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Switching to bictegravir/emtricitabine/tenofovir alafenamide from efavirenz/emtricitabine/tenofovir disoproxil in virologically suppressed people with HIV: findings from a non-randomized clinical trial (EBONY study)☆

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ABSTRACT

Objectives: No previous studies specifically explored the switch from efavirenz to bictegravir (BIC)-containing three-drug antiretroviral regimens. This study aimed to evaluate the efficacy and safety outcomes of a treatment switch from efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) given once daily (OD) or on alternate days (ATAD) to BIC/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) in virologically suppressed people with HIV (PWH).
Methods: A pilot, single-arm, prospective study was conducted.
Results: Overall, 234 PWH were enrolled. 217 of 234 (92.7%, 95% confidence interval [CI], 88.6-95.7%) participants had HIV-RNA <40 cp/ml at 48 weeks. Virological failure occurred in three participants, none with documented resistance, and all resuppressed without antiretroviral therapy change. After 48 weeks, a slight increase in cluster of differentiation (CD)4 cell count was observed from the baseline (+ 59 cells/mmc, 95% CI, 31; 86, P <0.001), but not in CD4/CD8 ratio. A slight increase in creatinine (mean change +0.11 mg/dl, 95% CI 0.10; 0.13, P <0.001) and a decrease in total cholesterol (mean change −8 mg/dl, 95% CI −14; −3, P = 0.001) were also observed.
Conclusions: Our data showed that BIC/FTC/TAF demonstrated high virologic and immunologic efficacy and an excellent safety profile.

Introduction

Lifelong antiretroviral therapy (ART) increases the risk of long-term toxicity in people with HIV (PWH), negatively impacting age-related comorbidities and treatment adherence [1]. Optimization strategies aim to improve outcomes by reducing pill burden and minimizing drug number/frequency (long-acting injectables or intermittent dosing) [2]. Nevertheless, with the increasing availability of generic drugs in a health system where clinical treatments are free of charge, ART expenditure is still high, and healthcare funding has been reduced. Because various treatment regimens have similar effectiveness, it is appropriate to consider their cost-effectiveness for better resource allocation and ensuring equitable and universal access to treatment [3]. The fixed-dose combination of efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) 600 mg/200 mg/245 mg was the first single tablet

☆ Preliminary results of the EBONY study were presented at the 12th Italian Conference on AIDS and Antiviral Research (ICAR) 2020 (abstract OP34), at the 13th Italian Conference on AIDS and Antiviral Research (ICAR) 2021 (abstract OP3), and at the 18th European AIDS Conference in 2021 (abstract PE 2/47 and BPD1/7).

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regimen (STR) approved for HIV treatment, paving the way to substantial improvement in PWH's quality of life and outcomes [3]. It is currently an alternative first-line regimen, according to the World Health Organization, British HIV Association (BHIVA), and European AIDS Clinical Society (EACS) guidelines, and it is still used mainly in developing countries [5,7]. The question of whether to retain EFV-based regimens in patients who are well-adapted is a subject of debate. EFV-containing regimens were no longer recommended for the initial antiretroviral therapy, except for pregnancy and tuberculosis co-infection from most of the guidelines [2,4–7]. However, BHIVA guidelines considered EFV-based regimens also acceptable for maintenance of treatment in PWH with stably suppressed viremia unless considered the most clinically appropriate option [3]. Moreover, generic EFV remains widely used in resource-limited settings due to its low cost, proven safety and efficacy at 400 mg, and usability in pregnant women and those co-infected with tuberculosis [4]. EFV causes transient, sometimes persistent, neuropsychiatric side effects (insomnia, paranoia, mood swings, anxiety, nervousness) in about half of subjects [8] and the use of the drug was related to an increased suicidality risk [2]. These 5-hydroxytryptamine2A (5-HT2A) receptor-mediated effects are dose-dependent, affecting women, those with lower weight, and Cytochrome P450 2B6 (CYP2B6) low metabolizers more. Tenofovir plasma levels correlate with bone and renal toxicity risk [9,10]. Studies show that lowering the EFV dose in EFV/FTC/TDF to 400 mg maintains efficacy with improved safety [5]. Intermittent dosing has also been explored to reduce toxicity while maintaining efficacy, adherence, and lowering costs [11].

Integrase inhibitors (INSTI) are valuable for HIV treatment simplification [12]. Bictegravir (BIC), with its strong safety profile, few drug interactions, high potency, and a genetic barrier is ideal for both initial treatment and switching strategies in a daily coformulation with TAF/FTC [12,13]. The rapid ART approach with BIC/FTC/TAF has shown significant advantages over EFV 400 mg + 3TC + TDF in a recent randomized clinical trial, including improved adverse events (AEs), retention in care, and viral suppression rates [14] . Some benefits in terms of virological efficacy were also observed in an emulation trial of virologically suppressed patients switching from EFV/FTC/TDF to BIC/FTC/TAF [15]. No previous clinical trials have specifically explored switching from an EFV-containing regimen to a BIC-containing three-drug regimen, particularly in a population that has achieved virological suppression and has been stable on their current regimen for many years. This study aimed to prospectively evaluate the efficacy, safety, and tolerability of switching from EFV/FTC/TDF, both in once daily (OD) or on alternate days (ATAD) doses, to BIC/FTC/TAF OD in virologically suppressed PWH.

Materials and methods

Trial design and participants

EBONY is a single-arm, prospective, single-center, open-label, nonrandomized phase IV trial.

Eligible participants were all adults aged 18 or over with HIV-1 meeting the following criteria: (i) HIV-RNA <50 copies/ml for at least 24 weeks; (ii) treated with EFV/FTC/TDF OD or ATAD for at least 24 weeks; (iii) without major resistance mutations to nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI) or INSTI class on any previous genotype resistance test, if available; (iv) without history of previous virological failure (VF) with INSTI-containing regimens; (v) creatine clearance ≥50 mL/min. The main exclusion criteria included pregnancy, lactation, active opportunistic infection, and active cancer. Women with childbearing potential were required to have a negative serum pregnancy test at screening and to use a protocol-defined acceptably effective form of contraception. The complete list of inclusion and exclusion criteria is available in Supplementary Material S1.

The study took place at the HIV clinical unit of *Immunodeficienze Virali* of the National Institute of Infectious Diseases Lazzaro Spallanzani in Rome (Italy), which has about 6,000 PWH in active follow-up, from May 2019 to May 2022. Study participation was proposed to the virally suppressed PWH fulfilling the eligible criteria that were in active follow-up during that period. The study was approved by the internal Ethical Committee of the Lazzaro Spallanzani Institute (approval number 73/2018). Before entering the study, all participants gave their written informed consent. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, which followed the principles of the Declaration of Helsinki and the Council for International Organizations of Medical Sciences International Ethical Guidelines. All data have been collected anonymously into the Electronic Case Report Forms. The study was registered in the European Union Clinical Trials Register (EudraCT 2018-003880-79). The protocol was amended twice for minor modifications.

Intervention

At baseline (BL), participants enrolled in the study were switched to BIC/FTC/TAF one pill a day.

Outcomes and endpoints

The primary objective was to evaluate the efficacy of switching from EFV/FTC/TDF OD or ATAD to BIC/FTC/TAF.

The primary endpoint was the proportion of participants of the intention-to-treat (ITT) population with HIV-RNA <40 cp/ml at 24 weeks.

Secondary endpoints included the proportion of participants of the ITT population with VL <40 cp/ml at 48 weeks, the proportion of participants of the per-protocol (PP) population with discontinuation at 48 weeks, the proportion of participants of the ITT population with discontinuation at 48 weeks the development drug resistance, the occurrence of clinical and laboratory AEs, variation in cluster of differentiation (CD)4 cell count, HIV-DNA, blood lipid levels, renal function from BL to week 48. A *post hoc* analysis of body weight changes was performed too.

The following items were evaluated in three prespecified subgroups of a maximum of 80 participants, each one as an ancillary study: (i) patients' reported outcomes (PROs); (ii) plasma concentrations of BIC; (iii) renal tubular markers and bone mass density (BMD). Participation in the sub-studies was optional, thus each subject eligible and enrolled for the main study was invited to participate in ≥1 of these ancillary studies.

A PP analysis was also performed, including only PWH with HIV-RNA below 50 cp/ml at BL visit who received at least one dose of study therapy.

Statistical analysis

All longitudinal outcomes were analyzed using mixed-effects regression models. Each model included participant-level random intercepts and random slopes for time, with an unstructured covariance matrix to account for within-subject correlations. Follow-up time was treated as a categorical variable to allow for nonlinear changes at each specific time point, and the previous treatment group (OD vs ATAD) was included as a fixed effect; the interaction between time and previous treatment was also modeled. All models were adjusted for age (continuous) and sex (binary) as potential confounders. Missing data were handled inherently by the

mixed-effects approach under a missing at random assumption. Little's test for missing completely at random was non-significant ($\chi^2 = 400.88$, df = 1233, $P = 1.000$), supporting the validity of the missing at random assumption. Multiple pairwise comparisons at different follow-up time points were performed with Bonferroni correction to adjust for inflation of type I error. Finally, model-derived estimates adjusted for age and sex were plotted over time for each treatment group to illustrate the longitudinal trends.

Procedures

At the screening visit, the eligibility criteria were verified. At screening, BL and post-BL visits, medical history, physical examination, and laboratory tests were performed.

We conducted post-BL study visits at weeks 4, 8, 12, 24, 36, and 48. Laboratory tests included complete blood count, serum chemistry tests, pregnancy tests for women with childbearing potential, fasting lipid parameters, CD4 counts, CD4/CD8, and plasma HIV-1 RNA level (Aptima HIV-1 Quant Dx Assay by Hologic, Inc., San Diego, CA). HIV-DNA was measured at BL, weeks 24 and 48. Protocol-defined resistance testing consisted of genotypic analysis of integrase, protease, and reverse transcriptase (standard Sanger assay) for any participant who had a VF, defined as a confirmed plasma HIV-1 RNA ≥40 copies/mL (2 consecutive measurements) during the study.

Safety was assessed, and AEs, serious AEs (SAEs), which led to discontinuation of BIC/FTC/TAF, drug-related AEs, and laboratory abnormalities were recorded. AE were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1, July 2017. Procedures of the substudies are reported in Supplementary Materials S2.

Neurocognitive results of the EBONY study have already been published [16].

Results

Study population

The BL demographic and clinical characteristics of the study population (overall and according to the previous regimen) are shown in Table 1. A total of 234 virologically suppressed PWH were enrolled in this study: 37 (15.8%) females, the median age was 52 years (interquartile range, IQR, 44-58), 205 Caucasians (87.6%), 35 (15.0%) with previous AIDS-defining event, 113 (48.3%) reported men who have sex with men as main HIV risk factor, their median CD4+ cell counts was 656 cells/mmc (IQR 502-864), the median time from HIV diagnosis was 13 (IQR 9-17) years, the median time of ART was 11 (IQR 8-15) years and the median time on EFV-based regimens were 10.2 years (IQR 8.5-11.6). Of the participants, 175 (74.8%) PWH switched from EFV/FTC/TDF OD and 59 (25.2%) from EFV/FTC/TDF ATAD. Participants' flow diagram is shown in Figure 1.

Virological outcomes

The primary ITT analysis involved all 234 participants. At 24 weeks, 212 of 234 (90.6%, 95% confidence interval [CI], 86.1-94.0%) participants had HIV-RNA <40 cp/ml, five (2.1%) participants had HIV-RNA ≥ 40 cp/ml, 17 (7.3%) participants had no virological data (five of them discontinued the study to AE/death/VF, two were lost to follow-up and 10 were on study but with missing data in window). At 48 weeks, 217 of 234 (92.7%, 95% CI, 88.6-95.7%) participants had HIV-RNA <40 cp/ml, two (0.9%) participants had HIV-RNA ≥40 cp/ml, 15 (6.4%) participants had no virological data (nine of them discontinued the study to AE/death/VF, three were lost to follow-up and three were on study but with missing data in window).

Figure 1. Participants' flow diagram.

A VF occurred in three participants: one at 4 weeks from BL (HIV-RNA 64 and 53 copies/ml at confirmation), one at 12 weeks (HIV-RNA 63 and 155 copies/ml), the other at 24 weeks (HIV-RNA 80 and 48 copies/ml). The historical genotype (pre-ART) was wild-type in all three cases. In two of three participants, no relevant resistance mutations for NRTI and INSTI were detected after failure. In the other case, the genotype resistance test performed at VF did not amplify. All the cases were related to low adherence according to clinicians' judgment and suppressed without ART change.

BIC plasma concentrations were adequate in one individual with VF (2775 ng/ml in a sample collected 12 weeks before the VF and 1268 ng/ml in another sample collected 9 weeks after), while they were not performed in the other two cases.

The PP analysis included 227 participants (seven participants with detectable HIV-RNA at BL were excluded from the PP analysis): 168, 74% PWH switched from EFV/FTC/TDF OD and 59, 26% from EFV/FTC/TDF ATAD. A total of 206 (90.8%, 95% CI 86.2-94.2%)

Table 1
Descriptive characteristics of people with HIV included in the study.

	Overall population (n = 234)	Switch from EFV/TDF/FTC QD (n = 175)	Switch from EFV/TDF/FTC ATAD (n = 59)
Female sex, n (%)	37 (15.8%)	27 (15.4%)	10 (16.9%)
Age, median (IQR)	52 (44-58)	54 (44-58)	50 (46-55)
Mode of HIV transmission, n(%)	8 (3.4%)	7 (4%)	1 (1.7%)
IVDU	113 (48.3%)	74 (42.3%)	39 (66.1%)
Homosexual contacts	87 (37.2%)	71 (40.6%)	16 (27.1%)
Heterosexual contacts	26 (11.1%)	23 (13.1%)	3 (5.1%)
Other/unknown			
Previous AIDS diagnosis, n(%)	35 (15%)	30 (17.1%)	5 (8.5%)
CD4+ at BL, cell/mmc, median (IQR)	656 (502-864)	611 (484-847)	704 (576-908)
CD4/CD8, median (IQR)	1.02 (0.80-1.38)	1.03 (0.80-1.38)	0.99 (0.82-1.50)
Time from HIV diagnosis, years, median (IQR)	13 (9-17)	13 (9-18)	13 (0-16)
Time from starting ART, years, median (IQR)	11 (8-15)	11 (8-16)	10 (8-14)
Time on EFV-based regimens, years, median (IQR)	10.2 (8.5-11.6)	8.2 (6.3-10.4)	7.9 (6.6-9.6)
Time of virological suppression, years, median (IQR)	10 (7-12)	10 (7-12)	9 (7-10)
Caucasian ethnicity, n (%)	205 (87.6%)	152 (86.9%)	53 (89.8%)

CD, clusters of differentiations; IQR, interquartile range; IVDU, intravenous drug users; EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; QD, quaque die; ATAD, administered on alternate days.

participants had HIV-RNA<40 cp/ml at 24 weeks and 212 (93.4%, 95% CI 89.3-96.3%) at 48 weeks.

A total of 12 treatment discontinuations occurred in the ITT population overall, with a proportion of treatment discontinuations of 5.1% (95% CI 2.7-8.8%) at 48 weeks.

Reasons for treatment discontinuation were: five AEs (two intolerance, one elevated transaminase, one prostatitis, and one sexual dysfunction), one death, three VFs (that discontinued the study but did not discontinue BIC/FTC/TAF regimen), and three losses to follow-up.

In the PP analysis, 11 treatment discontinuations occurred, with a proportion of 4.8% (95% CI 2.4%;8.5%). Reasons for treatment discontinuation were: five AEs (two intolerance, one elevated transaminase, one prostatitis, one sexual dysfunction), one death, two VFs (that discontinued the study but did not discontinue BIC/FTC/TAF regimen), three losses to follow-up.

No significant changes in HIV-DNA from BL were observed at 24 and 48 weeks.

Evolution of immunologic and metabolic parameters

Changes in CD4 cell count, CD4/CD8, creatinine, glycemia, blood lipids, and transaminases after the switch to BIC/FTC/TAF in the overall population and according to pre-BL regimen are depicted in Figures 2, 3, and 4. Of note, after 48 weeks, a slight increase in CD4 cells count was observed from the BL: overall + 58.76 cells/mmc (95% CI 28.40; 89.12, P <0.001), +51.96 cells/mmc (95% CI 18.16-85.77, P <0.001) in PWH switching from EFV/FTC/TDF OD and +79.37 cells/mmc (95% CI 12.40; 146.35, $P = 0.011$) in PWH switching from EFV/FTC/TDF ATAD. In the comparison among groups, the recovery of CD4 cell count was more pronounced in those switching from EFV/FTC/TDF ATAD ($P = 0.026$). After 48 weeks, a slight decrease of CD4/CD8 was observed in the overall population of –0.04 (95% CI, –0.08; –0.01, $P = 0.002$), not different in the two groups. An increase of creatinine (mean change +0.12 mg/dl, 95% CI 0.09; 0.14, P <0.001) and a decrease in total cholesterol (mean change –8.45 mg/dl, 95% CI –14.58; –2.36, $P = 0.002$) and high-density lipoprotein (HDL) (mean change –4.66 mg/dl, 95% CI –6.31; –3.02, P <0.001) were observed.

No changes over time in glycemia ($P = 1.000$), low-density lipoprotein (LDL)-cholesterol ($P = 0.321$), triglycerides ($P = 1.000$), aspartate aminotransferase ($P = 1.000$) and alanine aminotransferase ($P = 1.000$) were observed overall nor in the two groups.

A small but significant increase in body weight was observed both at 24 weeks (+1.51 kg, 95% CI 0.91;2.11, P <0.001) and at 48 weeks (+2.04 kg, 95% CI 1.30-2.78, P <0.001), slightly higher in those switching from EFV/FTC/TDF OD (+2.17 kg 95% CI 1.31-3.03; P <0.001 at week 48) vs those switching from EFV/FTC/TDF ATAD (+1.63 kg; 95% CI 0.20-3.09; $P = 0.021$ at week 48).

Clinical and laboratory adverse events

Overall, 106 clinical AE of any grade occurred during the study. Details about clinical AE are summarized in Table 2.

A total of 13 SAEs occurred, none considered related to the study treatment by local investigators.

Grade 3 or 4 laboratory AEs were rare, and none of them were deemed related to the study treatment by local investigators. These are summarized in Table 3.

Ancillary studies

Results of the analysis of the HIV medical outcomes survey (MOS-HIV) questionnaire (Supplementary materials S2.1), administered at BL, weeks 4, 24, and 48, showed that general health was rated “very good” by the majority of evaluated participants and remained substantially stable over time (34/70 at BL, 30/64 at week 4, 31/58 at week 24 and 25/52 at week 48). Participants who reported “excellent” in this item were 14/70 at BL, 16/64 at week 4, 10/58 at week 24, and 15/52 at week 48.

In addition, general health was not limited to performing the activities of daily living (physically demanding and moderate activity, walking uphill, bending down, walking about 100 meters, eating, dressing, and washing up) for 63/70 at BL, 59/64 at week 4,

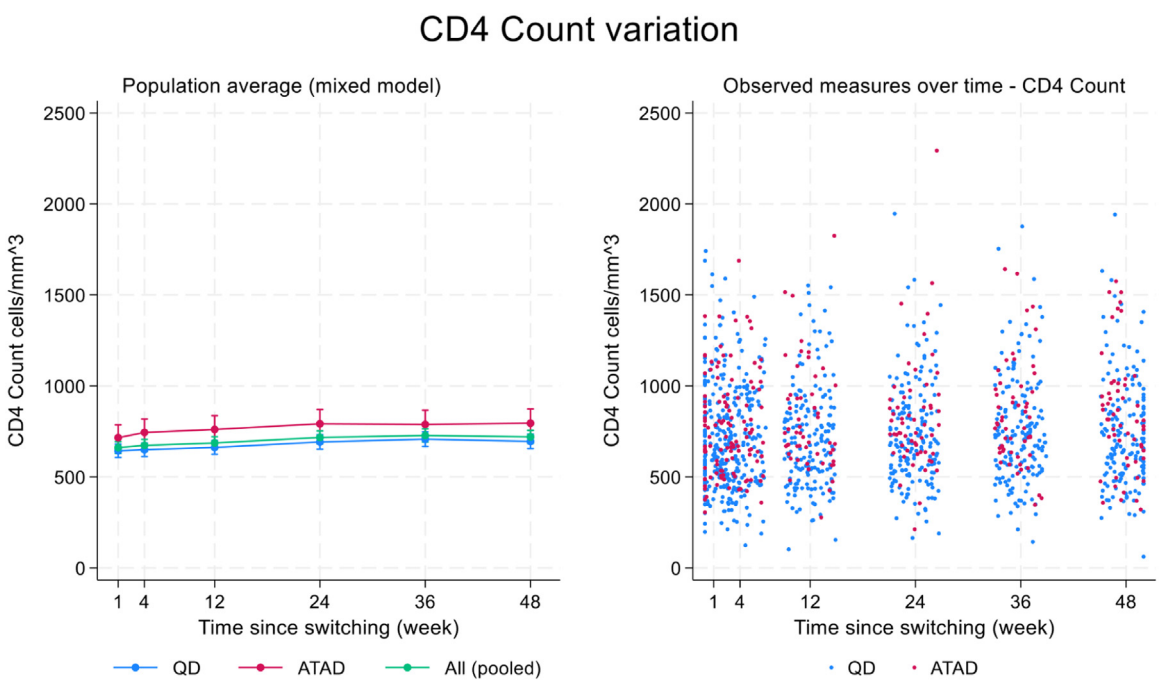

Figure 2. Changes from baseline to week 48 of CD4 cells count, CD4/CD8.
CD, clusters of differentiations.

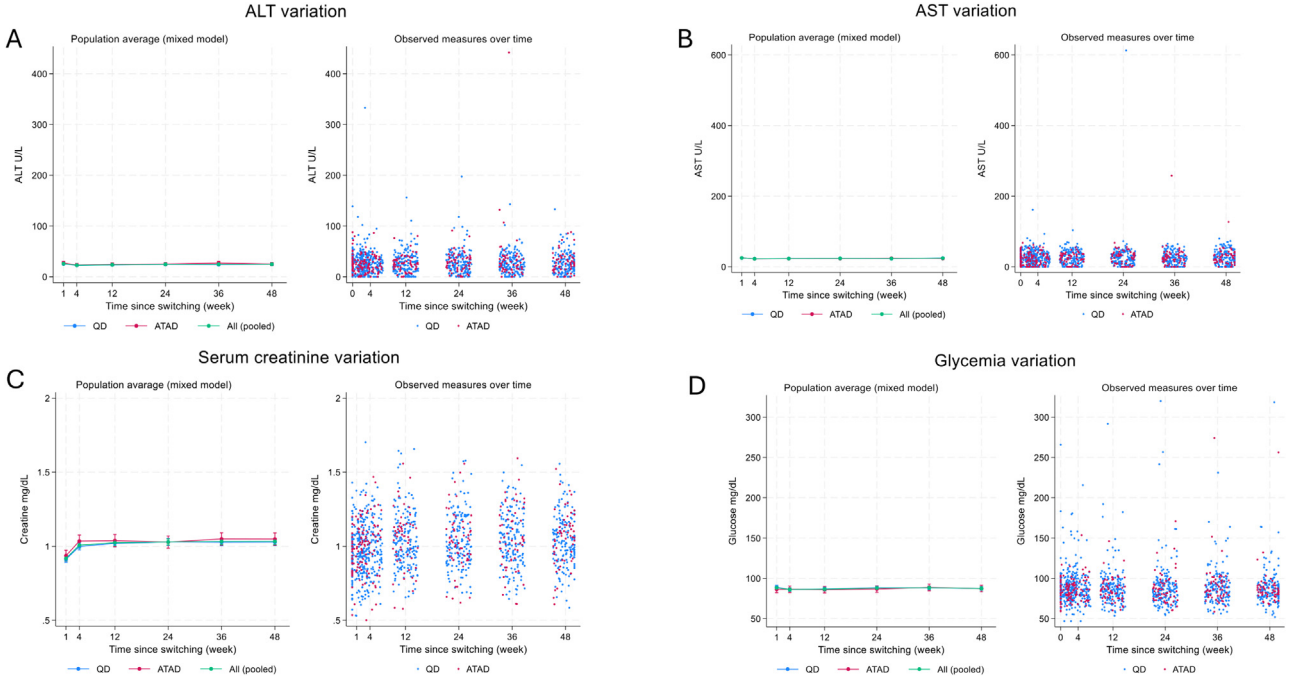

Figure 3. Changes from baseline to week 48 of ALT, AST, creatinine, and glycemia.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATAD, alternate days; OD, once daily.

55/58 at week 24 and 49/51 at week 48 (they choose the answer "no, not at all").

Finally, they reported that general health did not restrict normal social activities (such as visiting friends or family members) for 64/70 at BL, 56/64 at week 4, 51/59 at week 24, and 44/51 at week 48 (answer choice: "none of the time").

Mean BIC plasma levels were 3263 ng/ml at week 4 (in 54 participants, their BL demographic and clinical characteristics are shown in Supplementary Material S4), 4167 ng/ml at week 24 (in 53 participants), and 3911 ng/ml at week 48 (in 54 participants), all above 164 ng/ml (therapeutical concentration).

No statistically significant changes in femoral BMD, lumbar BMD, and beta 2-microglobulin were detected from BL to week 48.

Discussion

To our knowledge, this is the first study that specifically explored the switch from EFV/FTC/TDF to BIC/FTC/TAF in a real-world

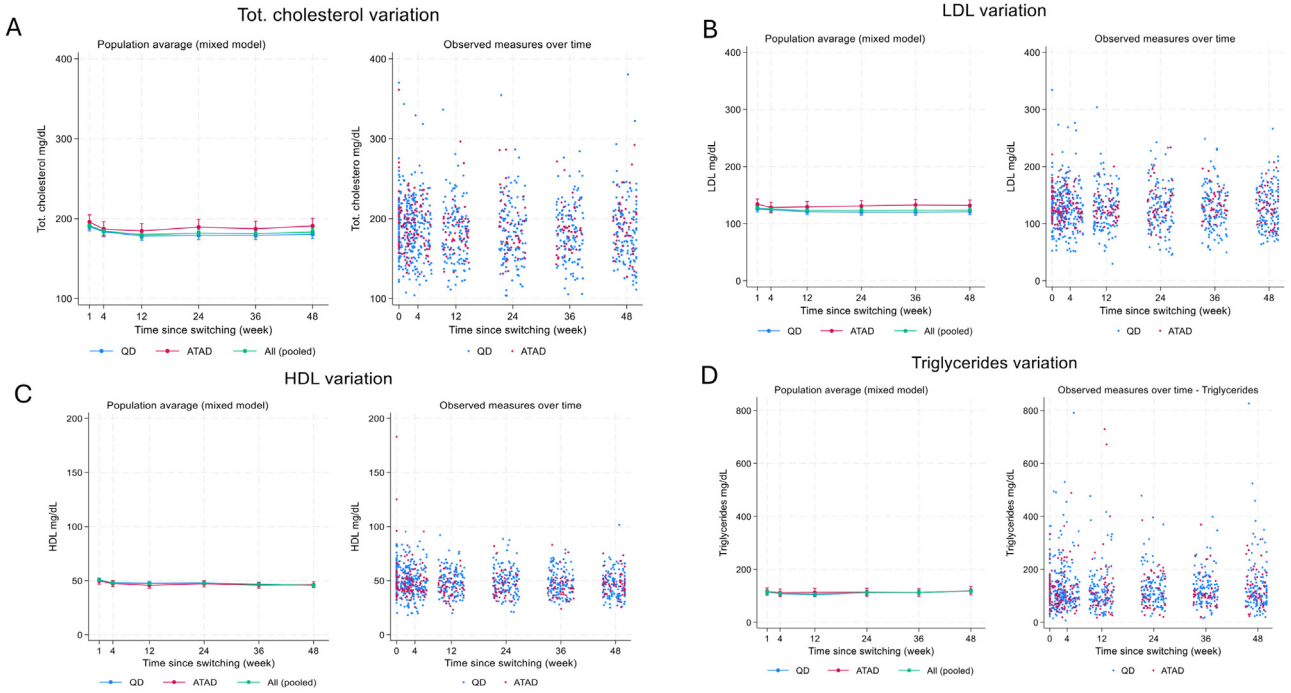

Figure 4. Changes from baseline to week 48 of total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.
ATAD, alternate days; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OD, once daily.

Table 2
Clinical adverse events.

Type	
Gastrointestinal disorders	14
Infections	12
Bone disorders	10
Renal disorders	10
Arthralgias	8
Upper respiratory disorders	7
Dermatologic disorders	5
Neurological disorder	5
Insomnia	4
Cardiovascular disorders	3
Urologic disorders	3
Fever	2
Headache	2
Liver disorders	2
Lower respiratory disorders	2
Diarrhea	1
High serum creatinine	1
Hypercholesterolemia	1
Hypovitaminosis D	1
Others	13
Any clinical adverse event	106

Table 3
Grade 3-4 laboratory adverse events.

Adverse event, grade 3 or 4	Overall population, at any time, n (%)
Triglycerides	7 (2.9%)
Alanine aminotransferase	2 (0.8%)
Aspartate aminotransferase	2 (0.8%)
Hemoglobin	0 (0%)
Platelets	0 (0%)
White cells	0 (0%)
Total cholesterol	0 (0%)
Creatinine	0 (0%)

setting. We enrolled individuals virologically suppressed at BL who were stable on EFV-based regimens for a median of 10 years. We have continued this strategy despite the availability of newer antiretroviral therapies. Most patients reported "excellent" or "very good" quality of life on the MOS-HIV questionnaire at BL, and very few had limitations in daily living activities with the current regimen. Our results showed the efficacy, safety, and tolerability of switching to BIC/FTC/TAF in this setting and provided further evidence of the high genetic barrier to resistance conferred by BIC, consistent with clinical and pre-clinical observations [17].

The proportion of virologically suppressed participants at week 48 was 92.7% at the ITT analysis and 93.4% at the PP analysis, and no ART modification for VF was made. Interestingly, consistent with other real-life BIC/FTC/TAF switch studies, our population demonstrated a mean improvement in CD4 cell count after 48 weeks (+59 cells/mmc overall; +52 cells/mmc for PWH switching from EFV/FTC/TDF OD; +80 cells/mmc for those switching from ATAD). However, contrary to previous literature where switches involved various regimens, our study observed a minimal reduction in the CD4/CD8 ratio (-0.04) in both groups [18].

Overall, 106 clinical AEs were detected. Discontinuations in our cohort were driven almost equally by AEs and loss to follow-up, accounting for 5.1% of the ITT cohort and 4.8% of the PP cohort. Although discontinuation rates were more than double among participants switching from an EFV/FTC/TDF alternating-day regimen compared to those on an OD regimen, the small sample size limits definitive conclusions, and this observation should be interpreted with caution. The low proportion of treatment discontinuation due to toxicity mainly due to minor and not drug-related side effects, aligns with recent literature on switch studies examining experienced individuals transitioning to a BIC/FTC/TAF regimen. A retrospective, real-life study conducted in Spain, involving 1584 PWH starting BIC/FTC/TAF (mainly as a switch treatment and a minority as a first-line regimen), demonstrated a 2.6% discontinuation rate due to toxicities at 6 months of follow-up. Furthermore, this study reported a low VF rate of 0.4%, which aligns with our results [19]. In contrast, a recent Italian study involving 290 PWH who switched to B/T/FTC from various dual or 2NRTIs-backbone-based antiretroviral regimens (73% of whom were on an INSTI-based reg-

imen) found a considerably higher proportion of treatment discontinuation due to drug-related toxicity (5.8%) compared to our study population [18]. Due to the absence of a control arm, the EBONY study does not directly compare AEs associated with switching to EFV-based versus BIC-based regimens. Furthermore, no data are currently available in the literature regarding this comparison. In our study, the proportion of VF at 48 weeks was very low, at 3/234 (1.3%) in the ITT analysis. Participants who experienced VF continued the study drug without developing resistance according to genotype testing, confirming the efficacy and high genetic barrier of the BIC/FTC/TAF combination. Accordingly, many studies on switching to BIC/FTC/TAF have shown negligible treatment discontinuations due to VF, ranging from 0-0.4% [18,19]. However, according to a recently published emulated target trial, switching to BIC could be more effective in maintaining viral suppression than continuing ART with EFV, but with a slight difference of 1.2% at 12 months [15]. The EBONY sub-study on neurocognitive and neuropsychiatric parameters in this population showed improvement in anxiety and depression scores and a slight improvement in sleep quality [16]. Although neurocognitive performance was mainly stable, there was some decline in NPZ-12 scores and certain cognitive areas. Interestingly, PROs remained relatively stable over time.

Chronic administration of EFV is associated with negatively impacting metabolic profiles. It can induce hyperglycemia, potentially increasing the risk of insulin resistance and diabetes. Additionally, EFV can contribute to hypertriglyceridemia and hypercholesterolemia, increasing both LDL-cholesterol and HDL-cholesterol [20]. However, the long-term clinical significance of these changes, meaning whether they definitively translate into a higher rate of cardiovascular events, is still debated. Compared to EFV, lower toxicity in the lipid profile was also detected with elvitegravir/cobicistat and raltegravir-containing regimens [21].

Consistent with real-life switch studies examining transitions from EFV to other INSTI-based regimens (namely dolutegravir), our study observed an improved total cholesterol profile after the switch, particularly within the OD population [22]. Conversely, no significant changes in blood glucose, LDL-cholesterol, or triglycerides were detected over time. Using FTC/TAF as a backbone, rather than FTC/TDF, may have attenuated the expected improvements in the lipid profile observed in our cohort. This potential attenuation is noteworthy, given the known impact of TAF on triglycerides and LDL-cholesterol, as well as the concomitant loss of TDF's intrinsic lipid-lowering effect [23]. As expected, a slight increase in body weight was observed at both 24 and 48 weeks with the current switch strategy [24]. This difference may be attributed to multiple factors, such as the removal of TDF, the action of TAF on body mass index [25], and the known effect of EFV in attenuating weight gain proportionally to its blood concentration [26]. Indeed, within our population, weight gain was slightly higher in those switching from EFV/TDF/FTC OD than from ATAD. A thorough review of significant clinical trials recently concluded that TDF-based regimens, especially when combined with EFV, may reduce weight gain. At the same time, dolutegravir (DTG), BIC, and TAF do not contribute to excessive weight gain [27].

Creatinine levels slightly significantly increased within a year. Our findings align with previous reports, demonstrating a non-progressive pattern in this change, which stabilized 4 weeks after treatment initiation [28]. Indeed, all INSTIs have been associated with elevated creatinine levels, mainly due to inhibiting organic cation transporter 2 in proximal tubular cells. This mechanism reduces tubular uptake and creatinine clearance from the blood without significantly impacting the glomerular filtration rate [29]. With generic DTG available since 2018, switching strategies between DTG-based and EFV-based regimens are increasingly common in low-income countries. A network metanalysis conducted on 156 publications (68 clinical trials) assessed DTG-based regimens as preferred to EFV-based regimens even among TB-HIV co-infected persons and pregnant women [30].

The EBONY study, although the only published clinical trial on switching from EFV/TDF/FTC to BIC/FTC/TAF to date, has several limitations that significantly impact the generalizability of its findings. These include the absence of a control group, a single-center design, sample size disparities between the ATAD and OD EFV/TDF/FTC groups, the limited number of PROs collected, a small proportion of women and non-Caucasian PWH, a short follow-up duration, and the lack of a cost-effective analysis. Furthermore, the SARS-CoV-2 pandemic could have affected retention in care for participants in this study. Moreover, given the current cost and limited availability of BIC in low- and middle-income settings, the findings of this study may be most applicable to high-income countries. In summary, this study highlights BIC/FTC/TAF as a viable switching strategy for PWH currently on an OD or alternating-day regimen of EFV/FTC/TDF. Ultimately, switching from EFV/FTC/TDF to BIC/FTC/TAF in a population with optimal efficacy and tolerance of the current regimen should be considered in light of available resources. Generic low-dose EFV-based regimens could remain valuable in a few specific settings for PWHs who tolerate them.

Declaration of competing interest

RG received consultation fees from Gilead, Viiv, and MSD. MC received an institutional grant, support for attending meetings, and speakers' honoraria from Gilead Science. SL received consultation fees from Gilead, ViiV, and MSD. GDD received an institutional research grant and payments to her institution from Gilead Sciences, speakers' honoraria, and support for attending meetings and/or travel from ViiV Healthcare and Gilead Sciences. AA has served as a paid consultant to Astra-Zeneca, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Merck, Moderna, Mylan, Pfizer, Sharp and Dohme, Roche, Theratotecnologies and ViiV Healthcare and received research institutional grants from Gilead Sciences, Janssen-Cilag and ViiV Healthcare, payment or honoraria from Gilead Science and ViiV Healthcare and support for attending meetings and/or travel from ViiV Healthcare and AbbVie. RB received a grant for speaker's honoraria/advisory board from ViiV Healthcare, MSD, Janssen-Cilag, and Gilead Sciences. IM received an institutional research grant and support for attending meetings and/or travel from Gilead Sciences. AM received speakers' honoraria from Gilead Sciences, and ViiV Healthcare, a travel fee from ViiV Healthcare, and participated in advisory boards sponsored by ViiV Healthcare. CP received a personal fee from Gilead Sciences for a case presentation and a travel grant and served on an advisory board for Janssen-Cilag. AV received an institutional grant from Gilead Sciences, speakers' honoraria/educational activities from Merck Sharp & Dohme and Janssen-Cilag, and served as an adviser for Janssen-Cilag. VM received an institutional grant from Gilead Sciences, and speakers' honoraria/educational activities from ViiV and Viatris. The other co-authors declare no conflicts of interest for this work.

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Author contributions

RG: Conceptualization, Investigation, Writing; MC: Conceptualization, Investigation, Writing; SL formal analysis; RB, AM: Conception and design of the study, Investigation, Writing; GDD, SO, FDZ, EG, AM, AV, VM, CP and IM: Investigation, Revision and editing; MMP, MF and JP: Study coordination, Data collection, Revision and editing; MT: TDM analysis, Revision and editing; AA Conceptualization, Investigation, Writing.

All authors have approved the final article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.107961.

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