AIDS, Publish Ahead of Print

DOI: 10.1097/QAD.0000000000003865

Switch to Bictegravir/Emtricitabine/Tenofovir Alafenamide From Dolutegravir-Based Therapy: 96-Week Pooled Analysis

Chloe ORKIN,[1] Andrea ANTINORI,[2] Jürgen K ROCKSTROH,[3] Santiago MORENO-GUILLÉN,[4] Claudia T MARTORELL,[5] Jean-Michel MOLINA,[6] Adriano LAZZARIN,[7] Franco MAGGIOLO,[8] Yazdan YAZDANPANAH,[9] Kristen ANDREATTA,[10] Hailin HUANG,[10] Jason T HINDMAN,[10] Hal MARTIN,[10] Anton POZNIAK[11]

[1]Queen Mary University of London, London, UK; [2]National Institute for Infectious Diseases, Lazzaro Spallanzani IRCCS, Rome, Italy; [3]University Hospital Bonn, Bonn, Germany; [4]Hospital Ramón y Cajal, Madrid, Spain; [5]The Research Institute, Springfield, MA, USA; [6]University of Paris Cité, Department of Infectious Diseases, Hôpital Saint-Louis and Lariboisière, Paris, France; [7]San Raffaele Hospital Milan, Milan, Italy; [8]Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy; [9]AP-HP Hôpital Bichat, Paris, France; [10]Gilead Sciences, Inc., Foster City, CA, USA; [11]Chelsea and Westminster Hospital, London, UK

Running head: Switch from DTG-based ART to B/F/TAF

Corresponding author*:*

Chloe Orkin

Address: Queen Mary University of London, London, UK

Email: c.m.orkin@qmul.ac.uk

Prior presentation: Data were previously presented in poster format at Glasgow HIV 2022 and published as an abstract in *J Int AIDS Soc* 2022;25 Suppl 6:e26009.

Disclosures: This work was supported by Gilead Sciences, Inc. (Foster City, CA, USA).

Conflicts of interest and source of funding: CO has received grants or contracts from Janssen, Gilead Sciences, ViiV Healthcare, MSD and AstraZeneca (paid to institution); payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Janssen, Gilead Sciences, ViiV Healthcare and MSD; and is President of the Medical Women's Federation (unpaid) and a governing council member of International AIDS Society (unpaid). AA has received grants or contracts from Gilead Sciences, AstraZeneca and ViiV Healthcare; consulting fees from Gilead Sciences, AstraZeneca, GSK, Merck, Janssen-Cilag, Moderna, Mylan, Pfizer and ViiV Healthcare; and support for attending meetings and/or travel from Gilead Sciences. JKR has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Gilead Sciences, Janssen, MSD and ViiV Healthcare; and honoraria for consulting from

Boehringer. S-MG has received grants or contracts from Gilead Sciences, ViiV Healthcare, Janssen Pharmaceutical and MSD; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Gilead Sciences, ViiV Healthcare, Janssen Pharmaceutical and MSD; support for attending meetings and/or travel from Gilead Sciences, ViiV Healthcare, Janssen Pharmaceutical and MSD; and payment for participation on a data safety monitoring board or advisory board from Gilead Sciences, ViiV Healthcare, Janssen Pharmaceutical and MSD. CTM has received payments or honoraria for speaker bureaus from Gilead Sciences, ViiV Healthcare, Theratechnologies, and AbbVie. J-MM has received grants or contracts from Gilead Sciences (paid to institution); consulting fees from Gilead Sciences, Merck and ViiV Healthcare; and payment for participation on a data safety monitoring board or advisory board for Aelix. KA, HH, JTH and HM are employees of Gilead Sciences and hold stocks. AP has received grants or contracts from Gilead Sciences and ViiV Healthcare (paid to institution); payment or honoraria for lectures, presentations or educational events from Gilead Sciences and ViiV Healthcare; support for attending meetings and/or travel from Gilead Sciences and ViiV Healthcare; and is President of NEAT ID and a member of guideline committees for BHIVA and EACS. AL, FM and YY have nothing to disclose.

Abstract

Objective: To evaluate the efficacy and safety of 96 weeks of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) treatment in participants switching from dolutegravir (DTG)-based therapy.

Design: Studies 1489 (NCT02607930) and 1490 (NCT02607956) were phase 3 randomized, double-blind, active-controlled, first-line therapy trials in people with HIV-1. After 144 weeks of DTG-based or B/F/TAF treatment, participants could enter a 96-week open-label extension (OLE) of B/F/TAF.

Methods: A pooled analysis evaluated viral suppression (HIV-1 RNA <50 copies/mL) and changes in CD4+ cell count at OLE Weeks 48 and 96, treatment-emergent resistance, safety and tolerability after switch from a DTG-based regimen to B/F/TAF. Outcomes by prior treatment were summarized using descriptive statistics and compared by two-sided Wilcoxon rank sum test.

Results: At OLE Week 96, participants who switched to B/F/TAF (N=519) maintained high levels of virologic suppression (99.5% and 99.1% in those switching from DTG/abacavir/lamivudine and DTG+F/TAF, respectively) and CD4+ cell count, with no treatment-emergent resistance to B/F/TAF. Twenty-one participants experienced drug-related adverse events (AEs) after switching, with diarrhea, weight gain and headache occurring most commonly. There were no cases of proximal renal tubulopathy, drug-related Grade 4 AEs or serious AEs. Two participants discontinued B/F/TAF due to treatment-related AEs. Participants who switched from DTG/abacavir/lamivudine experienced statistically significant greater weight gain than those who switched from DTG+F/TAF; however, median weight change from the blinded phase baseline to OLE Week 96 was numerically similar across treatment groups.

Conclusions: This medium-term analysis demonstrates the safety and efficacy of switching to B/F/TAF from a DTG-containing regimen in people with HIV-1.

Key words: HIV-1, antiretroviral therapy, regimen switch, efficacy, safety, tenofovir alafenamide, bictegravir

Introduction

The number of people with HIV accessing antiretroviral therapy (ART) is increasing, from 7.8 million in 2010 to 28.7 million in 2021 [1]. Furthermore, increased longevity on HIV therapy means that people will require decades of ART. Managing emerging comorbidities and drug interactions as people age on ART is an increasing challenge [2, 3]. Simplification of treatment regimens and treatment switches to optimize care may be needed [2-4].There are many different reasons why a provider or patient may want or need to switch their ART regimen. Evaluating medium- and long-term clinical trial outcomes, where available, can guide decisions on optimal treatment options for specific subpopulations.

Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a three-drug, fixed-dose, single-tablet regimen containing an integrase strand transfer inhibitor, bictegravir, and two nucleoside reverse transcriptase inhibitors, emtricitabine and TAF. Clinical trial results have shown that B/F/TAF is highly effective and well-tolerated in adults [5-10]. There is also growing evidence supporting the use of B/F/TAF in routine clinical practice [11-13].

B/F/TAF (50/200/25 mg) is approved for adults in many countries around the world [14, 15] and is recommended in international HIV guidelines in high-income countries, both as first-line and as a switch regimen for those with virological suppression [2-4].

Study 1489 and Study 1490 are randomized, double-blinded, phase 3 clinical trials that evaluated the long-term efficacy and safety of either dolutegravir (DTG)-based treatment or B/F/TAF over 144 weeks [7, 16, 17]. Here, we report the efficacy and safety of 96 weeks of B/F/TAF treatment in participants who switched from DTG-based therapy on completion of the blinded phase at 144 weeks.

Methods

Study design and participants

Studies 1489 (GS-US-380-1489, NCT02607930) and 1490 (GS-US-380-1490, NCT02607956) were phase 3, randomized, double-blind, multicenter, active-controlled studies. Study 1489 was conducted in Europe, Latin America, and North America; Study 1490 in Australia, Europe, Latin America and North America [7, 16, 17]. Detailed methods for these studies and eligibility criteria were described previously [16, 17].

In short, participants with plasma HIV-1 RNA levels ≥500 copies/mL and no more than 10 days of prior ART were randomized 1:1 in Study 1489 to receive first-line therapy with B/F/TAF (n=316) or DTG/abacavir/lamivudine (DTG/ABC/3TC; n=315) and in Study 1490 to receive first-line therapy

with B/F/TAF (n=327) or DTG+F/TAF (n=330) in a double-blinded fashion. Participants with chronic hepatitis B virus (HBV) infection or who were HLA-B*5701 positive at screening were excluded from Study 1489; participants with acute hepatitis within 30 days prior to study entry were excluded from both studies.

Both studies were conducted in accordance with the Declaration of Helsinki, with the understanding and the informed written consent of each participant. Site-specific independent ethics committees approved the protocols.

Study endpoints and assessments

The primary endpoints of both studies were published previously [16, 17]. The open-label extension (OLE) endpoints in both studies included the following secondary endpoints: the proportion of participants who achieved HIV-1 RNA <50 copies/mL at OLE Weeks 48 and 96, as defined by missing = excluded (M=E) and missing = failure (M=F) analyses; and changes from B/F/TAF start in CD4+ cell count at OLE Weeks 48 and 96. Other endpoints included treatment-emergent resistance, safety (including change in weight) and treatment discontinuations.

In the OLE phase, efficacy and safety were assessed at Week 12 and subsequently every 12 weeks for at least 96 weeks. Safety was assessed by physical examination (including vital signs measurements and weight), laboratory tests, and review of concomitant medications and adverse events (AEs; coded using the Medical Dictionary for Regulatory Activities version 24.0). AEs and laboratory abnormalities were graded according to the Gilead Sciences, Inc (GSI) Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (version 01 April 2015). Laboratory tests included measurement of plasma HIV-1 RNA, CD4+ cell counts, hematological analyses (chemistry profile, metabolic assessments [fasting glucose and lipid parameters], estimated glomerular filtration rate [eGFR]) and urine sample analysis. The Cockcroft–Gault formula was used to calculate eGFR [18].

Participants with HIV-1 RNA ≥200 copies/mL at the last on-treatment visit or at the visit following HIV-1 ≥50 copies/mL (confirmed virologic failure) without resuppression of HIV-1 RNA to <50 copies/mL while on treatment were assessed for genotypic and phenotypic resistance. Resistance testing methods and a list of surveillance resistance-associated mutations have been published previously [19].

Statistical analysis

Demographic and baseline characteristics were summarized using standard descriptive methods, including sample size, mean, standard deviation, median, quartile (Q) 1 and Q3, minimum and maximum for continuous variables, and frequency and percentages for categorical variables. The proportion of participants who achieved HIV-1 RNA <50 copies/mL was defined by M=E and M=F algorithms and summarized together with 95% confidence intervals (CIs) calculated using the Clopper–Pearson exact method. The changes from B/F/TAF start in CD4+ cell count, safety data and other outcomes were summarized by prior treatment using descriptive statistics. Changes in weight

were summarized by prior treatment as absolute change from B/F/TAF start and as an annual change. A two-sided Wilcoxon rank sum test was used to compare groups.

Results

Demographics and clinical characteristics at the time of B/F/TAF start

Overall, 519/534 (97.2%) participants who completed 144 weeks of DTG-based ART were switched to B/F/TAF and included in this analysis: 254/260 participants from Study 1489 and 265/274 participants from Study 1490. In total, 457/519 (88.1%) participants completed Week 240 (OLE Week 96); 221/254 (87.0%) participants from Study 1489 and 236/265 (89.1%) from Study 1490 (**Figure 1**). Demographics and clinical characteristics for participants at the time of B/F/TAF start are shown in **Table 1**. Participants in OLE of both studies were predominantly male (88.6% in Study 1489 and 90.2% in Study 1490). The median age at time of B/F/TAF initiation was 36 years in Study 1489 and 38 years in Study 1490. In both studies, approximately one-third of participants who switched to B/F/TAF were Black and over one-fifth were Hispanic/Latinx. The median CD4 count at the time of B/F/TAF start was 766 cells/μL in Study 1489 and 730 cells/μL in Study 1490.

Efficacy

At Week 240 (OLE Week 96), rates of virologic suppression were similar among participants who switched from DTG-based regimens and those initially randomized to B/F/TAF (**Figure 2**). In the M=E analysis, participants who switched to B/F/TAF from DTG/ABC/3TC or DTG+F/TAF maintained high levels of virologic suppression (HIV RNA <50 copies/mL) until OLE Week 96 (**Figure 2a**). At OLE Week 96, virologic suppression rates were 99.5% (95% CI, 97.5–100.0; M=E; 217/218 participants) in those who switched from DTG/ABC/3TC and 99.1% (95% CI, 96.9–99.9; M=E; 232/234 participants) in those who switched from DTG+F/TAF. In the M=F analysis, rate of virologic suppression at OLE Week 96 in participants who switched from DTG/ABC/3TC to B/F/TAF was 85.4% (95% CI, 80.5–89.5; 217/254 participants) and for those switching from DTG+F/TAF, it was 87.5% (95% CI, 83.0–91.3; 232/265 participants) (**Figure 2b**).

At OLE Week 96, data were missing for 36/254 (14.2%) participants who switched from DTG/ABC/3TC and 31/265 (11.7%) participants who switched from DTG+F/TAF. Two (0.6%) participants receiving blinded DTG/ABC/3TC had HIV-1 RNA ≥200 copies/mL at the time of switch, both of whom had a M184V substitution and resuppressed on B/F/TAF (Supplementary Figure 1, http://links.lww.com/QAD/D123). In total, 3/254 (1.2%) participants who switched from DTG/ABC/3TC met criteria for resistance testing during the OLE phase (one participant at OLE Week 36 and one participant at OLE Week 72, both of whom also met the criteria for resistance testing during the blinded treatment phase; and one participant at OLE Week 96) and 1/265 (0.4%) who switched from DTG+F/TAF met criteria for resistance testing (at OLE Weeks 12 and 24; also met criteria during blinded treatment phase). None of these participants developed treatment-emergent resistance during the OLE.

Immunological outcomes

In participants who switched to B/F/TAF from DTG/ABC/3TC, the median (Q1, Q3) changes in CD4 cell count from B/F/TAF start to OLE Week 48 and OLE Week 96 were -6 (-113, 104; n=212) cells/μL and -6 (-116, 82; n=204) cells/μL, respectively. In those who switched to B/F/TAF from DTG+F/TAF, the median changes (Q1, Q3) in CD4 count were +14 (-83, 117; n=223) cells/μL and +3 (-91, 110; n=225) cells/μL, respectively.

Safety and tolerability

Overall, 214/254 (84.3%) of participants who switched from DTG/ABC/3TC and 215/265 (81.1%) of those who switched from DTG+F/TAF experienced AEs by OLE Week 96 (**Table 2**). Drug-related AEs were experienced by 13/254 (5.1%) participants who switched from DTG/ABC/3TC and 8/265 (3.0%) participants who switched from DTG+F/TAF. The most common drug-related AEs in the OLE were diarrhea (3/519 [0.6%] of participants), weight gain (3/519 [0.6%] of participants) and headache (2/519 [0.4%] of participants). The incidence of nausea and diarrhea declined numerically after switching from a DTG-based regimen to B/F/TAF in the OLE (Supplementary Figure 2, http://links.lww.com/QAD/D123). Drug-related nausea and diarrhea were reported in 1/254 (0.4%) and 2/254 (0.8%) participants, respectively, who switched to B/F/TAF from DTG/ABC/3TC (no incidence of drug-related nausea or diarrhea from OLE Week 8 to 96 in evaluable participants). In participants who switched from DTG+F/TAF, no drug-related nausea or diarrhea were reported in evaluable participants during the OLE.

No drug-related Grade 4 AEs or serious AEs were reported. There was one Grade 3 AE that was designated by the investigator as study drug-related. The investigator deemed existing diabetes mellitus in one participant (first reported during the blinded phase while on DTG+F/TAF) to have worsened on Day 1 after switching to B/F/TAF. The event (worsening of diabetes without accompanied excessive weight gain) resolved within 15 weeks and did not result in study discontinuation. None of the participants who switched to B/F/TAF experienced drug-related cardiovascular events after the switch (Supplementary Table 1, http://links.lww.com/QAD/D123). Hypertension was reported in 12/254 (4.7%) and 11/265 (4.2%) participants, who switched to B/F/TAF from DTG/ABC/3TC and DTG+F/TAF, respectively. No new-onset HBV infections were reported in participants on B/F/TAF.

In total, of 519 participants across both studies, 23 (4%) participants initiated anti-hypertension medication, 17 (3%) participants initiated lipid-lowering agents and 7 (1%) initiated anti-diabetes agents during OLE.

Median eGFR changes were negligible in participants receiving B/F/TAF during the OLE (Supplementary Figure 3, http://links.lww.com/QAD/D123), with no reported cases of proximal renal tubulopathy.

Discontinuations

Across both studies, 2/519 participants (0.4%) experienced a drug-related AE that led to discontinuation of the study drug after switching (weight gain and obesity, respectively); both switched from DTG/ABC/3TC (**Table 2**). Other reasons for discontinuation included participant's decision (n=30), loss to follow-up (n=16), investigator's discretion (n=7), protocol violation (n=1), lack of efficacy (n=1) and pregnancy (n=1) (**Figure 1**). There were no discontinuations due to renal AEs. In total, five deaths occurred during the OLE, two in participants who switched from DTG/ABC/3TC (one due to seizures and one of unknown cause in a participant with known cardiovascular disease and risk factors) and three in participants who switched from DTG+F/TAF (one due to malignant neoplasm of urinary bladder and two of unknown cause, including one in a participant with known cardiovascular disease and risk factors and one in participant with no history of cardiovascular disease or risk factors). None of the participants who died had emergent hypertension, emergent diabetes, or initiated statins after the switch to B/F/TAF.

Laboratory abnormalities

Overall, 76/519 (15%) participants (34/254 [13%] of those who switched from DTG/ABC/3TC and 42/265 [16%] of those who switched from DTG+F/TAF) experienced any Grade 3 or 4 laboratory abnormality (**Supplementary Table 2**, http://links.lww.com/QAD/D123). The most common treatment-emergent Grade 3 or 4 laboratory abnormalities in participants who switched from DTG/ABC/3TC were increased creatine kinase (9/252 [4%] of participants), increased amylase and increased aspartate aminotransferase (5/252 [2%] of participants each); none were associated with clinical symptoms of pancreatitis. In those who switched from DTG+F/TAF, the most common laboratory abnormalities were increased creatine kinase (7/264 [3%] of participants), non-fasting hyperglycemia (5/143 [3%] of participants), increased fasting low-density lipoprotein (8/257 [3%] of participants) and glycosuria (9/264 [3%] of participants, all with concomitant hyperglycemia).

Minor changes in lipids were observed among participants who switched to B/F/TAF (Supplementary Figure 4, http://links.lww.com/QAD/D123). Median (95% CI) change from Week 144 (OLE Week 0) in fasting total cholesterol-to-high-density lipoprotein (HDL) ratio at Week 240 (OLE Week 94) was 0.1 (-0.3, 0.5) in those who switched from DTG/ABC/3TC and 0.1 (-0.4, 0.5) in participants who switched from DTG+F/TAF.

Changes in weight

At Week 144 (OLE Week 0), significantly smaller median weight changes from baseline were observed with DTG/ABC/3TC than with DTG+F/TAF: +3.5 kg versus +5.0 kg (P=0.025) (**Figure 3**). Between Weeks 144 and 240 (OLE Weeks 0 and 96), participants who switched from DTG/ABC/3TC had greater weight changes than those who switched from DTG+F/TAF. Median (Q1, Q3) at Week 240 (OLE Week 96) was +2.4 (-0.4, +5.6) kg versus +1.3 (-1.9, +5.0) kg (P=0.007), respectively. Cumulative median (Q1, Q3) weight changes at Week 240 (OLE Week 96) from baseline in the blinded phase were numerically similar for all treatment groups: 6.8 (1.6, 11.1) kg in those who switched from DTG/ABC/3TC; 5.4 (1.4, 11.3) kg in those who switched from

DTF+F/TAF; 6.1 (2.0, 11.1) kg in those originally randomized to B/F/TAF in Study 1489; and 6.1 (2.3, 12.6) kg in those originally randomized to B/F/TAF in Study 1490.

Discussion

During the blinded phase of studies 1489 and 1490, B/F/TAF demonstrated noninferior efficacy and safety to DTG/ABC/3TC or DTG+F/TAF in people on first-line ART over 144 weeks [6, 9, 17]. The OLE phase of these studies evaluated the impact of switching from DTG-based treatment to B/F/TAF at the end of the 144-week blinded treatment phase. In the OLE phase we saw consistent efficacy and safety results after 96 weeks of B/F/TAF treatment in participants who had initially been randomized to DTG-based treatment.

During the follow-up, adults who switched from DTG-based treatment to B/FTAF in studies 1489 and 1490 maintained high rates of virologic suppression with no treatment-emergent resistance to B/F/TAF during 96 weeks of treatment [10]. Two participants with M184V had HIV-1 RNA ≥200 copies/mL at the time of switching from DTG/ABC/3TC. Both participants subsequently had sustained resuppression on B/F/TAF. Consistent with findings seen in other clinical trials [15], there were no cases of treatment-emergent resistance with B/F/TAF. These data confirm and extend the previous 144- and 240-week follow-up results of B/F/TAF in the blinded and open-label phases, respectively [6, 10], and 48-week follow-up results of B/F/TAF switch from DTG/ABC/3TC [5].

Safety in the OLE phase was consistent with the known profile of B/F/TAF [6, 8-11, 15, 17], and tolerability was reflected by few discontinuations. Outside of a clinical trial setting, results from a large observational cohort have demonstrated maintenance of virologic control and no new or unexpected safety findings after switching to B/F/TAF from other regimens in people with HIV in routine clinical care [13].

The two most common AEs with DTG-based regimens in the blinded phase of studies 1489 and 1490 were nausea and diarrhea [6, 16]. However, consistent with previous reports [7, 16, 20], the incidence and prevalence of nausea and diarrhea improved after switching to B/F/TAF, possibly due to better gastrointestinal tolerability of TAF than ABC in Study 1489 [21, 22]. The median lipid changes were small and the impact of the switch to B/F/TAF on total cholesterol-to-HDL ratio was minimal, similar to those observed during the 240-week follow-up in participants initially randomized to receive B/F/TAF [10]. Subsequently, the number of participants who initiated lipid-lowering agents, anti-hypertensives and anti-diabetic agents after the switch was also small. No cases of proximal renal tubulopathy and no discontinuations due to renal AEs were observed in participants receiving B/F/TAF, providing further evidence of the renal safety profile of B/F/TAF.

During the first 144 weeks (blinded phase) of the study, participants on DTG/ABC/3TC had lower weight gain than those who were on DTG+F/TAF (3.5 kg versus 5.0 kg; P=0.025). This observation is consistent with a previously reported differential effect of ABC and TAF on weight [22, 23]. Between Week 144 (OLE Week 0) and Week 240 (OLE Week 96), significantly greater weight increases were observed in participants who switched to B/F/TAF from DTG/ABC/3TC (2.4 kg) compared with those who switched from DTG+F/TAF (1.3 kg), suggesting that the differential effect

of ABC versus TAF on weight gain is reversed on switching to B/F/TAF. The mechanism underlying this effect is unknown. Cumulative weight changes from blinded phase baseline at Week 240 (OLE Week 96) were similar across all treatment groups.

Although one case of new-onset HBV infection was reported in the DTG/ABC/3TC group during the blinded phase, no cases were reported in participants on B/F/TAF, consistent with the prophylactic activity of TAF against HBV [4].

This study has several limitations. While the first 144 weeks of studies 1489 and 1490 were blinded, the data presented here are based on an optional OLE of those studies. This open-label design may have introduced some bias into the study results. Although a 96-week treatment period allows us to monitor medium-term efficacy and safety, we cannot exclude the possibility of AEs or complications that can only be detected with longer follow-up. However, the efficacy and safety results were consistent with outcomes during the first 144 weeks [10]. The timing of the switch was protocol-defined in this study, so it may not reflect how people chose to switch regimens in real life. A proportion of data was also missing for some participants, and some of the follow-up visits did not take place because of the COVID-19 pandemic; however, similar rates of discontinuation were observed in other antiretroviral studies conducted during this time period [24, 25]. In our study, the most common reasons for discontinuation were participant decision, loss to follow-up and investigator's decision; there was also a very low percentage of participants who discontinued due to an AE (2% in those who switched from DTG/ABC/3TC; 0% in those who switched from DTG+F/TAF). However, M=E and M=F analyses of viral suppression should sufficiently account for any missing data. Descriptive statistics were used for most outcomes.

Conclusion

Participants in studies 1489 and 1490 who switched to B/F/TAF from a DTG-containing regimen maintained high rates of virologic suppression, with no emergent resistance. The treatment was well-tolerated and there were no new safety signals reported during medium-term B/F/TAF treatment. These results provide further medium-term evidence of B/F/TAF safety and efficacy in people with HIV who switch from a DTG-based therapy.

Acknowledgments

We thank all participants and their families, participating sites, investigators and study staff involved in the study. This work was supported by Gilead Sciences, Inc. (Foster City, CA, USA). Medical writing support, including development of a draft outline and subsequent drafts in consultation with the authors, collating author comments, copyediting, fact checking and referencing, was provided by Joanna Nikitorowicz-Buniak, PhD and Victoria Warwick, PhD at Aspire Scientific (Bollington, UK), and funded by Gilead Sciences, Inc. (Foster City, CA, USA).

Author contributions

CO, AA, JKR, SM-G, CTM, J-M M, AL, FM, YY and AP contributed to data collection and data analysis or interpretation. KA and JTH contributed to data analysis or interpretation. HH and HM

contributed to study design and data analysis or interpretation. All authors have read and approved the text as submitted.

Data sharing statement

Gilead Sciences shares anonymized individual patient data upon request or as required by law or regulation with qualified external researchers based on submitted curriculum vitae and reflecting non-conflict of interest. The request proposal must also include a statistician. Approval of such requests is at Gilead Sciences' discretion and is dependent on the nature of the request, the merit of the research proposed, the availability of the data and the intended use of the data. Data requests should be sent to datarequest@gilead.com.

References

1. UNAIDS. Global HIV and AIDS statistics. 2022. Available at: https://www.unaids.org/en/resources/fact-sheet. [Accessed 14 August 2023].

2. European AIDS Clinical Society. Guidelines Version 11.1. October 2022. Available at: https://www.eacsociety.org/media/guidelines-11.1_final_09-10.pdf. [Accessed 14 August 2023].

3. Gandhi RT, Bedimo R, Hoy JF, Landovitz RJ, Smith DM, Eaton EF, *et al.* **Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2022 recommendations of the International Antiviral Society-USA Panel**. *JAMA* 2023; **329**:63–84.

4. Department of Health and Human Services. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. September 2022. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/adult-adolescent-arv/guidelines-adult-adolescent-arv.pdf. [Accessed 14 August 2023].

5. Molina JM, Ward D, Brar I, Mills A, Stellbrink HJ, Lopez-Cortes L, et al. Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet HIV 2018; 5:e357–e365.

6. Orkin C, DeJesus E, Sax PE, Arribas JR, Gupta SK, Martorell C, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. Lancet HIV 2020; 7:e389–e400.

7. Sax PE, Rockstroh JK, Luetkemeyer AF, Yazdanpanah Y, Ward D, Trottier B, et al. Switching to bictegravir, emtricitabine, and tenofovir alafenamide in virologically suppressed adults with HIV. Clin Infect Dis 2020; 73:e485–e493.

8. Stellbrink HJ, Arribas JR, Stephens JL, Albrecht H, Sax PE, Maggiolo F, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet HIV 2019; 6:e364–e372.

9. Wohl DA, Yazdanpanah Y, Baumgarten A, Clarke A, Thompson MA, Brinson C, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet HIV 2019; 6:e355–e363.

10. Sax PE, Arribas JR, Orkin C, Lazzarin A, Pozniak A, DeJesus E, et al. Bictegravir/emtricitabine/tenofovir alafenamide as initial treatment for HIV-1: five-year follow-up from two randomized trials. EClinicalMedicine 2023; 59:101991.

11. Ambrosioni J, Rojas LJ, Berrocal L, Inciarte A, de la Mora L, González-Cordón A, et al. Real-life experience with bictegravir/emtricitabine/tenofovir alafenamide in a large reference clinical centre. J Antimicrob Chemother 2022; 77:1133–1139.

12. Mounzer K, Brunet L, Fusco JS, McNicholl IR, Diaz CH, Sension M, et al. Advanced HIV infection in treatment-naïve individuals: effectiveness and persistence of recommended 3-drug regimens. Open Forum Infect Dis 2022; 9:ofac018.

13. Esser S, Brunetta J, Inciarte A, Levy I, D'Arminio Monforte A, Lambert JS, et al. Twelve-month effectiveness and safety of bictegravir/emtricitabine/tenofovir alafenamide in people with HIV: Real-world insights from BICSTaR cohorts. HIV Med 2023; [Epub ahead of print]. doi: 10.1111/hiv.13593.

14. Gilead Sciences. Biktarvy 50 mg/200 mg/25 mg film-coated tablets: European summary of product characteristics. 2018. Available at: https://www.ema.europa.eu/en/documents/product-information/biktarvy-epar-product-information_en.pdf. [Accessed 14 August 2023].

15. Gilead Sciences. Biktarvy highlights of US presribing information. 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210251s013lbl.pdf. [Accessed 14 August 2023].

16. Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczer D, Tebas P, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for

initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. Lancet 2017; 390:2063–2072.

17. Sax PE, Pozniak A, Montes ML, Koenig E, DeJesus E, Stellbrink HJ, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. Lancet 2017; 390:2073–2082.

18. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41.

19. Acosta RK, Willkom M, Martin R, Chang S, Wei X, Garner W, et al. Resistance analysis of bictegravir-emtricitabine-tenofovir alafenamide in HIV-1 treatment-naive patients through 48 weeks. Antimicrob Agents Chemother 2019; 63:e02533–18.

20. Lagi F, Botta A, Ciccullo A, Picarelli C, Fabbiani M, di Giambenedetto S, et al. Early discontinuation of DTG/ABC/3TC and BIC/TAF/FTC single-tablet regimens: a real-life multicenter cohort study. HIV Res Clin Pract 2021; 22:96–101.

21. Sax PE, Erlandson KM, Lake JE, McComsey GA, Orkin C, Esser S, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. Clin Infect Dis 2020; 71:1379–1389.

22. Wood BR, Huhn GD. Excess weight gain with integrase inhibitors and tenofovir alafenamide: what is the mechanism and does it matter? Open Forum Infect Dis 2021; 8:ofab542.

23. Erlandson KM, Carter CC, Melbourne K, Brown TT, Cohen C, Das M, et al. Weight change following antiretroviral therapy switch in people with viral suppression: pooled data from randomized clinical trials. Clin Infect Dis 2021; 73:1440–1451.

24. Osiyemi O, De Wit S, Ajana F, Bisshop F, Portilla J, Routy JP, et al. Efficacy and safety of switching to dolutegravir/lamivudine versus continuing a tenofovir alafenamide-based 3- or 4-drug regimen for maintenance of virologic suppression in adults living with human immunodeficiency virus type 1: Results through week 144 from the phase 3, noninferiority TANGO randomized trial. Clin Infect Dis 2022; 75:975–986.

25. Overton ET, Richmond G, Rizzardini G, Thalme A, Girard PM, Wong A, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with human immunodeficiency virus 1 type 1 infection: 152-week results from ATLAS-2M, a randomized, open-label, phase 3b, noninferiority **study**. *Clin Infect Dis* 2023; **76**:1646–1654.

Figure 1. Participant disposition from baseline to Week 240 (OLE Week 96)

*Two participants randomized and not treated; †Seven participants randomized and not treated; ‡Five participants randomized and not treated.
AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; D/C, discontinuation; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG+F/TAF, dolutegravir plus emtricitabine and tenofovir alafenamide; OLE, open-label extension.

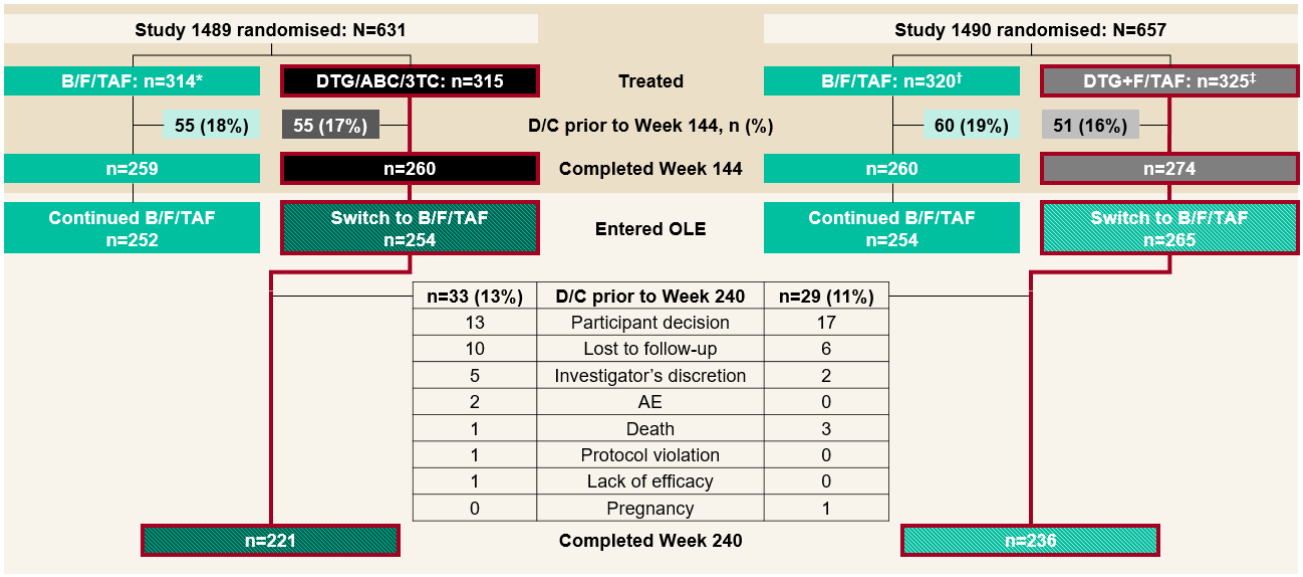


Figure 2. Proportion of participants with HIV-1 RNA <50 copies/mL to OLE Week 96. (A) M=E analysis and (B) M=F analysis

HIV-1 RNA data were missing at Week 240 (Week 96 of the OLE) for three participants who switched to B/F/TAF in Study 1489 and two participants who switched to B/F/TAF in Study 1490. Bold numbers display M=E results for participants who switched to B/F/TAF from DTG-based regimens. *For participants who switched to B/F/TAF from DTG-based regimens, 'weeks on B/F/TAF' indicates the time since the start of the OLE; for participants who remained on B/F/TAF throughout the blinded and OLE phases, 'weeks on BF/F/TAF' indicates the time since the start of the blinded phase.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG+F/TAF, dolutegravir plus emtricitabine and tenofovir alafenamide; M=E, missing = excluded; M=F, missing = failure; OLE, open-label extension.

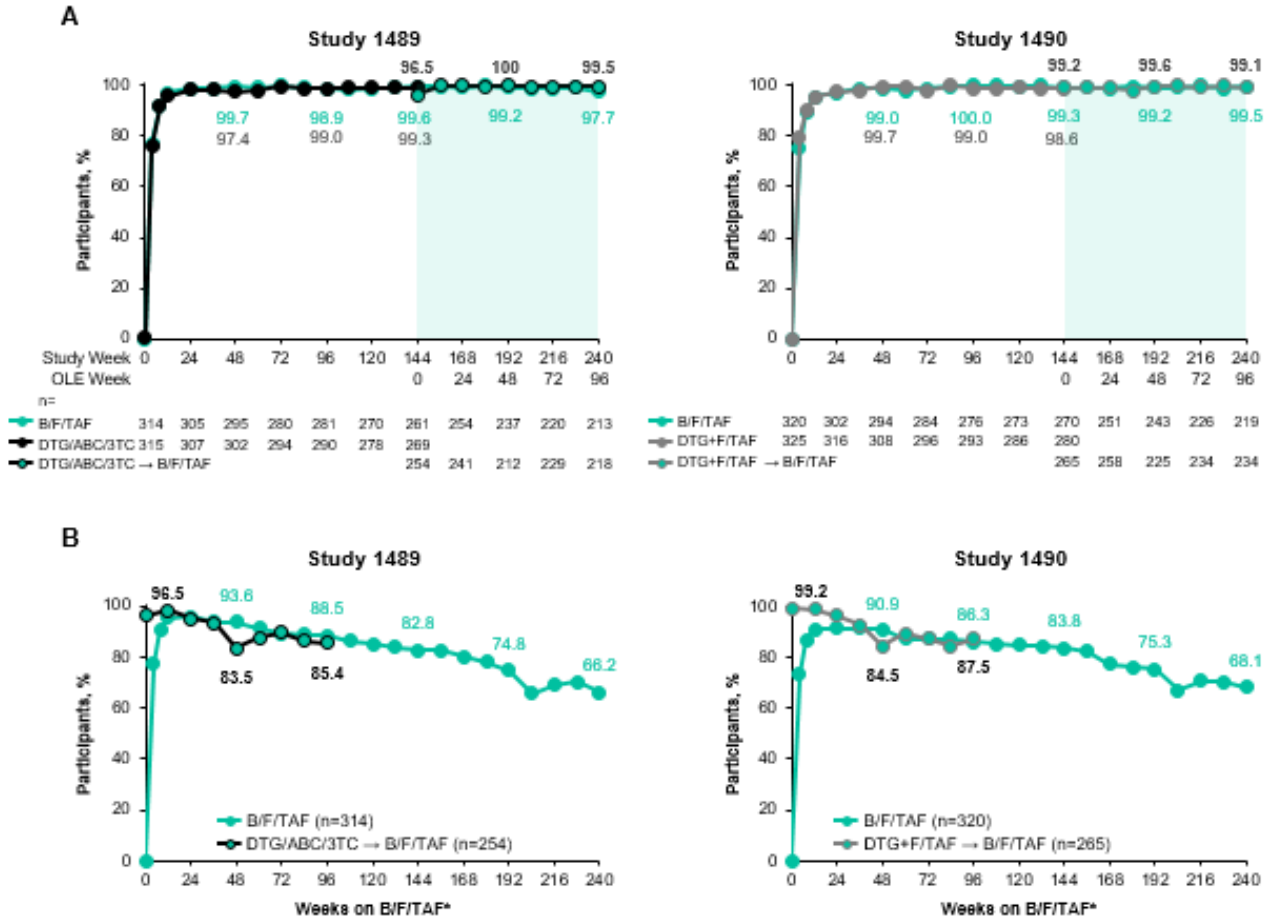
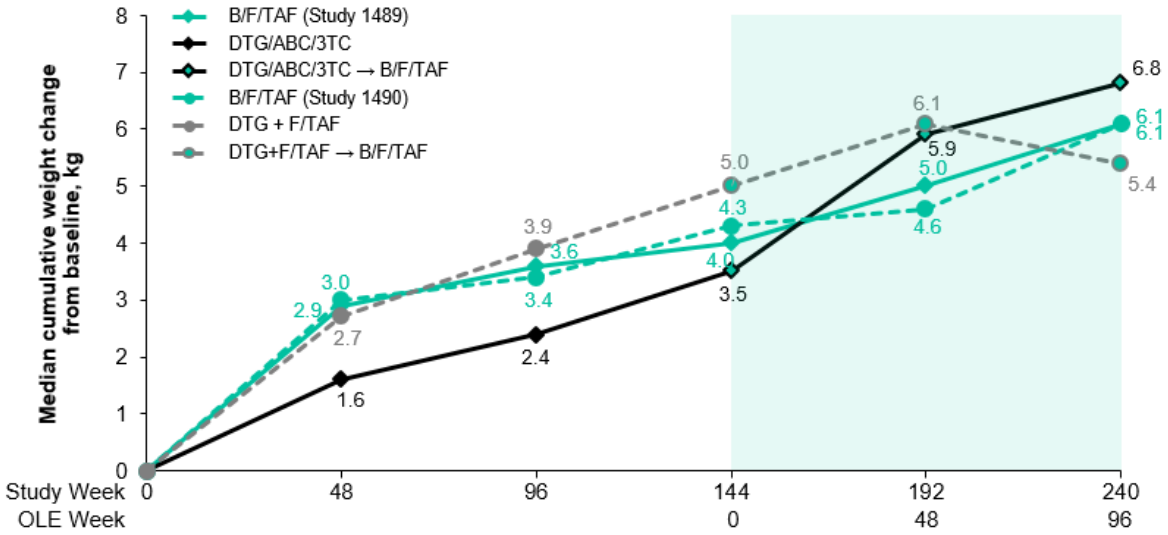


Figure 3. Weight changes from baseline through Week 240 (OLE 96).

Numbers plotted indicate median cumulative weight changes from baseline at each time point and numbers in the table show median weight changes for the time periods specified. *P value for comparison of median weight change in the DTG/ABC/3TC switch to B/FTAF group versus the DTG+F/TAF switch to B/F/TAF group.
B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG+F/TAF, dolutegravir plus emtricitabine and tenofovir alafenamide; OLE, open-label extension.



Study Week	Study 1489 B/F/TAF	Study 1489 DTG/ABC/3TC → B/F/TAF	Study 1490 B/F/TAF	Study 1490 DTG+F/TAF → B/F/TAF	P value*
0–144	4.0	3.5	4.3	5.0	0.0246
144–192	1.0	2.4	0.3	1.2	0.0262
144–240	2.1	2.4	1.8	1.3	0.0073
0–240	6.1	6.8	6.1	5.4	0.7136

Table 1. Demographics and disease characteristics at the time of B/F/TAF start*,†

	Study 1489 DTG/ABC/3TC switch to B/F/TAF (N=254)	Study 1490 DTG+F/TAF switch to B/F/TAF (N=265)
Age, median (Q1, Q3), years	36 (30, 45)	38 (30, 48)
Sex at birth, n (%)		
Male	225 (88.6)	239 (90.2)

Female	29 (11.4)	26 (9.8)
Race, n (%)		
White	144 (56.7)	160 (60.4)
Black	94 (37.0)	80 (30.2)
Asian	8 (3.1)	7 (2.6)
Other	8 (3.1)	18 (6.8)
Ethnicity, n (%)		
Hispanic/Latinx	54 (21.3)	73 (27.5)
Non-Hispanic/Latinx	199 (78.7)	192 (72.5)
Missing	1 (0.4)	0
Weight, median (Q1, Q3), kg	83.0 (72.6, 94.3)	81.7 (71.0, 96.0)
BMI, median (Q1, Q3), kg/m^2	26.3 (23.5, 30.4)	26.3 (23.5, 30.8)
HIV-1 RNA		
Median (Q1, Q3), log_{10} copies/mL	1.28 (1.28, 1.28)	1.28 (1.28, 1.28)
<50 copies/mL, n (%)	245 (96.5)	263 (99.2)
50 to <200 copies/mL, n (%)	3 (1.2)	1 (0.4)
≥200 copies/mL, n (%)	6 (2.4)	1 (0.4)
CD4 cell count		
Median (Q1, Q3), cell/μL	766 (599,1023)	730 (550, 958)
≥50 to <200 cell/μL, n (%)	0	3 (1.1)
≥200 to <500 cell/μL, n (%)	40 (15.7)	46 (17.4)
≥500 cell/μL, n (%)	214 (84.3)	216 (81.5)
$eGFR_{CG}$, median (Q1, Q3), mL/min	115.6 (98.5, 137.6)	111.0 (95.1, 134.8)

*Baseline value for switch to B/F/TAF was defined as the last non-missing value obtained during or before the first dose of open-label B/F/TAF; †Missing values were excluded from the percentage calculations.

B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BMI, body mass index; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG+F/TAF, dolutegravir plus emtricitabine and tenofovir alafenamide; $eGFR_{CG}$, estimated glomerular filtration rate by Cockcroft–Gault; Q, quartile.

Table 2. Adverse events during Weeks 144–240 (OLE)*†

	Switch from DTG/ABC/3TC to B/F/TAF (N=254)	Switch from DTG+F/TAF to B/F/TAF (N=265)
Any AE, n (%)	214 (84.3)	215 (81.1)
Drug-related AEs, n (%)	13 (5.1)	8 (3.0)
≥2 participants in either group or overall, n (%)		
Diarrhea	3 (1.2)	0
Weight increased	2 (0.8)	1 (0.4)
Headache	1 (0.4)	1 (0.4)
Grade 3 or 4 drug-related AEs, n (%)	0	1 (0.4)
Any SAE	19 (7.5)	32 (12.1)
Drug-related SAE	0	0
Discontinued B/F/TAF due to drug-related AEs‡	2 (0.8)	0
Deaths	2 (0.8)	3 (1.1)

*Severity grades were defined by Gilead Grading Scale for Severity of AEs and Laboratory Abnormalities; †Relatedness to study drug was assessed by the investigator; ‡The drug-related AEs leading to B/F/TAF discontinuation were weight gain and obesity.
AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; DTG/ABC/3TC, dolutegravir/abacavir/lamivudine; DTG+F/TAF, dolutegravir plus emtricitabine and tenofovir alafenamide; OLE, open-label extension; SAE, serious adverse event.