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Authors

Hill, Lucas
Smith, Shawn R
Karris, Maile Young

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REVIEW

Profile of bictegravir/emtricitabine/tenofovir alafenamide fixed dose combination and its potential in the treatment of HIV-1 infection: evidence to date

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Lucas Hill[1]
Shawn R Smith[1]
Maile Young Karris[2]

[1]University of California San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences, San Diego, CA, USA; [2]Department of Medicine, University of California San Diego, San Diego, CA, USA

Abstract: Modern pharmacologic management of people living with HIV involves the use of fixed dose combinations of antiretrovirals that are simple to take, well tolerated, and highly effective. Specific recent pharmacologic advancements include 1) the second-generation integrase strand transfer inhibitors (dolutegravir and bictegravir) that consistently show less side effects, high tolerability, minimal drug interactions, and rapid rates of HIV viral load decline and 2) tenofovir alafenamide, a prodrug of tenofovir that concentrates in lymphoid tissue and minimizes off target effects. Bictegravir/emtricitabine/tenofovir alafenamide or B/F/TAF is a recently approved fixed dose combination that incorporates these new advancements in the management of HIV. This review focuses on the data supporting the use of B/F/TAF, reviews clinically relevant findings, and highlights the unanswered questions that may limit its clinical utility.

Keywords: Biktarvy, HIV care, review, integrase strand transfer inhibitor

Introduction

Advancements in antiretroviral therapy (ART) broadened the treatment options for people living with HIV (PLWH) who are both naïve to therapy and treatment experienced. Newer classes of medications provide high genetic barriers to resistance, excellent tolerability, and are often co-formulated into fixed dose combinations that simplify the dosing. Recently, the US Food and Drug Administration (FDA) added to the available options for many PLWH with the approval of bictegravir (BIC).

BIC is a novel integrase strand transfer inhibitor (INSTI) approved by the FDA in February 2018 for PLWH who are treatment naïve and for PLWH virologically suppressed on current ART for at least 3 months with no history of prior treatment failure or resistance to any component of the BIC single tablet regimen (STR). BIC has been shown to potently inhibit strand transfer activity at concentrations similar to that of elvitegravir (EVG) and dolutegravir (DTG) with its unique structure minimizing drug–drug interactions, increasing protein binding, and improving solubility. BIC has a favorable pharmacokinetic (PK) profile in that it can be dosed once daily and is not impacted by renal or hepatic impairment. Although BIC is a substrate of CYP3A4 and UGTI1A1, it does not require pharmacologic boosting resulting in minimal drug interactions. In vitro, BIC demonstrates a high genetic barrier to resistance allowing it to maintain activity against variants with INSTI resistance.[1–5] Currently, BIC 50 mg daily is available only as a fixed dose combination with tenofovir alafenamide (TAF) 25 mg daily and emtricitabine (FTC) 200 mg daily (B/F/TAF).

Correspondence: Lucas Hill
University of California San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences, 200 W. Arbor Drive #8765, San Diego, CA 92103-8765, USA
Tel +1 619 543 4995
Fax +1 619 543 7841
Email luhill@ucsd.edu

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In this review, we aimed to 1) review the available literature supporting approved and potential off-label use of BIC, 2) discuss the clinical situations in which it might be used, and 3) review some of the unanswered questions about its place in therapy.

Evidence in treatment-naïve PLWH

BIC first demonstrated promise in a Phase Ib study of 20 HIV-infected ART naïve adults randomized to once daily BIC (5, 25, 50, or 100 mg) or placebo for 10 days.[6] BIC showed rapid absorption, had a half-life period supporting once daily therapy, and was well tolerated with no discontinuations due to adverse events. Most importantly, significant reductions in plasma HIV-1 RNA occurred with all BIC doses. Thus BIC proceeded to a Phase II double-blind trial that randomized 98 participants 2:1 to receive oral once daily BIC 75 mg or DTG 50 mg with matching placebo plus the fixed dose combination of 200 mg FTC and 25 mg TAF for 48 weeks.[7] Previously untreated PLWH aged ≥18 years with HIV RNA ≥1,000 copies per mL (c/mL), CD4 counts of at least 200 cells/μL, and estimated glomerular filtration (eGFR) rates of at least 70 mL/min were included. Participants were excluded if they were hepatitis B or hepatitis C co-infected, had new AIDS-defining conditions within 30 days of screening, or were pregnant. Interestingly, 97% of participants in the BIC group achieved viral suppression at 24 and 48 weeks, vs 94% at 24 weeks and 91% at 48 weeks in the DTG arm. Treatment-emergent adverse events were reported by 55 (85%) of 65 participants in the BIC group vs 22 (67%) of 33 in the DTG group. The most common adverse events were diarrhea (8 [12%] vs 4 [12%]) and nausea (5 [8%] vs 4 [12%]) in the BIC and DTG groups, respectively. These promising results then led to two Phase III trials of B/F/TAF.

Gallant et al conducted a multicenter non-inferiority study in Europe, Latin America, and North America (Trial 1489) where participants (n=629) were randomly assigned to co-formulated B/F/TAF or co-formulated DTG 50 mg, abacavir 600 mg (ABC), and lamivudine 300 mg (3TC), with matching placebo, once daily for 144 weeks.[8] Eligibility criteria included treatment-naïve HIV-1 infected adults, HIV-1 RNA ≥500 c/mL, HLA-B*5701-negative, and eGFR rate of ≥50 mL/min. Patients with hepatitis B infection were excluded. Randomization was stratified by HIV-1 RNA (≤100,000 c/mL,>100,000 to≤400,000 c/mL, or >400,000 c/mL), CD4 count (<50 cells/μL, 50–199 cells/μL, or ≥200 cells/μL), and region (USA or ex-USA). Study participants were predominantly males (90%–91%), white (57%), with median CD4 444–450 cells/μL. Both the arms demonstrated a high level of viral suppression at 48 weeks with 92% of participants in the B/F/TAF arm and 93% of participants in the DTG/ABC/3TC arm demonstrating non-inferiority (P=0.78). The DTG arm had numerically higher suppression rates in certain populations such as patients with viral loads >100,000 c/mL (86% vs 94%), CD4 counts <200 cells/μL (95% vs 100%), and those with poor adherence (84% vs 90%). However, these differences were not statistically significant. Adverse events were less common in the B/F/TAF group vs the DTG/ABC/3TC group (26% vs 40%) driven predominantly by the higher incidence of drug-related nausea in the DTG/ABC/3TC group (5% vs 17%; P<0.001).

In a second Phase III randomized controlled clinical trial (Trial 1490), Sax et al evaluated B/F/TAF for non-inferiority compared to DTG+F/TAF in 645 participants.[9] This study focused on treatment naïve HIV-infected adults with HIV-1 RNA ≥500 c/mL and eGFR ≥30 mL/min, but also allowed chronic hepatitis B virus and hepatitis C co-infection. Similar to Trial 1489, the study population was predominantly male (88%–89%), white (57%–60%), and had a median CD4 440–441 cells/μL. At week 48, 89% of participants in the BIC group and 93% in the DTG group achieved viral suppression showing non-inferiority of BIC regimen to the DTG regimen (P=0.12). Again, study drug–related adverse events were less common in the BIC group (18%) than in the DTG group (26%) with the most common adverse events being headache, diarrhea, and nausea.

A pooled efficacy and resistance analysis of the two Phase III trials demonstrated that treatment with B/F/TAF, DTG/ABC/3TC, or DTG+F/TAF was highly efficacious through week 48 with no development of resistance.[10] Pre-existing drug resistance did not affect the efficacy outcomes and no participants developed resistance to study drugs on B/F/TAF or in any other treatment group. Collectively, these studies (summarized in Table 1) confirm the efficacy of B/F/TAF in treatment-naïve patients and lead to the Department of Health and Human Services recommending B/F/TAF as a preferred treatment regimen in treatment-naïve PLWH.[4,5]

Evidence in treatment-experienced PLWH

BIC use in PLWH who are treatment experienced is limited to studies that evaluate switching ART in PLWH who are virologically suppressed with no known resistance to any component in B/F/TAF (summarized in Table 2). As such, the outcomes included virologic suppression, and other clinically relevant outcomes including kidney function, cholesterol, and other adverse drug effects. Trial 1844, a

Table 1 Summary of treatment-naïve studies

Trial	Study design	Population	Outcome
Antiviral Activity, Safety, and Pharmacokinetics of Bictegravir as 10-Day Monotherapy in HIV-1-Infected Adults	• Phase Ib study evaluating the antiviral activity, safety, and pharmacokinetics • Six groups treated for 10 days • BIC 5, 25, 50, 100 mg or placebo once daily	Inclusion: • Previously untreated adults aged ≥18 years with HIV-1 infections	• Significant reductions in plasma HIV-1 RNA from baseline at day 11 for all BIC doses compared with placebo and increased BIC exposures correlated with increased reduction in plasma HIV-1 RNA from baseline • Well tolerated with no discontinuations due to adverse events • Displayed rapid absorption and a half-life supporting once daily therapy

Safety and Efficacy of Bictegravir + Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1-Infected, Antiretroviral Treatment-Naïve Adults	• Phase II
	• Two groups treated for 48 weeks
	  • BIC 75 mg + FTC 200 mg/TAF 25 mg=65
	  • DTG 50 mg + FTC 200 mg/TAF 25 mg=33
	• Primary outcome
	  • Proportion of participants with HIV-1 RNA <50 copies/mL at week 24
		Inclusion:
		• Previously untreated adults aged ≥18 years with HIV-1 infection
		Exclusion:
		• Hepatitis B-co-infected
		• Hepatitis C-co-infected
		• New AIDS-defining conditions within 30 days of screening
		• Pregnant
			• At week 24, 63 (96.9%) of 65 in the BIC group had HIV-1 RNA <50 vs 31 c/mL (93.9%) of 33 in the DTG group (weighted difference 2.9%, 95% CI –8.5–14.2; *P*=0.50)
			• Adverse events
			  • 55 (85%) of 65 participants in the BIC + FTC/TAF group vs 22 (67%) of 33 in the DTG + FTC/TAF group
			  • Diarrhea was most common

Trial 1489: Safety and Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide Versus Abacavir/Dolutegravir/Lamivudine in HIV-1-Infected, Antiretroviral Treatment-Naïve Adults	• Phase III, non-inferiority
	• Two groups treated for 144 weeks
	  • BIC 50 mg, FTC 200 mg, and TAF 25 mg=314
	  • DTG 50 mg, ABC 600 mg, and 3TC 300 mg=315
	• Primary endpoint: proportion of participants with HIV-1 RNA <50 copies/mL at week 48
		Inclusion:
		• Previously untreated adults aged ≥18 with HIV-1 infection
		• HLA-B*5701-negative
		• eGFR rate of ≥50 mL/min
		• Screening genotypes showing sensitivity to FTC, TAF, 3TC, and ABC
		Exclusion:
		• Hepatitis B virus infection
			• At week 48, HIV-1 RNA <50 c/mL was achieved in 92.4% of patients (290/314) in the B/F/TAF group and 93% of patients (293/315) in the DTG/ABC/3TC group (CI –4.8–3.6; *P*=0.78), demonstrating non-inferiority of B/F/TAF to DTG/ABC/3TC
			• Less nausea in patients given B/F/FTC than in those given DTG/ABC/3TC (10% [n=32] vs 23% [n=72]; *P*<0·0001)

Trial 1490: Safety and Efficacy of Bictegravir/Emtricitabine/Tenofovir Alafenamide Versus Dolutegravir + Emtricitabine/Tenofovir Alafenamide in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults	• Phase III, non-inferiority
	• Two groups treated for 48 weeks
	  • BIC 50 mg plus FTC 200 mg, and TAF 25 mg=320
	  • DTG 50 mg plus FTC 200 mg and TAF 25 mg=325
	• Primary endpoint: proportion of participants with HIV-1 RNA <50 copies per mL at week 48
		Inclusion:
		• Previously untreated adults aged ≥18 years with HIV-1 infection
		• eGFR ≥30 mL/min
		• Chronic hepatitis B virus or hepatitis C co-infection was allowed
			• At week 48, HIV-1 RNA <50 c/mL was achieved in 286 (89%) of 320 participants in the BIC group and 302 (93%) of 325 in the DTG group (CI –7.9–1.0, *P*=0.12)
			• Demonstrated non-inferiority of the BIC regimen to the DTG regimen
			• Adverse events:
			• Incidence and severity of adverse events were similar between groups
			• Study drug-related adverse events were less common in the BIC group than in the DTG group (57 [18%] of 320 vs 83 [26%] of 325, *P*=0.022)

Pooled Week 48 Efficacy and Baseline Resistance: B/F/TAF in Treatment-Naïve Patients (Abstract)	• HIV-1 genotypic data at screening were obtained for all participants and consisted of population genotype of RT and PR • Resistance analysis population included confirmed virologic failure or HIV viral load >200 c/mL at week 48	Study 1489 and 1490 participants	• Treatment with B/F/TAF, DTG/ABC/3TC, or DTG+F/TAF was highly efficacious through week 48 with no subject developing resistance to the study drug • Rapid viral load suppression approached 80% of patients at week 4 • HIV-1 subtype did not affect efficacy outcome • Pre-existing drug resistance did not affect efficacy outcome • These results provide support for future studies of BIC and B/F/TAF in INSTI- and NRTI- resistant populations

Abbreviations: 3TC, lamivudine; ABC, abacavir; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide single tablet; BIC, bictegravir; DTG, dolutegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PR, protease; RT, reverse transcriptase; TAF, tenofovir alafenamide.

Table 2 Summary of treatment-experienced switch studies

Trial	Study design	Population	Outcome

Trial 1844: Safety and Efficacy of Switching From Dolutegravir and ABC/3TC or DTG/ABC/3TC to B/F/TAF in HIV-1 Infected Adults Who Are Virologically Suppressed	• Phase III, non-inferiority
	• Two groups treated
	  • B/F/TAF 50/200/25 mg daily =282
	  • DTG/ABC/3TC 50/600/300 mg daily =281
	  • Primary endpoint: proportion of participants with HIV-1 RNA ≥50 c/mL at week 48
		Inclusion:
		• HIV-1-infected adults
		• Virologically suppressed (HIV-1 RNA <50 c/mL for ≥3 months) on regimen containing DTG, ABC, and 3TC
		• eGFR ≥50 mL/min
		Exclusion:
		• Active HBV infection
		• Resistance to study drugs
			• At week 48, HIV-1 RNA ≥50 c/mL occurred in 3 (1.1%) of 282 participants in the BIC group and 1 (0.4%) of 281 participants in the DTG/ABC/3TC group (*P*=0.62)
			• Switching to B/F/TAF was non-inferior to remaining on DTG/ABC/3TC
			• No participant developed treatment emergent resistance
			• B/F/TAF was well tolerated with adverse events comparable between arms at week 48

Trial 1878: Safety and Efficacy of Switching from Regimens Consisting of Boosted Atazanavir or Darunavir Plus Either Emtricitabine/Tenofovir or Abacavir/Lamivudine to Bictegravir/Emtricitabine/Tenofovir Alafenamide in Virologically Suppressed HIV-1-Infected Adults	• Phase III, non-inferiority
	• Two groups
	  • B/F/TAF once daily =290
	  • Continue on baseline regimen of either boosted DRV or ATV + 2 NRTIs=287
	• Primary endpoint: Proportion of participants with plasma HIV-1 RNA ≥50 c/mL at week 48
		Inclusion:
		• HIV-1-infected adults
		• Virologically suppressed receiving DRV or ATV + 2 NRTIs (ABC/3TC or FTC/TDF)
		• HIV-1 RNA <50 c/mL for 6 months
		• eGFR ≥50 mL/min
			• At week 48, HIV-1 RNA ≥50 c/mL occurred in 5 (1.7%) of 290 participants in the BIC group and 5 (1.7%) of the 287 in the protease inhibitor group (CI –2.5–2.5, *P*=1.00)
			• Switching to B/F/TAF was non inferior to remaining on DRV or ATV + 2 NRTIs
			• No treatment-emergent resistance was found in B/F/TAF group
			• No difference in grade 3 or 4 laboratory abnormalities was observed between the arms except for bilirubin abnormalities due to ATV use

Resistance Analysis of the B/F/TAF Switch Studies	• Plasma viral RNA genotyping and phenotyping of PR, RT, and IN were attempted for all participants in the RAP
	• Baseline proviral DNA genotyping was conducted retrospectively on select participants:
	  • Participants included in the RAP
	  • Participants who switched to B/F/TAF with ≥10 years prior ARV treatment or unknown ARV initiation date
		Participants from studies 1844 and 1878	• No participants in the B/F/TAF or ABC/DTG/3TC groups developed resistance
			• One participant in the PI + 2 NRTI group on boosted DRV + ABC/3TC had virologic failure with treatment-emergent L74V in RT
			• High rates of virologic suppression were maintained among participants who switched to B/F/TAF (93% overall), regardless of preexisting resistance substitutions

Safety and Efficacy of Switching to a fixed dose combination of B/F/TAF from E/C/F/TAF, E/C/F/TDF, or ATV + RTV + FTC/TDF in Virologically Suppressed HIV-1-Infected Women	• Phase III, non-inferiority
	• Two groups:
	  • B/F/TAF once daily =234
	  • Remain on baseline regimen =236
	• Primary endpoint: proportion of participants with HIV-1 RNA ≥50 c/mL at week 48
	• Secondary endpoint: proportion of participants with HIV-1 RNA <50 c/mL at week 48
		Inclusion:
		• HIV-1-infected adults
		• Virologically suppressed women (HIV-1 RNA <50 c/mL for ≥6 months) on E/C/F/TAF or E/C/F/TDF or ATV + RTV + F/TDF
		• Baseline CrCl ≥50 mL/min
			• At week 48, HIV-1 RNA ≥50 c/mL occurred in 4 (2%) of 234 participants in the B/F/TAF and 4 (2%) of 236 in the same baseline regimen group
			• Switching to B/F/TAF was non-inferior to continuing standard of care PI and INSTI-based regimens at week 48
			• No treatment-emergent resistance was observed in women receiving B/F/TAF
			• B/F/TAF was well tolerated with no adverse events leading to discontinuation

(*Continued*)

Table 2 (*Continued*)

Trial	Study design	Population	Outcome
Bictegravir/FTC/TAF Single-Tablet Regimen in Adolescents: Week-24 Results	• Phase II/III, open-label, multicenter, multicohort, single-arm treated for 48 weeks • B/F/TAF group =24 • Primary endpoint: to determine the plasma PK of BIC and evaluate the safety and tolerability of B/F/TAF through 24 weeks of treatment in HIV-1-infected adolescents • Secondary endpoint: to evaluate the safety and tolerability of B/F/TAF through 48 weeks, and its antiviral activity at 24 and 48 weeks	Inclusion: • HIV-1-infected • Virologically suppressed adolescents • Aged 12 to <18 years • Weight ≥35 kg • HIV-1 RNA <50 c/mL for ≥6 months • CD4 count ≥200 cells/μL • eGFR ≥90 mL/min	• Exposures of FTC and TAF were within the safe and efficacious range with similar BIC exposures observed in adolescents and adults • Maintenance of virologic suppression at week 24: HIV-1 RNA <50 c/mL in all 24 participants (100%) • Data support further pediatric studies of B/F/TAF, which may be an important unboosted INSTI option for HIV-infected adolescents and children

Abbreviations: 3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; ATV, atazanavir; BIC, bictegravir; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide single tablet; CrCl, creatinine clearance; DRV, darunavir; DTG, dolutegravir; E/C/F/TAF, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; E/C/F/TDF, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; FTC, emtricitabine; IN, integrase; INSTI, integrase strand transfer inhibitor; PK, pharmacokinetic; PR, protease; RAP, resistance analysis population; RT, reverse transcriptase; RTV, ritonavir; TAF, bictegravir; TAF, tenofovir alafenamide; PI, protease inhibitor.

Phase III, randomized, double-blind, multicenter study evaluated 282 participants who switched from DTG + ABC/3TC or DTG/ABC/3TC to B/F/TAF and 281 who continued DTG + ABC/3TC or DTG/ABC/3TC.[11] Patients with active hepatitis B co-infection or eGFR <50 mL/min were excluded from participation. As in previous studies, the participants were predominantly male (88%–90%), white (73%), with median CD4 661–732 cells/μL. In the FDA snapshot analysis at 48 weeks, 1.1% in the BIC arm and 0.4% in the DTG arm had HIV-1 RNA ≥50 c/mL for a difference of 0.7% meeting non-inferiority end-point. Fewer participants in the BIC arm reported drug-related adverse events (8%) as compared to the DTG arm (16%) (P=0.01). The most common adverse events were headache, abnormal dreams, diarrhea, fatigue, flatulence, nausea, and insomnia. A statistically significant difference in the change in eGFR at week 48 was observed, with a 1 mL/min increase in the BIC arm and a 1.8 mL/min decrease in the DTG arm (P=0.001); however, no significant differences in markers of tubular damage were observed (ie, urine albumin:creatinine ratio, retinol binding protein:creatinine ratio, or β-2-microglobulin:creatinine ratio). In addition, there were no significant differences in spine and hip bone mineral density, total cholesterol, LDL, or HDL. The BIC group did have a slight reduction in triglyceride levels of 5 mg/dL compared to a 3 mg/dL increase in the DTG group (P=0.028). Overall, the clinical relevance of these differences remains unknown.

The efficacy of switching from boosted protease inhibitors to B/F/TAF has also been evaluated (Trial 1878) in a Phase III multicenter, randomized, open-label trial.[12] Participants on either ritonavir-boosted darunavir (DRV) or atazanavir (ATV) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) were randomized to stay on their current regimen (n=287) or switch to B/F/TAF (n=290). Again, the study included primarily white males with well controlled HIV. A slightly higher proportion of participants were on a DRV-based regimen (54%–57%) than on an ATV-based regimen (43%–46%) but most were combined with a NRTI backbone of tenofovir disoproxil fumarate (TDF)/FTC. The primary outcome was the proportion of patients with HIV-1 RNA ≥50 c/mL at week 48 using the FDA snapshot analysis with a non-inferiority margin of 4%. At week 48, 1.7% in both the arms had HIV-1 RNA ≥50 c/mL demonstrating non-inferiority. In the BIC arm, 92.1% were virologically suppressed at week 48 compared to 88.9% in the boosted protease inhibitor (PI) arm demonstrating a non-statistically significant difference. Again, no treatment-emergent resistance occurred in the participants switched to B/F/TAF. In terms of safety, 12% in the BIC arm and 4% in the boosted PI arm reported an adverse event, with the difference driven primarily by headache (12% vs 4%); however, the majority were mild in severity. Overall, discontinuations due to adverse events were similar between the two arms. The median change in eGFR in the BIC arm was –4.3 mL/min vs 0.2 mL/min in the boosted PI arm (P<0.001). This observation was not anticipated given the demonstrated improvement in urine albumin to creatinine ratio when switching from TDF to a TAF-based regimen in this study (10% vs –2% respectively). Thus, the authors hypothesized that eGFR differences were likely due to the inhibition of creatinine secretion by BIC.

No differences in change from baseline in total cholesterol, LDL, or HDL cholesterol were observed between the two arms; however, switching to the BIC regimen resulted in a median change of –6 mg/dL vs 4 mg/dL in triglycerides (P=0.002) and a median change of –0.2 verses 0 in the total cholesterol: HDL ratio (P=0.033).

In these two studies, participants with known resistance to the components of B/F/TAF were excluded; however, no genotype testing was done at screening and historical genotypes were only collected if available. To better evaluate if pre-existing HIV resistance to any components in B/F/TAF impacted study outcome, a pooled HIV resistance analysis of participants in these studies was conducted.[13] The resistance analysis population included confirmed virologic failures (defined as two consecutive visits with HIV-1 RNA ≥50 c/mL and ≥200 c/mL at the confirmation visit or having a HIV-1 RNA ≥200 c/mL at week 48), that also had a phenotype, genotype, or proviral DNA genotype (archived genotype) and all participants who switched to B/F/TAF with ≥10 years of ARV experience or unknown ARV start date who had a proviral DNA genotype. This resulted in 405 participants in the B/F/TAF arm, 125 patients in the PI + 2 NRTI arm, and 138 in the ABC/3TC/DTG arm. In the total resistance cohort of 405 patients, 13% had NRTI resistance, 18% had non nucleoside reverse transcriptase inhibitor (NNRTI) resistance, and 6% had PI resistance at baseline. Only one participant in the B/F/TAF arm demonstrated primary (may have impact on INSTI susceptibility) INSTI resistance at baseline (T97A) but 51% out of 170 evaluated had secondary (unlikely to impact INSTI susceptibility) INSTI resistance. The important take away from the analysis is that no participants in the B/F/TAF arm developed resistance, and 35/36 (97%) of patients with archived FTC or TAF resistance (5/5 with K65R, 18/18 with M184V/I/T, 12/13 with M184V + other NRTI resistance, and 4/4 with ≥2 TAMs) maintained viral suppression through week 48.

Two other treatment-experienced studies involving B/F/TAF have been conducted. The first (study 1961) included virologically suppressed women on elvitegravir/cobicistat/FTC/TAF (E/C/F/TAF), elvitegravir/cobicistat/FTC/TDF (E/C/F/TDF), or TDF/FTC + ATV/ritonavir (ATV/r) and randomized them to stay on their current regimen (n=236) or switch to B/F/TAF (n=234).[14] The primary endpoint was HIV-1 RNA ≥50 c/mL at week 48 using the FDA snapshot algorithm with a 4% non-inferiority margin. The median age of the female participants was 39–40 years, 37% were black or African descent, 16% Hispanic/Latino with median CD4 T-cell counts of 667–704 cells/μL. In terms of ARV regimen at randomization, 53% were on E/C/F/TAF, 42% were on E/C/F/TDF, and 5% were on TDF/FTC + ATV/r. For the primary outcome, 1.7% in each arm had HIV-1 RNA ≥50 at week 48 demonstrating non-inferiority of B/F/TAF. Again, no treatment-emergent resistance was observed in patients receiving B/F/TAF. Similar rates of drug-related adverse events, 9% vs 6%, and serious adverse events, 5% vs 6%, were seen in the B/F/TAF and continuation of baseline regimen arms, respectively. Switching from a TDF- to a TAF-based regimen resulted in significant improvement in retinol binding protein:creatinine ratio and beta-2-microglobulin:creatinine ratio which are tubular biomarkers suggesting improved kidney function. In addition, there was no difference in median change in eGFR between BIC arm compared to continuation of baseline arm (−1.8% vs –2.7%). The only significant difference in lipid parameters was a 10 mg/dL decrease in triglycerides in the BIC arm vs a 4 mg/dL increase in the continuation arm (P<0.001).

The final switch study was conducted in children (age 6–11 years) and adolescents (age 12–17 years) who were suppressed on a regimen of two NRTIs plus a third agent.[15] The primary endpoint was steady-state PK parameters at week 2 or 4, but also included safety through week 24, and the secondary endpoint was viral suppression at week 24 and 48. In the interim analysis in 24 adolescents, 100% maintained virologic suppression at week 24. There was only one adverse event (grade 1 vomiting) attributed to B/F/TAF suggesting good tolerability in this small population of adolescents.

Other ongoing studies in treatment-experienced PLWH include a Phase III, randomized, double-blind, multicenter study in HIV-suppressed adults on DTG plus F/TDF or F/TAF randomized to stay on their current regimen or switch to B/F/TAF. In this study, participants with any NRTI, NNRTI, or PI resistance will be included; however, they must have no documented INSTI resistance or confirmed virologic failure while on an INSTI regimen. In addition, there is a Phase III, multicenter, open-label, single-arm study in HIV-suppressed adults aged ≥65 years who will be switched to B/F/TAF. Results for these studies are not yet available but will further inform the utility of B/F/TAF in treatment-experienced PLWH.

PKs and drug interactions

The PK of BIC and the other components of the single-tablet regimen allow for use in a broad population of patients. BIC has a plasma half-life period of 17.3 hours allowing for once daily dosing in combination with FTC and TAF which have intracellular half-lives of 39 and 150 hours, respectively.[4] BIC is not renally eliminated and therefore does not have

meaningful changes in plasma concentrations in patients with severe renal impairment. The PKs of TAF are also not significantly changed in patients with a creatinine clearance (CrCl) down to 15 mL/min; however, due to the renal elimination of FTC, B/F/TAF is not recommended in patients with a CrCl <30 mL/min.[1,4,16] BIC and TAF have been studied in patients with moderate hepatic impairment (Child-Pugh B), but not in patients with severe hepatic impairment, and due to lack of data, they are not recommended in this population. FTC is not hepatically metabolized and is expected to be safe to use in patients with hepatic impairment.[1,4,16]

BIC is metabolized by UGT1A1 and CYP3A4 and may be susceptible to drug interactions with strong inducers or inhibitors of these enzymes. One important drug interaction is with rifampin, a strong CYP3A4 inducer. Studies suggest that when rifampin is provided concurrently with B/F/TAF, BIC exposure is 60% lower with twice daily dosing and 80% lower when dosed once daily.[17] Therefore, the use of B/F/TAF in combination with rifampin, rifabutin, or rifapentin as well as other potent inducers such as the anticonvulsants carbamazepine, oxcarbazepine, and phenytoin is not recommended. Of note, the use of TAF with rifampin is still being evaluated as TAF is a p-glycoprotein (P-gp) substrate and rifampin is a P-gp inducer. A recent study suggested that although plasma concentrations of tenofovir are lowered (47% reduction) when TAF is given with rifampin, the intracellular concentrations of tenofovir diphosphate were still 82% higher as compared to the intracellular concentrations achieved with TDF without the use of rifampin.[18]

Another important interaction to consider is the impact of polyvalent cations on the absorption of BIC. When BIC was given with antacids containing aluminum, magnesium, or calcium simultaneously in a fasted state, BIC exposure decreased almost 80%, and when given 2 hours after the antacid, it decreased to 52%. However, if BIC was given 2 hours before the antacid, the area under the curve (AUC) of BIC was decreased by only 13%. When given with calcium or iron, BIC concentrations are not significantly altered even when given simultaneously as long as it is in a fed state. Therefore, BIC should be given 2 hours prior to aluminum, magnesium, or calcium containing antacids or simultaneously with calcium or iron as long as taken with food.[4]

Finally, BIC is an inhibitor of the drug transporters OCT2 and MATE1 that may impact other medications that are substrates for these transporters. In previous PK studies with DTG, also an OCT2 and MATE1 inhibitor, the combination of DTG and metformin resulted in an increase of about 80% in metformin exposure which is clinically significant.[19] As compared to placebo, co-administration with BIC increased metformin AUC by 39% when studied in 32 healthy subjects. Metformin-induced increases in lactate were similar between placebo and BIC group, suggesting this interaction may not be clinically significant.[20]

Comparison of available integrase inhibitors

The introduction of the integrase inhibitor class in 2007 was a significant advancement in the treatment of HIV as it provided a new class of medications with a novel mechanism of action, and treatment options for PLWH with acquired drug resistance to multiple classes of ARVs.[21] Literature extensively documents that INSTIs are very well tolerated and, with the exception of EVG which requires boosting by cobicistat or ritonavir, carry the advantage of limited drug interactions.[22–27] The first-generation INSTIs include raltegravir (RAL) and EVG. In addition to limitations that require twice daily dosing of RAL and issues with drug interactions with boosted EVG, the first-generation INSTIs have a low genetic barrier to resistance.[28] DTG, a second-generation INSTI has significant advantages over the first-generation INSTIs in that it can be dosed once daily in patients without documented or inferred INSTI resistance, has a high genetic barrier to resistance, limited drug interactions, and can be used in PLWH with INSTI resistance at doses of 50 mg twice daily.[29] BIC carries similar advantages to DTG in that it is dosed once daily and has limited drug interactions. In vitro data evaluating BIC against 47 clinical isolates with INSTI resistance mutations suggests a high genetic barrier to resistance which is discussed below in more detail.[30] BIC is also the only unboosted integrase inhibitor that is available co-formulated with TAF/FTC and is the smallest tablet size among the INSTI-based single-tablet regimens available. The primary limitation with BIC as compared to the other INSTI is that studies with BIC have been limited to either the treatment-naïve population or PLWH who are already suppressed on their current ARV regimen and switching to BIC. Unlike the other INSTIs, BIC has not been studied in treatment-experienced populations (Table 3). In addition, although BIC shows in vitro activity against INSTI-resistant strains, clinical trial data are absent to guide use in PLWH with documented or suspected INSTI resistance, as compared to DTG which carries an indication for PLWH with INSTI resistance.[31]

Unanswered questions

Despite significant clinical trial data in both treatment-naïve and virologically suppressed treatment-experienced

Table 3 Comparison of available integrase inhibitors

Integrase inhibitor	FDA-approved indications	Dosing	Adverse effects	Metabolism/drug interactions	Key clinical trials	Advantages	Disadvantages
Raltegravir (Isentress, Isentress HD)	• In combination with other antiretrovirals for the treatment of HIV-1 infection	• 400 mg twice daily or 1,200 mg (two 600 mg tablets) once daily	• Potentially life-threatening and fatal skin reactions • Insomnia, headache, dizziness, nausea, fatigue	• Metabolism via UGT1A1-mediated glucoronidation • Not a CYP substrate • Decreased absorption with cations	• STARTMRK: treatment naïve • BENCHMRK 1 and 2: treatment experienced • IMPAACT P1066: pediatric	• Studied in both treatment-naïve and treatment-experienced patients • Long-term clinical experience • Well tolerated • Few drug interactions, can be used with rifampin • Pediatric indication	• Limited experience with once daily dosing • Low genetic barrier to resistance • Not available as a fixed dose combination, single-`t regimen
Elvitegravir (Vitekta, Genvoya, Stribild)	• Genvoya and Stribild for treatment-naïve or as an alternative regimen in patients with a suppressed viral load for at least 6 months • Vitekta in combination with an HIV protease inhibitor in treatment-experienced patients	• 150 mg daily when used in single-tablet regimens • 150 mg daily in combination with darunavir/r, fosamprenavir/r, tipranavir/r • 85 mg daily in combination with atazanavir/ritonavir or lopinavir/ritonavir	• Nausea, diarrhea	• CYP3A4 substrate • CYP inducers may lower concentrations • CYP inhibitors will increase the concentrations • Requires boosting with CYP3A4 inhibitor • Decreased absorption with cations	• Studies 104 and 111: treatment naïve • Study 109: virologically suppressed switch • Study 112: suppressed with renal impairment • Study 106: pediatric • Study 145: treatment-experienced	• Available as a fixed dose combination single tablet regimen • Once daily dosing • Studied in treatment experienced and treatment naïve • Well tolerated	• Requires boosting resulting in drug interactions • CYP substrate affected by CYP inducers • Low genetic barrier to resistance
Dolutegravir (Tivicay, Triumeq)	• Treatment naïve or treatment experienced including INSTI experienced with documented INSTI resistance	• 50 mg once daily in treatment naïve or treatment experienced INSTI naïve • 50 mg twice daily in INSTI experienced with certain INSTI associated resistance or suspected INSTI resistance	• Hypersenstivity reactions have been reported • Insomnia, headache	• Metabolism via UGT1A1-mediated glucoronidation with some contribution from CYP3A4. • Inhibits renal organic cation transporter OCT2 and multidrug and toxin extrusion transporter 1 (MATE1) • Decreased absorption with cations	• SPRING-2 and SINGLE: treatment naïve • SAILING: treatment experienced, INSTI naïve • VIKING-3: INSTI experienced	• Once daily dosing for most patients • Available as fixed dose combination single-tablet regimen • Ability to increase to twice daily in INSTI-experienced or due to drug interactions • Limited drug interactions, can be used with rifampin • Well tolerated • High barrier to resistance • Extensive clinical experience	• Not available as single-tablet regimen with TAF/FTC • Recent reports of possible cause of neural tube defects • Potential weight gain

Bictegravir (Biktarvy)	• Treatment naïve or to replace current regimen in those suppressed on a stable regimen for at least 3 months with no history of failure and no known substitutions associated with resistance to the individual components of BIC	• 50 mg once daily	• Diarrhea, nausea, headache	• Substrate of both UGT1A1 and CYP3A4 • Inhibits OCT2 and MATE1 • Decreased absorption with cations	• Trial 1489 and 1490: treatment naïve • Trials 1844 and 1878: virologically suppressed switch	• Only INSTI co-formulated in single-tablet regimen with TAF/FTC • Once daily dosing • Well tolerated • Likely high barrier to resistance	• Not available as a single agent • Not studied in patients with a history of resistance • Susceptible to some drug interactions, particularly CYP3A4 inducers

Abbreviations: FDA, The Food and Drug Administration; INSTI, integrase strand transfer inhibitor; *r*, ritonavir.

populations, unanswered questions about the use of B/F/TAF in certain clinical situations still remain. The first being in PLWH with documented integrase resistance, or suspected integrase resistance based on virologic failure while on an integrase-based regimen. To date, this represents a relatively small population of patients; however, the use of integrase inhibitors is growing at a rapid pace and the potential for increasing class resistance (including transmitted resistance) is a real possibility. When tested against 47 patient-derived isolates with INSTI resistance mutations, BIC showed a reduced fold change as compared to wild type when compared to DTG, EVG, and RAL. Specifically BIC demonstrated <2.5-fold change in half maximal effective concentration in 70% of the clinical isolates vs 49% for DTG.[30] However, the only clinical data that exist is the observation that one participant in a treatment-naïve study with transmitted INSTI (G140S and Q148H) and reverse transcriptase (RT) mutations (K70R and K103N) achieved viral suppression by week 4 with B/F/TAF that was maintained through week 72.[10] Significantly more clinical trial data exist for the use of DTG in PLWH with documented or suspected integrase resistance. For example, in the VIKING-3 study, DTG at 50 mg twice daily was studied in 183 subjects who failed an RAL- or EVG-containing regimen with documented INSTI resistance. Using DTG with an optimized background, regimen resulted in 69% of subjects achieving a HIV viral load of <50 c/mL at week 24.[29]

It also remains unknown if B/F/TAF can attain and maintain viral suppression in PLWH with NRTI resistance, particularly in PLWH starting B/F/TAF with a M184V mutation that confers resistance to 3TC or FTC. In switch studies, B/F/TAF did maintain viral suppression in participants with an isolated M184V; however, these numbers were relatively small and participants were virologically suppressed at the time of exposure to B/F/TAF.[13] Related to this is the question of the impact of drug interactions on the role of B/F/TAF in salvage regimens. As stated previously, BIC is a substrate of UGT1A1 but also CYP3A4. The impact of CYP3A4 inducers such as rifampin has been studied with BIC, with a significant decrease in BIC concentrations; however, BIC has not been studied with most other antiretrovirals.[4] Specifically, the clinical impact of drug interactions with other antiretrovirals such as DRV in combination with ritonavir or cobicistat (which would be expected to increase BIC concentrations) or etravirine (which would be expected to decrease in BIC concentrations) remains unanswered. In addition, there are ongoing efforts to identify strategies to reduce medication exposure while maintaining viral suppression, and it is

unclear how BIC may fit into this strategy, particularly since it is only available as a three-drug fixed dose combination.

A final unanswered question centers around the recent warning issued for DTG in which a higher prevalence of neural tube defects (0.9%, 4/426 patients) was observed as compared to the background prevalence (0.1%) in women in Botswana receiving DTG either during contraception or in the first trimester of pregnancy.[32] This information is relatively new and still being investigated to determine if this is a true effect of the medication. DTG and BIC are similar molecules, and until more information is available, a similar concern for increased risk of neural tube defects should be considered for BIC.

Conclusion

The approval of BIC introduces the first unboosted integrase inhibitor in a fixed dose combination with TAF/FTC. The evidence for use of B/F/TAF in treatment-naïve and virologically suppressed treatment-experienced patients without resistance is strong, with the clinical trials demonstrating an equivalent rate of virologic suppression as compared to the most frequently used modern ART regimens. In addition, there was no documented resistance to BIC or any component of the STR that occurred in the clinical trials, suggesting a high barrier to resistance. Confidence in the use of BIC in treatment-experienced patients with documented or presumed resistance is yet to be established; however, it is expected that more data will accumulate over time for this specific population of PLWH.

Disclosure

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