Enhanced metabolic health and immune response with bictegravir/emtricitabine/TAF: Insights from a 96-week retrospective study

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Abstract. Bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF), as a fixed dosed combination, is effective in people living with human immunodeficiency virus (PLWH) previously treated with other therapeutic regimens. The aim of the present retrospective observational real-life study was to analyze virological suppression and immunological, metabolic and safety profile of B/F/TAF. Data were collected from 127 PLHW who switched from any regimen to B/F/TAF. Viral load and virological suppression (viral load <50 copies/ml) were assessed by using real-time PCR methodologies; CD4 and CD8 T cell count as well as CD4/CD8 ratio were determined by cytofluorimetric analyses; other metabolic parameters such as total cholesterol, triglycerides, High- and Low-Density Lipoproteins were assessed by using immuno-enzymatic assay. All of the aforementioned parameters were assessed at different timepoints (Baseline, 48 and 96 weeks) for the patients switching to B/F/TAF. Of 127 PLHW [96 (75.6%) male and 31 (24.4%) female, with a mean age of 46.8±10.7 years], 107 PLHW were included in the analysis. The percentage of virologically suppressed PLWH increased from 66.4 to 74.8% at 96 weeks. A statistically significant increase in absolute CD4 (P<0.0001) and CD8 T cell count (P=0.002) was observed. Of importance, there was a significant increase in CD4/CD8 ratio from 0.95 (0.52-1.31) to 1.16 (0.75-1.39) (P=0.003) after 96 weeks. There was a significant decrease in the median values of triglycerides (P<0.0001) and total cholesterol (P<0.0001). Serum creatinine showed a significant increase (P=0.0001). In real life, switching to B/F/T was safe and highly effective both virologically and immunologically. Decrease in cholesterol and triglyceride levels suggested a favorable metabolic profile, which may decrease inflammation, leading to a healthier state and less organ damage.

Introduction

The management of human immunodeficiency virus (HIV) infection has evolved over the past decades, with antiretroviral therapy (ART) serving a critical role in achieving virological suppression and improving immune function. Despite the efficacy of various ART regimens, the need for optimizing treatment persists to enhance patient outcomes, minimize adverse effects and treat comorbidities and associated infection (1-3).

Novel ART regimens are designed to be highly potent while maintaining a better safety profile. Integrase strand inhibitors (INSTIs) have emerged as a cornerstone in first-line treatment regimens. These include first-generation INSTIs such as raltegravir and elvitegravir and second-generation agents such as dolutegravir, bictegravir and cabotegravir (4,5-7). Bictegravir, available as a fixed-dose combination tablet with the nucleos(t)ide reverse transcriptase inhibitors (NRTIs) emtricitabine and tenofovir alafenamide (B/F/TAF), has been

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approved both by the U.S. Food and Drug Administration and European Medicines Agency for once-daily treatment. Landmark phase III trials have demonstrated its efficacy in both treatment-naïve people living with HIV (PLWH) and as a switch regimen (4-7). B/F/TAF does not require pre-treatment molecular detection of Human Leukocyte Antigen B allele, which has already been associated with hypersensitivity to the nucleoside-reverse transcriptase inhibitor (NRTI) abacavir (8). The B/F/TAF regimen exhibits activity against hepatitis B virus and HIV-1 non-B subtypes and is suitable for 'rapid start' treatment, since it is has a high genetic barrier against resistance development (9). Additionally, it has low drug-drug interactions, comes as a fixed-dose combination and has simple administration guidelines regarding meals, making it a convenient option for PLWH (4,10). As an effective switch strategy, B/F/TAF has shown non-inferiority to continuing a number of regimens, including those with pre-existing NRTI mutations, in several randomized controlled trials (4-7,9,10). Real-world studies further support the virological efficacy and safety of B/F/TAF as a switch regimen (4-7,9,10).

The aim of the present retrospective study was to evaluate the efficacy of B/F/TAF in a real-world setting, focusing on virological, immunological, safety and metabolic profiles.

Materials and methods

Cohort. Data from a cohort of 127 PLWH enrolled from April 2019 to May 2022 at ARNAS Garibaldi in Catania, Italy, were statistically analyzed to determine a safety and efficacy profile of B/F/TAF. Cohort's age ranged from 23 to 72 years, with a mean age of 46.8 (±10.7) years. The majority of the cohort (75,6%) was composed by male individuals, and sexual transmission was the main cause of infection (88.1%).

The inclusion criteria were as follows: i) HIV-1 infection, ii) age >18 years and iii) written informed consent. Exclusion criteria were pregnancy and other ongoing treatments incompatible with B/F/TAF.

Measurements. Epidemiological and clinical data were collected from 107 patients. The epidemiological data gathered at baseline included age, sex, ethnicity, previous regimen, height, weight, comorbidities (such as viral co-infection, hypertension, obesity, diabetes, dyslipidaemia, cancer, osteoporosis, hyperthyroidism, hypothyroidism and psychiatric disease), acquired immune deficiency syndrome (AIDS)-associated diseases (oesophageal candidiasis, Kaposi's sarcoma, cerebral toxoplasmosis, lymphoma, *Pneumocystis jirovecii* pneumonia, progressive multifocal leukoencephalopathy, atypical mycobacterial infection, cervical carcinoma, hepatitis B or C and other co-infection), time since onset of HIV, CD4 nadir, sexual orientation, transmission mode, recreational habits, cigarette smoking and alcohol consumption. Clinical parameters were assessed using clinical laboratory automated instrumentation: High- and low-density lipoproteins (HDL and LDL), triglycerides, Total cholesterol, creatinine, Glutamate-Pyruvate transaminase (GPT) and Glutamate-Oxalate Transaminase (GOT) were assessed using the DxC 500 AU Chemistry Analyzer by Beckman Coulter; HIV Viral Load (VL) was analyzed using the HIV-1 COBAS test on COBAS 4800 (Roche Diagnostics Corporation); CD4+ and CD8+ T lymphocytes levels were assessed using cytofluorimetric automated instrumentation BD Facs Canto II (BD Biosciences) using the BD Multitest™ CD3 FITC/CD8 PE/CD45 PerCP/CD4 APC with BD Trucount™ Tubes (BD Biosciences), a specific four-color reagent useful to determine the absolute count of CD4+ and CD8+ lymphocytes per microliter by gating all mature lymphocytes (CD3+) using a specific fluorophore (Fluorescein Isothiocyanate, FITC). Mature lymphocytes expressing both CD3+ and $CD8^+$ glycoproteins are gated by assessing the fluorescence of both the respective fluorophores (FITC and Phycoerithrin). The same process is performed also for the CD4+ T lymphocytes, using Allophycocyanin (APC) as a specific fluorophore. The total leukocytes count is performed by targeting CD45+ cluster of differentiation, expressed on all white blood cells. Peridinin-Chlorophyll-Protein (PerCP) was used as the specific fluorophore for CD45+ glycoprotein. This allows to obtain also the relative quantification of both CD4+ and CD8+ cells.

Statistical analysis. Qualitative data were summarized using absolute and relative frequencies. Quantitative variables are presented as either mean and SD or medians and interquartile range. The normal distribution was evaluated using Shapiro-Wilk test. The McNemar test was used to compare qualitative variables between study time-points. Comparisons of biochemical parameters were evaluated using either one-way ANOVA for repeated measures followed by post hoc Bonferroni's test or the non-parametric Friedman test. $P<0.05$ was considered to indicate a statistically significant difference. STATA17 software (2021. Stata: Release 17; StataCorp LLC.) was used for statistical computations.

Results

Cohort. A total of 127 patients were enrolled, 96 (75.6%) male and 31 (24.4%) female, with a mean age of 46.8±10.7 years (Tables I and II), at the Infectious Disease Unit of the Hospital Azienda di Rilievo Nazionale ed Alta Specializzazione Garibaldi, University of Catania (Catania, Italy). Patients were predominantly Caucasian (88.1%), heterosexual (54.7%), men who wave sex with men (37.6%), with some bisexual (7.7%); thus, the mode of HIV transmission was primarily sexual (88.1%; Table I). A total of 49.6% of patients were smokers, 12.6% used alcohol, 9.5% were drug users and 11% reported substance abuse (Table I). The primary therapeutic regimens were elvitegravir + cobicistat + Emtricitabine (FTC) + TAF (53.54%), dolutegravir + TAF + FTC (7.88%), raltegravir + TAF + FTC (7.09%) and darunavir + cobicistat + FTC + TAF (7.09%). The primary reasons for treatment switch were proactive strategy (34.52%), simplification (27.38%) or adverse events (21.42%).

Virological trends. At baseline, 71 patients had viral load <50 copies/ml (Table III) while 36 had viral load >50 copies/ml. Over time, no statistically significant changes in the number or percentage of virus-suppressed patients were recorded, although the percentage of virologically suppressed PLWH increased from 66.4 to 67.3 after 48 weeks and to 74.8% at 96 weeks. Only one patient had a viral load >200 copies/ml (212 copies/ml) at 96 weeks.

Table I. Patient characteristics.

Variable	Value
Mean age, years	46.8±10.7
Male (%)	96 (75.6)
Men who have sex with men (%)	44 (37.6)
Ethnicity (%)	
African	10 (7.9)
Arabic	1 (0.8)
Asian	1 (0.8)
Caucasian	111 (88.1)
Latin American	3 (2.4)
Median years since HIV onset (IQR)	14.1 (8.8-25.1)
Median CD4 nadir (IQR)	283 (122-398)
Sexual orientation (%)	
Bisexual	9 (7.7)
Heterosexual	64 (54.7)
Homosexual	44 (37.6)
Transmission route (%)	
Sexual	103 (88.1)
Accidental exposure	1 (0.8)
Drug use	12 (10.3)
Transfusion	1 (0.8)
Substance abuse (%)	14 (11.0)
Smoking status (%)	
Non-smoker	56 (44.1)
Current smoker	63 (49.6)
Former smoker	8 (6.3)
Drug use (%)	12 (9.5)
Alcohol use (%)	16 (12.6)

HIV, human immunodeficiency virus.

Table II. Patient comorbidities.

Variable (%)	Value
Comorbidity	108 (85.0)
Hypertension	27 (21.3)
Dyslipidemia	36 (28.4)
Cancer	6 (4.7)
Diabetes	6 (4.7)
Osteoporosis	4 (3.2)
Hypothyroidism	3 (2.4)
Hyperthyroidism	3 (2.4)
Psychiatric disorder	19 (15.0)
AIDS-associated disease	76 (59.8)
Co-infection	69 (54.3)

AIDS, acquired immune deficiency syndrome.

Table III. Number of virologically suppressed patients (<50 copies/ml).

Time point	Patients with <50 copies/ml (%)
Baseline	71 (66.4)
48 weeks	72 (67.3)
96 weeks	80 (74.8)

Immunological profile. A significant increase in absolute CD4 cell count was observed from 658 (459.5-900.5) to 726 (562-974) after 48 weeks and to 882.5 (647.5-1169) cells/μl after 96 weeks (Table IV; Fig. 1A). Furthermore, the CD8 lymphocyte count significantly increased. Baseline values of 760.5 (511.0-1044.5) were recorded, while after 48 weeks the values were 837.6 (641-1066) and after 96 weeks 859.5 (648.5-1181; Fig. 1B) cells/μl. Finally, there was a significant increase in CD4/CD8 ratio from 0.95 (0.52-1.31) to 1.00 (0.61-1.29) after 48 weeks and 1.16 (0.75-1.39) after 96 weeks (Fig. 1C).

Metabolic and clinical trends. At a metabolic level, there was a significant decrease in the median values of triglyceride levels from a median value of 128 (91-200) at baseline to 105 (73-143.5) at 48 and 100 (74-135) mg/dl at the 96 weeks (Table V; Fig. 1C). A significant decrease was also observed for total cholesterol levels from a mean value of 204.2±47.5 at baseline to 188.6±38.5 after 48 weeks and 190.1±38.8 mg/dl after 96 weeks (Fig. 1E). Serum creatinine showed a significant increase from 0.83 (0.73-0.91) to 0.91 (0.81-1.02) after 48 weeks and to 0.90 (0.82-1.02) mg/dl after 96 weeks (Fig. 1F). Finally, significant changes in median GPT values were found from 26.5 (18.5-38.5) at baseline to 29 (20-38.5) U/l after 48 weeks. The value decreased to 25.5 (20-40) U/l after 96 weeks. Median GPT values remained between normal ranges of 5 to 35 U/l.

Discussion

The present study confirmed the virological and immunological efficacy of B/F/TAF, as well as a favorable metabolic profile. B/F/TAF led to a statistically significant increase in CD4/CD8 ratio >1, which is clinically associated with a lower probability of serious non-AIDS events (11,12).

Success of ART is measured by virological suppression (viral load <50/copies/ml) or the ability to maintain viral load <200 copies/ml (8,13,14). ART can lower the viral load not only in blood, but also in the semen and cervicovaginal and anorectal secretions, reducing the risk of sexual transmission (14,15). Hence, viral suppression is crucial in HIV treatment. Switching to B/F/TAF has been shown to maintain viral load <50 copies in previous studies (16-31). The present study confirmed the aforementioned data, showing a higher percentage of patients who were virus-suppressed at 96 weeks.

HIV exhibits a specific tropism for CD4 lymphocytes, targeting and killing these cells and decreasing their plasma concentration (32,33). ART lowers viral load, which leads

Table IV. CD4 and CD8 cell count and CD4/CD8 ratio.

Variable	Baseline	48 weeks	96 weeks	P-value
Median CD4 cell count (IQR)	658.00 (459.50-900.50)	726.00 (562.00-974.00)	882.50 (647.50-1169.00)	<0.0001
Median CD8 cell count (IQR)	760.50 (511.00-1,044.50)	837.60 (641.00-1066.0)	859.50 (648.50-1181.00)	0.0020
Median CD4/CD8 ratio (IQR)	0.95 (0.50-1.30)	1.00 (0.6-1.29)	1.16 (0.75-1.39)	0.0100

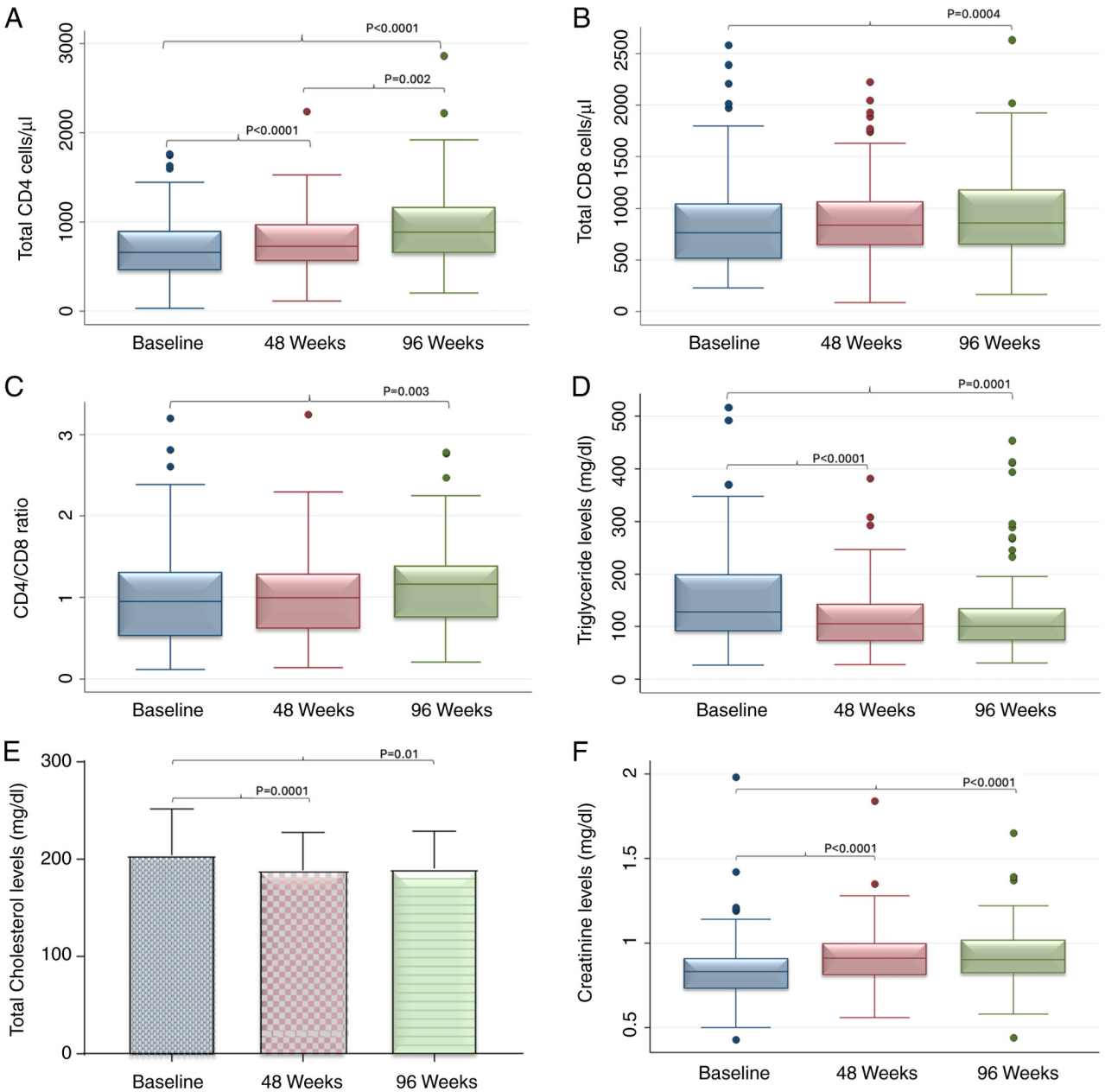

Figure 1. Immunologic and metabolic parameters. (A) CD4 and (B) $CD8^+$ T cell count. (C) CD4/CD8 ratio. (D) Triglyceride, (E) total cholesterol and (F) creatinine levels.

to an increase in CD4 count (34,35). A higher CD4 cell count is associated with decreased risk of clinical progression in PLWH (12). In the literature, patients who switch to B/F/TAF maintained the CD4 count induced by previous therapy (18,25,26). Absolute CD4 count increases but to the best of our knowledge, only Chen *et al* (18), Lazzaro *et al* (25) and Lazzaro *et al* (26) found a significant increase in CD4 count in patients who switched to B/F/TAF.

During the asymptomatic stage of HIV infection, naive CD8 T cells are progressively depleted (36,37). Although the total number of CD8 T cells increases during this stage, the number of naive CD8 T cells decreases in parallel with overall

Table V. Triglyceride, total cholesterol, serum creatinine and GPT levels.

Variable	Baseline	48 weeks	96 weeks	P-value
Median triglyceride levels, mg/dl (IQR)	128.00 (91.00-200.00)	105.00 (73.00-143.50)	100.00 (74.00-135.00)	<0.0001
Mean total cholesterol, mg/dl	204.20±47.50	188.60±38.50	190.10±38.80	<0.0001
Median serum creatinine, mg/dl (IQR)	0.83 (0.73-0.91)	0.91 (0.81-1.02)	0.90 (0.82-1.02)	0.0001
Median GPT levels, U/l (IQR)	26.50 (18.50-38.50)	29.00 (20.00-38.50)	25.50 (20.00-40.00)	0.0200

GPT, glutamate pyruvate transaminase.

CD4 T cell count (36,37). The use of ART during primary HIV infection helps preserve HIV-specific $CD8^+$ T cells both physically and functionally, while sustaining HIV-specific T helper cells (38). Patients who maintain high CD8 lymphocyte count (>1,500 cells/μl) despite ART are at a higher risk of developing adverse events (12). Conditions with increased incidence in these patients include myocardial infarction (39), restenosis following coronary stenting (40), cancer (41) and non-AIDS-associated mortality (42). CD4/CD8 ratio is an important marker of inflammation and associated with serious non-AIDS events (12). As aforementioned, ART typically increases CD4 count and CD4/CD8 ratio (11,12). Low CD4/CD8 ratio is associated with older age in PLWH (43). Chronic HIV infection has been observed to cause immunological changes similar to those seen in natural aging (44). Low CD4/CD8 ratio is associated with impaired vaccine response (45), bacterial (46), fungal (47) and zoonotic infections (48), myocardial infarction (43), cancer (49) and non-AIDS mortality (12). The present study found a significant increase in both CD4 and CD8 T cell count and CD4/CD8 ratio in patients who switched to B/F/TAF. Despite the increase in CD8 T cells, the simultaneous increase in CD4 T cells increased CD4/CD8 ratio. Similar results were observed in studies that measured both CD8 count and CD4/CD8 ratio, with both metrics showing significant increases (25,26).

HIV-1, via its accessory protein Nef, impairs the efflux of cholesterol from macrophages (50). This virus-mediated shift redirects cholesterol transport from normal physiological efflux to virus-controlled transport, thereby decreasing the cell ability to export excess cholesterol (50). ART is not always successful in keeping triglyceride or LDL levels low (51). This is due to several factors, including continuous inflammation and immune activation (as ART achieves viral suppression but not elimination), mitochondrial dysfunction and altered distribution of adipose tissue (52). Frequent dyslipidemia leads to increased cardiovascular risk in PLWH (52,53). Switching to B/F/TAF has been shown to be effective in maintaining lipid levels in the normal range: Most studies have found no significant changes in lipid profile (17,20,27,28,31,54,55). However, certain studies have showed significant decreases in triglyceride (18,19,21,22,56), total cholesterol (18,25,30,55) and LDL levels (18,25,30) and total cholesterol/HDL ratio (19,25,56) and increased HDL levels (18,21,25). Chen *et al* (18) revealed also a significant increase in patients taking lipid lowering agents. Lazzaro *et al* (26) confirmed that after 96 weeks, lipid values remained constant. Here, significant decreases in triglyceride and total cholesterol levels were recorded, suggesting that switching to B/F/TAF may lead to an improvement in lipid profile.

Serum creatinine concentration is serves as a measure of the glomerular filtration rate and is commonly used as an index of renal function in clinical practice (57,58). In HIV infection, renal damage can occur due to both the infection and the therapy (59), particularly with the use of TAF (60). Significant increases in serum creatinine were recorded by Lazzaro *et al* (25,26), a small increase was reported by Kityo *et al* (22), while Molina *et al* (28) did not record significant changes. Here, a significant increase in serum creatinine levels was reported in patients switching to B/F/TAF. However, values remained within normal range (0.63-1.16 for male and 0.48-0.93 mg/dl for female patients) (61).

GPT is an enzyme used as a marker of hepatocyte lysis, systemic inflammation and oxidative stress (62). The persistent activation of immune cells by HIV, along with ongoing inflammation and oxidative stress related to HIV infection, leads to increased GPT levels, even in patients on Highly Active Antiretroviral Therapy (HAART) (63). Lazzaro *et al* (25,26) showed a decrease in GPT levels at 48 weeks and increase at 96 weeks in patients who switched to B/F/TAF, however, these changes were not significant. Another study found that naïve patients on B/F/TAF experienced decrease in GPT levels, while patients who switched to B/F/TAF treatment showed an increase in GPT levels (56). The present study showed significant changes in GPT levels: At 48 weeks there was an increase, but at 96 weeks there was a decrease. However, the median value did not exceed the cut-off threshold of 40 U/l, a value beyond which it becomes an indicator of liver damage (64,65).

One of the primary limitations of the present study is the small samples size (127 patients). This is mainly due to the real-world nature of the study, with patients enrolled and followed by only one center. Additionally, lipid levels showed a significant reduction, but it was not possible to retrieve data on administration of statins and dietary supplements to lower lipid levels, thus is not possible to determine the effects of these molecules on lipid levels. Due to the real-world nature of the cohort, it was not possible to obtain data regarding adherence to treatment, which may have been useful to determine the impact of therapeutic adherence on outcomes.

In real life, switching to B/F/TAF was safe and highly effective both virologically and immunologically. The present study reported a decrease in cholesterol and triglyceride levels, showing a favorable metabolic profile, which may reduce inflammation, leading to a healthier state and less organ damage.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BC, SS, GNC and AM conceived the study. VF, GF, VR, BMC and GFP designed the study. MVP, GS and RB analyzed data. EVN, EVR, GN, NV, AM, VC, MSPR, EP and VB performed experiments. EVR and GN wrote the manuscript. VF and GF reviewed the manuscript. BC, EVN and GN supervised the study. All authors have read and approved the final manuscript. SS and GN confirm the authenticity of all the raw data.

Ethics approval and consent to participate

All participants provided written informed consent to partake in the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the Provincial Ethics Committee of Messina (approval no. 34/17 of the 22/03/2017).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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