC/TAF treatment group

	Percentage of participants in the BIC/FTC/TAF group (*n* or *n*/*N*)			
		outcomes at week 48 (LOCF)		
Resistance category	total	HIV-1 RNA <50 copies/mL	HIV-1 RNA ≥50 copies/mL	RAP
PR/RT and/or IN baseline data available	543	98.3% (534/543)	1.7% (9/543)	0.9% (5/443)
no pre-existing primary resistance substitutions in PR/RT and/or IN	60.0% (326)	98.5% (321/326)	1.5% (5/326)	0.9% (3/326)
any pre-existing primary resistance substitutions in PR/RT and/or IN	40.0% (217)	98.2% (213/217)	1.8% (4/217)	0.9% (2/217)
any pre-existing primary resistance substitutions in RT and/or IN	34.6% (188)	97.9% (184/188)	2.1% (4/188)	1.1% (2/188)
1-class drug resistance	30.0% (163)	97.5% (159/163)	2.5% (4/163)	1.2% (2/163)
NRTI-R	8.7% (47)	93.6% (44/47)	6.4% (3/47)	2.1% (1/47)
NNRTI-R	14.4% (78)	98.7% (77/78)	1.3% (1/78)	1.3% (1/78)
PI-R	5.3% (29)	100% (29/29)	0	0
INSTI-R[a]	1.7% (9)	100% (9/9)	0	0
2-class drug resistance	8.1% (44)	100% (44/44)	0	0
NRTI-R + NNRTI-R	4.8% (26)	100% (26/26)	0	0
NRTI-R + PI-R	1.3% (7)	100% (7/7)	0	0
NNRTI-R + PI-R	1.5% (8)	100% (8/8)	0	0
NNRTI-R + INSTI-R[b]	0.4% (2)	100% (2/2)	0	0
PI-R + INSTI-R[c]	0.2% (1)	100% (1/1)	0	0
INSTI-R + NRTI-R	0	–	–	–
3-class drug resistance	1.8% (10)	100% (10/10)	0	0
NRTI-R + NNRTI-R + PI-R	1.7% (9)	100% (9/9)	0	0
NNRTI-R + INSTI-R + PI-R[d]	0.2% (1)	100% (1/1)	0	0

[a]The primary INSTI-R substitution T97A was observed in seven participants, and Y143H and Q148H were observed in one participant each.
[b]The primary resistance substitutions observed were: K103N (NNRTI-R) + E92G (INSTI-R) and K103N/V108I (NNRTI-R) + T97A (INSTI-R).
[c]The primary INSTI-R substitution S147G was observed in combination with the PI-R substitution V82A.
[d]The primary NNRTI-R substitution K103N was observed in combination with the INSTI-R substitution T97A and the PI-R substitution M46I.

phenotypic resistance: 5 in the combined BIC/FTC/TAF group, 5 in the boosted PI group and 2 in the DTG/ABC/3TC group (Table 4). Five of these 12 participants resuppressed their HIV-1 RNA to <50 copies/mL without a change in regimen (2 in the BIC/FTC/TAF group, 2 in the boosted PI group and 1 in the DTG/ABC/3TC group). Post-baseline PR/RT and/or IN genotypic and phenotypic data were available for 9 of the 12 participants analysed (2 in the BIC/FTC/TAF group, 5 in the boosted PI group and 2 in the DTG/ABC/3TC group). No participants in the BIC/FTC/TAF or DTG/ABC/3TC groups developed resistance to study drugs. One participant in the boosted PI group, who was on a regimen of ritonavir-boosted darunavir plus abacavir/lamivudine, developed virological failure with a treatment-emergent L74V resistance substitution in RT at week 4. No treatment-emergent resistance developed to any component of BIC/FTC/TAF.

Discussion

Despite entry criteria that excluded participants with known or suspected resistance to study drugs, high levels of pre-existing ART drug resistance were uncovered in studies 1878 and 1844, the first clinical trials demonstrating the efficacy and safety of switching to BIC/FTC/TAF in virologically suppressed adults. Initially, historical genotypes were evaluated but were only available for ∼50% of participants, and non-exclusionary PR/RT resistance substitutions were present in 20% (57/280) of participants in the BIC/FTC/TAF group. Retrospective proviral archive genotyping revealed high levels of pre-existing and previously undocumented exclusionary resistance: in the BIC/FTC/TAF group, 38% (198/516) of proviral genotypes reported PR/RT resistance and 12% (62/516) reported emtricitabine/tenofovir resistance. By aggregate historical and proviral archive genotypic data, pre-existing primary PR/RT and/or IN resistance substitutions were detected in 40% of participants in the BIC/FTC/TAF group. The high rates of BIC/FTC/TAF treatment efficacy observed among participants with pre-existing resistance substitutions and absence of new resistance indicate that baseline genotype did not affect BIC/FTC/TAF outcomes in suppressed participants switching regimens.

In suppressed patient populations, sources of pre-existing resistance include both transmitted and previously acquired resistance. The frequencies of baseline resistance found in studies 1878 and 1844 are higher than frequencies of transmitted drug resistance detected in many ART-naive patient populations,[14–17] suggesting that some of the pre-existing resistance observed developed during prior ART treatment. However, according to eligibility criteria participants were not supposed to have previously

switched regimens due to virological failure to limit the risk of acquired resistance. Nonetheless, 10% (54/543) of participants had major pre-existing resistance to emtricitabine and lamivudine in the form of M184V or M184I. The average time on ART therapy for participants with M184V/I was longer than that for those with WT M184; however, archived M184V/I was also detected in participants who initiated ART therapy <3 years ago. The high levels of pre-existing resistance observed in these studies, which were designed to minimize pre-existing resistance, indicate that there may be significant underlying resistance among patients with HIV-1 RNA suppression, including those recently infected.

M184V/I substitutions are among the most common NRTI-R substitutions detected in HIV-infected individuals who have experienced virological failure on emtricitabine- or lamivudine-based therapy.[18–21] Resuppressed patients harbouring M184V/I may eventually need to switch regimens, but most guideline-recommended fixed-dose combinations containing emtricitabine or lamivudine are not indicated for patients with known resistance to any component of the regimen.[22–27] In studies 1878 and 1844, retrospective archive genotyping revealed previously undocumented M184V/I in a large subset of participants who were suppressed on boosted PI-based triple therapy (atazanavir or darunavir plus two NRTIs) or DTG/ABC/3TC and switched to BIC/FTC/TAF (10%). BIC/FTC/TAF treatment maintained viral suppression, with only two cases of virological failure related to poor BIC/FTC/TAF adherence. *In vitro*, viral isolates with M184V/I substitutions have reduced viral fitness and increased susceptibility to tenofovir.[28–30] Consequently, in medical practice emtricitabine/tenofovir-based treatment is continued in the context of M184V/I to maintain selective pressure for a less fit, tenofovir-hypersusceptible virus. Taken together, current clinical and *in vitro* data suggest that BIC/FTC/TAF may be an effective treatment option for suppressed patients with archived M184V/I. However, additional studies of BIC/FTC/TAF efficacy in viraemic patients are needed to further determine the utility of BIC/FTC/TAF in HIV-infected individuals harbouring M184V/I, which may increase the risk of further development of drug resistance.

DNA genotyping of the proviral archive is becoming increasingly popular to obtain resistance data for HIV-infected patients who are virologically suppressed and do not have a recent historical plasma RNA genotype. There are some limitations to proviral DNA genotyping, including interference from replication-defective proviral genomes. Extensive guanosine-to-adenosine (G-to-A) hypermutation by the cellular factor APOBEC3G can cause the M184I (but not M184V) substitution; however, APOBEC also induces stop codons rendering many of these genomes non-viable.[31–34] For studies 1878 and 1844, proviral genotyping was performed using the commercially available GenoSure Archive® assay, which utilizes bioinformatics filters to remove hypermutated sequences as part of the quality control data analysis. Other genetic alterations may also lead to defective integrated proviruses,[33] leading some to question the reactivation competency of HIV with any archived resistance. In study 1878, one participant had reactivation of archived M184V during virological failure due to drug non-adherence, which substantiates the relevance of archived resistance. Thus, all cases of pre-existing M184V/I should be considered clinically relevant when making treatment decisions.

Proviral archive genotyping also has sampling limitations. Small blood volumes and low frequency of circulating and latently infected T cells yield only a small sampling of the total HIV archive. Deep sequencing methods are utilized but are limited to low proviral DNA copy numbers. A recent study of suppressed participants with documented M184V/I by historical genotype showed that M184V/I was detected by the GenoSure Archive® assay in only 43% (16/37) of cases.[35] Other published reports have similarly found that proviral genotyping can fail to detect all resistance substitutions that were previously detected by plasma HIV-1 RNA sequencing.[36,37] Reporting cut-offs may also limit assay sensitivity: Thielen *et al.*[38] recently reported that a 15% proviral DNA deep sequencing cut-off only detected M184V in <50% of patients who had previously documented M184V, but with a 1% assay cut-off M184V was detected in almost 70%. Given these limitations, the high frequencies of M184V/I and other resistance substitutions detected by proviral genotyping in studies 1878 and 1844 are likely an under-representation of total archived resistance.

Clinically, pre-existing resistance could create risks for suppressed patients who switch ARTs, especially when fewer than two drugs are fully active, as archived resistance may re-emerge under suboptimal therapy and result in virological failure and development of more resistance. The baseline data from studies 1878 and 1844 suggest that pre-existing resistance to emtricitabine and lamivudine and NNRTIs such as rilpivirine is frequent in suppressed patient populations, with pre-existing M184V/I and rilpivirine resistance each detected in 10% of our participants. Furthermore, incomplete historical resistance documentation and proviral assay limitations significantly underestimate the levels of major drug resistance in the viral archive. Switching suppressed patients with underlying M184V/I or rilpivirine resistance to a dual combination of dolutegravir/lamivudine or dolutegravir/rilpivirine, respectively, would result in functional dolutegravir monotherapy. Previously, dolutegravir monotherapy has led to a high frequency of virological failure and resistance development, and is not recommended.[2,39–42] Additionally, any potential benefit of decreased viral fitness by M184V/I on the efficacy of dolutegravir/lamivudine may not outweigh the risk of virological failure with INSTI-R development, as it is possible for M184V and INSTI-R to co-develop while failing a dolutegravir/lamivudine regimen.[43] *In vitro* studies further suggest that viral fitness defects can be overcome by drug resistance in the presence of antiretroviral drugs: HIV-1 with M184V and INSTI-R (E92Q, Q148R or N155H) grows more efficiently than WT HIV-1 in the presence of emtricitabine and the INSTI elvitegravir at physiological concentrations.[44,45] Moreover, tenofovir hypersusceptibility of M184V/I may also play a role in the efficacy of tenofovir-containing three-drug regimens such as BIC/FTC/TAF against archived M184V/I, but this would not be applicable to dolutegravir/lamivudine.

In studies 1878 and 1844, high levels of pre-existing resistance substitutions were detected among suppressed patients switching to BIC/FTC/TAF, including previously unidentified M184V/I in 54 participants. At week 48, switching to BIC/FTC/TAF was non-inferior to remaining on boosted PI-based regimens or DTG/ABC/3TC, with low rates of virological failure and high maintenance of HIV-1 RNA suppression, regardless of pre-existing resistance. High rates of virological suppression for up to 48 weeks and the absence of treatment-emergent resistance indicate that the three-drug regimen BIC/FTC/TAF is a treatment option for suppressed patients, including those with evidence of archived resistance, such as M184V/I, or without historical resistance data.

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Transparency declarations

All authors are current or former employees and shareholders of Gilead Sciences, Inc.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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