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ORIGINAL ARTICLE

Efficacy, durability, and tolerability of bictegravir/emtricitabine/tenofovir alafenamide for the treatment of HIV in a real-world setting in Belgium

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Abstract

Objectives: Our objective was to evaluate the efficacy, durability, and tolerability of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) in a real-world setting in Belgium.

Methods: This was a retrospective, multicentre cohort study involving adult treatment-naïve (TN) and treatment-experienced (TE) people living with HIV receiving BIC/FTC/TAF between 1 January 2019 and 30 September 2020. The primary outcome was rate of virological suppression (plasma HIV-1 viral load <50 copies/mL; on-treatment analysis) at weeks 24 and 48. The main secondary outcomes included loss of virological suppression (LVS; two consecutive viral loads of >200 copies/mL after being virologically suppressed) by week 48 and analysis of resistance-associated mutations at time of LVS; tolerability of BIC/FTC/TAF over the 48-week study period; and change in weight and proportion of participants reporting a >10% weight gain at week 48.

Results: Overall, 2001 participants were included. Through 48 weeks, overall rate of virological suppression was 93.5%, with similar results observed in the following subgroups: age ≥50 years (92.7%), women (92.8%), Black sub-Saharan African (91%), TN (94%), TE (93.2%), and non-suppressed at baseline (86.6%). LVS was observed in 0.7% ($n = 14$) of participants, with one participant developing resistance-associated mutations to nucleoside reverse transcriptase inhibitors (184 V) and integrase strand transfer inhibitors (263KR). Of the 131 (6.5%) treatment discontinuations, the most common reason was an adverse event (2.4%), with the most frequent being central nervous system/psychiatric (0.4%) and gastrointestinal (0.4%) toxicity. Median weight gain at week 48 was 2 kg (interquartile range −1 to 5), and a >10% weight increase was observed in 11.6% of participants.

Conclusion: In this large real-world cohort, BIC/FTC/TAF showed excellent virological efficacy in a diverse population of patients with HIV. Rare

occurrence of emergent drug resistance was observed, and treatment was well tolerated.

KEYWORDS
bictegravir/emtricitabine/tenofovir alafenamide, efficacy, HIV, real-world data, tolerability

INTRODUCTION

Bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) is recommended by international guidelines as a first-line option for the treatment of most people living with HIV-1 [1–4]. Support for the use of BIC/FTC/TAF has come from several randomized clinical trials (RCTs) of treatment-naive [5–9] and treatment-experienced people living with HIV [10–12]. These trials showed that this regimen resulted in a rapid suppression of viraemia, was effective in maintaining virological suppression, was as tolerable as standard-of-care comparators, had a high genetic barrier to resistance, and had more favourable metabolic parameters. However, participants in RCTs are usually carefully selected, which can sometimes lead to certain groups being underrepresented. Furthermore, participants in the clinical trial setting tend to exhibit higher levels of treatment adherence than those in the real-world setting [13]. Therefore, real-world studies provide complementary information to that obtained from RCTs and ensure that those results can be generalized to broader populations seen in daily clinical practice. The aim of this study was to describe the baseline characteristics of people living with HIV in Belgium receiving BIC/FTC/TAF and to evaluate its efficacy, durability, and tolerability in a real-world setting.

METHODOLOGY

Study design and population

This was an observational, retrospective, multicentre study. Inclusion criteria were (i) treatment-naïve and treatment-experienced people living with HIV, aged ≥18 years, who received BIC/FTC/TAF between 1 January 2019 (which corresponds to the date of approval for use in Belgium) and 30 September 2020 and (ii) availability of an HIV-1 viral load (VL) within the baseline window (baseline was defined as the time at which BIC/FTC/TAF was initiated; baseline window = 12 weeks before and 1 week after baseline). If more than one VL was available during the baseline window, then the result closest to baseline was used. If a participant had received BIC/FTC/TAF on multiple or separate occasions, only data from the first occasion were included. People living with HIV receiving this regimen as part of a clinical trial or a medical need programme (defined as a programme in which a pharmaceutical company provides its medication(s) to a patient at no cost in the context of either an off-label use or as a potential life-saving measure) were excluded.

Study variables and outcomes

Data collected included (i) participant characteristics such as age, sex, ethnicity/race, weight, and co-morbidities; (ii) HIV-related characteristics such as HIV-1 acquisition, prior AIDS-defining illness, HIV treatment status at baseline, time on antiretroviral (ARV) therapy (ART) and number of ART regimens before baseline, last ART regimen prior to baseline, reasons for BIC/FTC/TAF initiation, ARV resistance profile using the Stanford HIV Drug Resistance Database, version 9.0 (resistance to an ARV was defined as substitutions conferring low-level, intermediate-level, or high-level resistance), $CD4^+$ and $CD8^+$ T-cell counts, HIV-1 VL, and discontinuation of treatment; and (iii) non-HIV-related laboratory characteristics such as current hepatitis B and C virus co-infection, lipid panel, and plasma glucose.

The primary outcome of this study was effectiveness of BIC/FTC/TAF, measured by the proportion of participants with a plasma HIV-1 VL <50 copies/mL at weeks 24 and 48 using an on-treatment analysis (on treatment, in follow-up, and with available data). Secondary outcomes included (i) proportion of participants who experienced protocol-defined loss of virological suppression by week 48 (defined as two consecutive VLs of >200 copies/mL after initially being virologically suppressed) along with an analysis of resistance-associated mutations (RAMs) at the time of loss of virological suppression; (ii) proportion of participants who experienced a viral blip at any time up to week 48 (defined as a VL between 50 and 200 copies/mL after having initially achieved virological suppression); (iii) safety and tolerability of BIC/FTC/TAF as assessed by the rate of, incidence of, reasons for, and time to discontinuation of treatment over the 48-week study period; (iv) overall change in weight, along with the proportion of participants reporting a 5%–10% and

>10% weight gain at week 48; (v) change in $CD4^+$ T-cell count and $CD4^+/CD8^+$ ratio at week 48; and (vi) change in lipid and glycaemic parameters at week 48.

Data source and ethics considerations

Data were gathered from 11 HIV reference centres (HRCs) in Belgium, which work in concert as members of the Belgium Research on AIDS and HIV Consortium. These HRCs provide HIV care services to more than 90% of people living with HIV and are distributed throughout various parts of the country, thereby allowing for an adequate sampling of the Belgian HIV population receiving BIC/FTC/TAF [14].

This study was conducted in accordance with the General Data Protection Regulation 2016/679. Study-specific informed consent was not required, as informed consent for the use of routinely obtained data from each participant had previously been obtained at each participating centre. Furthermore, the principal investigator or designee at each study site ensured that the dataset for each participant underwent de-identification prior to extraction. Ethical approval was obtained from a central ethics committee and from site-specific ethics committees before data collection.

Statistical analysis

Categorical values were reported as the number of available and missing data and as percentage. Continuous variables were conveyed as the number of available and missing data, median, and interquartile range (IQR). Comparisons were performed using Fisher's exact test and the sign test. Two-sided p-values < 0.05 were considered statistically significant. Analysis of all endpoints was performed on the overall study population and on several subgroups based on age, sex, men who have sex with men, Black sub-Saharan African (SSA; identified according to the United Nations Statistics Division classification [15]) ethnicity, HIV treatment status at baseline, time on ART and number of ART regimens prior to baseline, ART regimen immediately preceding BIC/FTC/TAF initiation, baseline ARV resistance, and baseline VL and $CD4^+$ T-cell count. All results were reported using the pairwise deletion approach for missing data. Ordinal logistic regression analysis using a stepwise variable selection algorithm was performed to examine associations between baseline variables and the following outcomes: discontinuation due to any reason, due to an adverse event (AE), and due to central nervous system (CNS)/psychiatric toxicity, and a >10% on-treatment weight gain at week 48. All statistical analyses were conducted using Statistical Analysis System (SAS) software v9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Study population

A total of 2001 participants met the criteria for inclusion in this study, with a median follow-up time of 89.3 (IQR 65.6–110.4) weeks (Table 1). Most were aged <50 years (59.2%), women represented 35.1% of the study cohort, and participants were primarily White (57.2%) and SSA (32.3%). The majority were treatment-experienced (79.6%), median $CD4^+$ T-cell count was 567 (IQR 367–793) cells/μL, and 68.1% were virologically suppressed at baseline. The median time on ART before baseline was 6 (IQR 0.9–12.3) years. The most common regimen prior to baseline was elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (19.9%). The most frequent reasons for starting BIC/FTC/TAF were treatment simplification/decrease pill burden (61.1%) and treatment initiation for a treatment-naïve person (20.4%). Less frequent causes included toxicity of previous regimen (7.3%) and drug–drug interactions (3%).

Virological suppression

At week 48, 93.5% of the overall cohort maintained virological suppression, with similar rates observed among women (92.8%), SSA participants (90.8%), and treatment-naïve (94%) and treatment-experienced participants (93.2%; Table 2). Compared with the overall study population, participants with a baseline $CD4^+$ T-cell count <350 cells/μL (86.8%) had a lower suppression rate, regardless of HIV treatment status at baseline (86.4% for treatment-naïve participants with baseline $CD4^+$ T-cell count <350 cells/μL; 87% for treatment-experienced participants with baseline $CD4^+$ T-cell count <350 cells/μL) and in those with a baseline VL ≥50 copies/mL (86.6%); however, these differences were not statistically significant. Further analyses revealed no difference in week-48 virological response based on pre-existing ARV resistance or ART regimen before switch.

Viral blips and loss of virological suppression

Over the 48-week study period, viral blips were detected in 29 (1.4%) participants overall, 17 (58.6%) of whom were treatment-experienced. Fourteen (0.7%) participants

TABLE 1 Baseline characteristics of the study population.

Characteristic	Overall ($N = 2001$)
Age (years), *n* (%)	
<50	1184 (59.2)
≥50	817 (40.8)
Sex, *n* (%)	
Male	1299 (64.9)
Female	702 (35.1)
Ethnicity, *n* (%)	
Caucasian	1145 (57.2)
Black sub-Saharan African	646 (32.3)
Other	146 (7.3)
Unknown	64 (3.2)
Weight (kg)	
Median (IQR)	76 (67–87)
Data not available, *n* (%)	283 (14.1)
Co-morbidities, *n* (%)	
Diabetes mellitus	76 (3.8)
Coronary heart disease	16 (0.8)
Non-AIDS-defining malignancy	68 (3.4)
Chronic renal disease	3 (0.1)
Data not available	470 (23.5)
Co-infections	
HBV co-infection	93 (4.7)
HCV co-infection	82 (4.1)
Data not available	617 (30.8)
HIV acquisition, *n* (%)	
MSM	884 (44.2)
Heterosexual	866 (43.3)
Other	80 (4)
Unknown	171 (8.5)
HIV treatment status, *n* (%)	
Treatment-naïve	408 (20.4)
Treatment-experienced	1593 (79.6)
INSTI-experienced	1108 (55.4)
Prior AIDS defining illness, *n* (%)	510 (25.5)
Nadir $CD4^+$ T-cell count (cells/μL)	
Median (IQR)	308 (157–492)
Data not available, *n* (%)	51 (2.5)
Total time on ART prior to baseline (years)	
Median (IQR)	6 (0.9–12.3)
Number of ART regimens prior to baseline	
Median (IQR)	2 (1–4)
ARV resistance data available, *n* (%)	387 (19.3)
EFV resistance	53 (13.7)
3TC/FTC resistance	39 (10.1)
ABC resistance	37 (9.6)
RPV resistance	34 (8.8)
DRV resistance	24 (6.2)
TDF resistance	18 (4.7)
EVG/RAL resistance	9 (2.3)
Most common ART regimen prior to baseline, *n* (%)	
EVG/c/FTC/TAF	399 (19.9)
DTG + FTC/TAF	241 (12)
EFV/FTC/TDF	92 (4.6)
DRV/c/FTC/TAF	80 (4)
DTG + FTC/TDF	59 (2.9)
HIV-1 viral load (copies/mL), *n* (%)	
<50	1363 (68.1)
≥50	638 (31.9)
$CD4^+$ T-cell count (cells/μL)	
Median (IQR)	567 (367–793)
$CD4^+$ T-cell count (cells/μL), *n* (%)	
<350	418 (21)
350–499	327 (16.3)
≥500	1063 (53.1)
Data not available	193 (9.6)
$CD4^+/CD8^+$ ratio	
Median (IQR)	0.7 (0.4–1.1)
Data not available, *n* (%)	741 (37)

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; ARV, antiretroviral; C, cobicistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; HBV, hepatitis B virus; HCV, hepatitis C virus; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; MSM, men who have sex with men; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

met the criteria for loss of virological suppression, and viral blips before loss of virological suppression were observed in 3 of 14 participants (Table S1). At the time of loss of virological suppression, one participant had RAMs to nucleoside reverse transcriptase inhibitors (NRTIs; 67 N, 70 R, and 184 V) but had no resistance data available before baseline, and one participant had RAMs to both NRTIs (184 V) and integrase strand transfer inhibitors (INSTIs; 263 KR), which were not present on resistance testing before baseline. The remaining

TABLE 2 Rates of virological suppression for the overall study population and for various subgroups at weeks 24 and 48.

	Week 24		Week 48	
Characteristics	***N***	**Rate of virological suppression (%)**	***N***	**Rate of virological suppression (%)**
All participants	1611	92	1361	93.5
Age (years)				
<50	939	91.7	785	94
≥50	672	92.6	576	92.7
Sex				
Male	1061	91.6	885	93.8
Female	550	92.9	476	92.8
MSM	725	94.3	624	94.7
Black sub-Saharan African	496	89.5	411	90.8
HIV treatment status				
Naïve	363	87.5	300	94
Experienced	1248	93.4	1061	93.2
INSTI-experienced	918	93.8	734	93.9
Total time on ART prior to baseline (years)				
≤6	1091	91.4	913	93.5
>6	520	93.5	448	93.3
Number of ART regimens prior to baseline				
≤2	693	91.6	566	93.9
>2	918	93.3	795	93.3
Baseline resistance				
EFV resistance	39	94.9	39	89.7
3TC/FTC resistance	33	84.8	30	83.3
ABC resistance	30	90	22	86.4
RPV resistance	32	87.5	26	88.5
DRV resistance	32	96.6	25	88
TDF resistance	17	94.1	14	78.6
EVG/RAL resistance	6	83.3	3	66.7
ART regimen prior to baseline				
ABC-containing	195	92.8	153	92.2
TDF-containing	249	88.8	229	91.7
TAF-containing	791	94.6	638	94.5
RPV-containing	63	93.7	60	92.8
EFV-containing	92	89.1	74	89.2
DTG-containing	431	92.6	358	93.6
Baseline HIV-1 viral load (copies/mL)				
<50	1098	97.2	921	96.7
≥50	513	81.1	440	86.6
Baseline $CD4^+$ T-cell count (cells/μL)				
<350	379	81.5	308	86.8
350–499	264	93.6	222	94.6
≥500	968	95.3	831	95.7

Abbreviations: 3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; INSTI, integrase strand transfer inhibitor; MSM, men who have sex with men; *N*, number of participants on treatment, in follow-up, and with available data; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

12 participants had either no RAMs detected or no resistance data available. Median HIV-1 VL at the time of loss of virological suppression was 1012 (IQR 418–21 000) copies/mL.

Treatment discontinuation

Overall, 131 (6.5%) participants discontinued their treatment over the 48-week study period (7.4 discontinuations per 100 patient-years). In total, 34/408 (8.3%) treatment-naïve participants and 97/1593 (6.1%) treatment-experienced participants discontinued BIC/FTC/TAF (Table S2). The most frequent reasons for discontinuation of BIC/FTC/TAF were an AE (2.4% overall, 3.7% treatment-naïve; 2.1% treatment-experienced) and switch to a two-drug ART regimen (1.3% overall, 1.2% treatment-naïve; 1.3% treatment-experienced). Among the infrequent causes of discontinuation, pregnancy – existing or intended – resulted in treatment discontinuation in 0.3% of participants overall, 0.5% of treatment-naïve participants, and 0.3% of treatment-experienced participants (Table S3). Most common AEs leading to treatment discontinuation were (i) CNS/psychiatric toxicity (0.4% overall, 0.7% treatment-naïve; 0.3% treatment-experienced) and (ii) gastrointestinal toxicity (0.4% overall, 0.7% treatment-naïve; 0.3% treatment-experienced). Multivariable logistic regression analysis showed no significant association with discontinuation of treatment due to any reason or due to an AE (data not shown). However, regression analysis did reveal that CNS/psychiatric toxicity resulting in the discontinuation of a previous ART regimen was significantly associated with discontinuation of BIC/FTC/TAF due to CNS/psychiatric toxicity (odds ratio [OR] 4.64; 95% confidence interval [CI] 1.24–17.38, $p = 0.03$). The most frequent ART regimen prescribed after treatment discontinuation was dolutegravir/lamivudine (40.5%).

Change in weight

At week 48, the median on-treatment weight gain overall was 2 kg (IQR −1 to 5), corresponding to a 2.6% change from baseline, and 11.6% of participants experienced a >10% weight gain (Table 3). Treatment-naïve participants experienced a greater median change in weight (3 kg [IQR 0–8]) than did treatment-experienced participants (1 kg; IQR −1 to 4). Logistic regression analysis did not show that age >50 years ($p = 0.16$), female gender ($p = 0.48$), or being SSA ($p = 0.78$) was associated with a >10% increase in weight. However, having been on a tenofovir disoproxil fumarate (TDF)-based regimen prior to BIC/FTC/TAF initiation (OR 2.29; 95% CI 1.31–4, $p = 0.006$) and having a baseline $CD4^+$ T-cell count <350 cells/μL (OR 6.12; 95% CI 3.48–10.77, $p < 0.001$) were associated with a >10% weight gain.

Laboratory parameters

Changes in $CD4^+$ T-cell count, $CD4^+/CD8^+$ ratio, lipid and glycaemic parameters for treatment-naïve and treatment-experienced participants are described in Table S4. At week 48, the median change from baseline in $CD4^+$ T-cell count and $CD4^+/CD8^+$ ratio for the overall study population was 50 (IQR −50 to 172) cells/μL and 0.1 (IQR 0–0.2), respectively.

DISCUSSION

This cohort of people living with HIV receiving BIC/FTC/TAF reflects the epidemiology of HIV infection in Belgium: a male-to-female ratio of approximately 2:1, with women accounting for 35% of the cohort, an ageing population (41% of the study population were aged >50 years), and SSA participants representing 32% of the cohort. Around 20% of the participants included in this cohort were treatment-naïve, which is a higher proportion than the overall treatment-naïve population in Belgium. However, as BIC/FTC/TAF is recommended as a first-line agent for the treatment of treatment-naïve people living with HIV, it is to be expected that a considerable proportion of participants receiving this regimen would be treatment-naïve.

The overall rate of virological suppression at week 48 was 93.5%, with similar rates observed among participants who were aged ≥50 years, women, SSA, and treatment-naïve and treatment-experienced people living with HIV. Despite lower rates of suppression, virological outcomes did not differ significantly among participants with baseline $CD4^+$ T-cell count <350 cells/μL, those who were non-suppressed at baseline, or by ART regimen before switch. Furthermore, there was no significant impact on virological suppression based on pre-existing resistance, including NRTI resistance, a finding that has been previously reported [16–19]. It is important to mention that a considerable portion of the study follow-up period occurred during the start of the severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019; COVID-19) pandemic, which may have affected not only the availability of data but also access to treatment and in turn, adherence. The overall virological efficacy observed in our study is consistent with week-48 results from clinical trials, which report suppression rates of

TABLE 3 Change in weight at week 48, along with the proportion of patients experiencing 5%–10% and >10% increase in weight from baseline for the study cohort and for various sub-groups.

Characteristics	*N*	Median change in weight (kg) from baseline (IQR)	5%–10% increase in weight from baseline (%)	>10% increase in weight from baseline (%)
All patients	741	2 (−1–5)	19.2	11.6
Age (years)				
<50	435	2 (0–5)	20	13.6
≥50	306	1 (−1–4)	18	8.8
Sex				
Male	487	1 (−1–3)	17.9	12.2
Female	254	2 (0–5)	21.2	10.6
MSM	334	1 (−1–5)	20.1	8.7
Black sub-Saharan African	250	2 (0–5)	19.6	12
HIV treatment status at baseline				
Naïve	160	3 (0–8)	21.3	25.6
Experienced	581	1 (−1–4)	17.8	7.6
INSTI-experienced	412	1 (−1–4)	17.4	7.2
Total time on ART prior to baseline (years)				
≤6	475	2 (0–5)	19.6	11.5
>6	266	1 (−1–4)	18.4	10.9
Number of ART regimens prior to baseline				
≤2	299	2 (1–5)	20.2	13.8
>2	442	1 (0–4)	18	9.9
ART regimen prior to baseline				
ABC-containing	90	2 (0–4)	16.7	8.9
TDF-containing	96	3 (0–7)	29.7	20.8
TAF-containing	376	1 (−1–3)	16.2	4
RPV-containing	23	1 (−2–2)	19.4	11.9
EFV-containing	36	3 (0–7)	21.9	13.6
DTG-containing	197	1 (−1–4)	16.8	9.6
Baseline HIV-1 VL (copies/mL)				
<50	511	1 (−1–4)	17.6	6.5
≥50	230	4 (1–8)	22.6	23
Baseline $CD4^+$ T-cell count (cells/μL)				
<350	215	4 (1–9)	26.1	24.8
350–499	126	2 (0–5)	24.6	7.1
≥500	400	1 (−1–3)	13.2	7.6

Abbreviations: ABC, abacavir; ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; MSM, men who have sex with men; *N*, number of participants on treatment, in follow-up, and with available data; RPV, rilpivirine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load.

89%–99% [6–8, 11, 12, 20, 21], and with real-world trials, which report suppression rates of 93%–97% [22–25]. Variations among these suppression rates can most likely be explained by two factors. First, participants in clinical trials undergo a thorough selection process in aspects such as prior adherence, history of virological failures, and presence of pre-existing or archived resistance, whereas real-world studies have less strict selection criteria and tend to include a heterogenous population. Second, the methodology used to measure

the rate of virological suppression differs: intention-to-treat versus on-treatment analysis.

Overall, 14 (0.7%) participants experienced loss of virological suppression by week 48. The majority of these were men and were treatment-experienced, with corresponding proportions to those observed in the overall study population. Interestingly, however, SSA participants represented 71.4% of those who experienced loss of virological suppression despite this subgroup representing only 32.3% of the overall cohort. Indeed, it has been reported that SSA people living with HIV were at higher risk of loss of virological suppression than non-SSA people with HIV [26]. Of the 14 participants experiencing loss of virological suppression, six did not have resistance data available at the time of loss of virological suppression. A further six had no RAMs, and since the most likely cause in these cases was suboptimal adherence, it is reassuring that those participants' future treatment options were not compromised. One participant had RAMs to NRTIs (67 N, 70 R, 184 V) but did not have resistance data available before baseline. Lastly, one participant, who was treatment-naïve with HIV subtype CRF06-cpx, who was not taking any concomitant non-ARV medications, and who had no co-morbidities, had RAMs to both NRTIs (184 V) and INSTIs (263 KR) at the time of loss of virological suppression, despite having no documented RAMs prior to baseline. Despite many clinical and real-world trials reporting no occurrence of treatment-emergent resistance [6–9, 11, 12, 20–22, 25], there have been few isolated reports of emergence of resistance while receiving BIC/FTC/TAF [27–29]. Nevertheless, the results of our study confirm that loss of virological suppression with BIC/FTC/TAF is extremely rare, in both treatment-naïve and treatment-experienced people living with HIV, and that the development of resistance to a component of the regimen is equally rare.

Of the 29 participants experiencing viral blips over the study period, only three experienced loss of virological suppression. However, it is important to note that the participant who developed treatment-emergent resistance to both NRTIs and INSTIs did experience one viral blip (182 copies/mL) before loss of virological suppression. The data concerning the clinical significance of viral blips are conflicting. Some trials have reported no association between viral blips and the occurrence of virological failure or drug resistance [30], whereas others have reported an association independent of the level of the HIV-1 VL [31] or only if the VL is above a specific threshold [32].

BIC/FTC/TAF was well tolerated, with 6.5% of participants discontinuing their treatment over the 48-week study period. The most common cause of discontinuation was an AE (2.4%). This finding is consistent with the results of clinical trials that described discontinuation rates due to an AE of 1%–2% [7, 10–12] and with those of observational studies reporting rates of 2%–6.2% [23–25]. Furthermore, the AEs leading to discontinuation described in our study were aligned with those reported in the aforementioned trials. The most frequent AEs leading to discontinuation were CNS/psychiatric (0.4%) and gastrointestinal (0.4%) toxicity. Investigational trials have reported discontinuation rates due to CNS/psychiatric toxicity of 0.3%–1.4% [7, 10–12], whereas real-world data has provided rates of 0.6%–1% [23–25]. Given that the follow-up period of our study was the same as those in the abovementioned reports and that our study population was, in many cases, larger than in those studies, the difference in discontinuation rates observed can most likely be explained by the differences in study populations. Indeed, the majority of the participants in our study were treatment-experienced (79.6%), with a considerable proportion being INSTI-experienced (55.4%). Furthermore, the median time on ART before BIC/FTC/TAF initiation was 6 years (IQR 0.9–12.3), with a median number of ART regimens of 2 (IQR 1–4). As such, our study population had been somewhat exposed to ARVs, and more specifically INSTIs, before study inclusion and would potentially be less likely to experience or more likely to tolerate AEs, thereby leading to fewer treatment discontinuations. No significant association between baseline variables and discontinuation of treatment due to any reason or due to an AE was observed. However, we did note that CNS/psychiatric toxicity resulting in the discontinuation of a previous ART regimen prior to baseline was significantly associated with discontinuation of BIC/FTC/TAF due to CNS/psychiatric toxicity (OR 4.64; 95% CI 1.24–17.38, $p = 0.03$).

The issue of weight gain and ARVs has become a major point of consideration when clinicians are contemplating which ART regimen to prescribe. BIC and TAF have been associated with increased weight gain [33–35]. In this real-world study, overall median on-treatment weight gain at week 48 was 2 kg (IQR −1 to 3), which corresponds to a 2.6% change from baseline. Data on weight gain associated with BIC/FTC/TAF are limited; however, our findings are consistent with previous reports describing week-48 median weight gains ranging between 1.05 and 2.9 kg [12, 20, 24, 25]. The varying weight gain observed in the aforementioned reports most likely reflects the heterogeneity of the populations studied, including differences in treatment status (treatment-naïve or treatment-experienced), baseline $CD4^+$ T-cell count, and the number of regimens and duration of treatment before inclusion. In total, 11.6% of participants experienced a >10% weight gain in this study. In contrast to previous studies reporting both female gender and Black race to be associated with greater weight gain while

on INSTIs [35–38], we found neither to be a significant risk factor. However, our results did show that having been on a TDF-based regimen before BIC/FTC/TAF initiation (OR 2.29; 95% CI 1.31–4, $p = 0.006$) was associated with a >10% increase in weight. This finding most likely reflects loss of the weight-suppressant effect that TDF has been reported to exert [35, 38, 39]. Additionally, we observed that having a baseline $CD4^+$ T-cell count <350 cells/μL (OR 6.12; 95% CI 3.48–10.77, $p < 0.001$) was associated with a >10% increase in weight. Indeed, weight gain after initiating ARV therapy is ubiquitous among treatment-naïve people living with HIV and those with advanced HIV-1, and a moderate weight increase among these people is usually expected as a manifestation of the return-to-health phenomenon. However, clinicians should be aware that, with an increasingly ageing HIV population, a rising prevalence of obesity and weight gain places older people living with HIV at an increased risk for comorbidities [40].

At week 48, a median increase of 50 cells/μL (IQR −50 to 172) in the overall $CD4^+$ T-cell count was observed, but this was not statistically significant. In addition, we noted no significant change in the $CD4^+$/$CD8^+$ ratio. In terms of the lipid profile, we observed a generally neutral effect on all serum lipids with no significant change from baseline. It is important to note that approximately half of the cohort were receiving an INSTI-based regimen directly before BIC/FTC/TAF initiation, and – as previously reported – no changes are typically observed in lipids when switching between INSTIs [41]. Furthermore, since 28% of the study population were on a TDF-based regimen directly before baseline, and given the fact that TDF has been previously reported to reduce lipid fractions [42], an increase in lipid parameters among people switching from TDF to TAF would have been expected but was not observed. We speculate that the most likely explanations for this result are that Belgian federal regulations require at least one dietitian be on staff at each HRC, providing regular follow-up to people living with HIV and that the environment surrounding participants in this study may be more health conscious than other settings.

This study has some limitations. A proportion of data was missing for some of the variables included, and individual chart review to evaluate for treatment adherence, when indicated, was not possible. Only AEs that led to treatment discontinuation were described, and it was not possible to report on the seriousness and severity of these AEs. Furthermore, it was not possible to account for the presence of any psychological or social factors that may have influenced certain variables such as CNS/psychiatric toxicity and weight gain. The instances of loss of virological suppression were minimal, leaving exploration for associations with potential predictors unfeasible. However, the main strength of this study is the substantial amount of data collected from a very large representative cohort of people living with HIV in Belgium and its observational nature. The lack of restrictions on the inclusion criteria allowed for an evaluation of treatment with BIC/FTC/TAF in various populations, some of whom are typically excluded from RCTs but are, in fact, representative of a real-world setting.

The data presented in this real-world study show that BIC/FTC/TAF is highly effective at achieving and maintaining virological suppression in various populations, including women, SSA people, those aged >50 years, treatment-naïve people living with HIV, and those switching from a previous regimen. In addition, BIC/FTC/TAF had a high genetic barrier to resistance with rare occurrence of emergent drug resistance. Treatment was well tolerated, with infrequent discontinuations due to AEs, the most common being CNS/psychiatric and gastrointestinal toxicity. On-treatment weight gain was minimal and was significantly associated with having been on a TDF-based regimen before baseline and having a baseline $CD4^+$ T-cell count <350 cells/μL. These data support the use of BIC/FTC/TAF in clinical practice, both as a first-line and as a switch treatment option, in a wide variety of people living with HIV.

AUTHOR CONTRIBUTIONS

Rakan Nasreddine and Stéphane De Wit conceptualized and designed the study. Eric Florence, Jean Cyr Yombi, Sophie Henrard, Gilles Darcis, Jens Van Praet, Linos Vandekerckhove, Sabine D. Allard, Rémy Demeester, Peter Messiaen, Nathalie Ausselet, Rakan Nasreddine, and Stéphane De Wit participated in data acquisition. Marc Delforge and Rakan Nasreddine performed the statistical analyses. Rakan Nasreddine drafted the first manuscript. All authors provided feedback on manuscript drafts and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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