

Analysis of the 2-year real-world efficacy and safety of bicitegravir/emtricitabine/tenofovir alafenamide in people living with HIV

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Abstract. Integrase strand transfer inhibitors (INSTIs) have proven to be effective and relatively safe drugs for people living with human immunodeficiency virus (HIV; PLWH). However, they have been found to be associated with an increased risk of developing cardiovascular events and weight gain. Bicitegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a relatively recent INSTI that has exhibited optimal efficacy in controlling the HIV viral load and restoring the immune system. The present study collected data from HIV-positive patients (n=38), 10 PLWH naïve to treatment and 28 experienced PLWH, in current therapy with B/F/TAF, comparing three different time points (T0, T1 and T2) in order to evaluate effectiveness, safety, lipid profile, hepatic and renal function, in a 2-year observational study since the commencement of the antiretroviral therapy regimen. The results revealed a statistically significant improvement in the lymphocyte CD4⁺ count from T0 to T1 (P-value 0.011) and T2 vs. T0 (P-value ≤0.001) in naïve PLWH, as well as an increase in cholesterol low-density lipoprotein levels (P-value 0.043) and weight gain (T2 vs. T0 P-value 0.003). No significant differences were found in experienced PLWH. During the study, numerous cases of HIV viraemia >50 cps/ml, but <500 cps/ml were observed. On the whole, the findings presented herein may add value to the

literature regarding the efficacy of B/F/TAF, particularly due to numerous cases exhibiting low-level viraemia.

Introduction

Improvements in antiretroviral therapy (ART) over the past few years have led to an increase in life expectancy in people living with human immunodeficiency virus (HIV; PLWH) and an equal improvement in quality of life (QoL). The increase in the life expectancy of PLWH has led to the ageing of the population and, therefore, to the onset of a number of other comorbidities that require chronic medication. The concept of polypharmacy represents the regular use of a number of drugs for the same individual. Since ART is a life-long treatment, the key challenges that currently need to be overcome are the improvement of QoL by reducing the ‘pill burden’, while guaranteeing the efficacy in viral suppression and as few adverse effects as possible, and reducing drug-drug interactions (DDIs) with other medications. Over the past years, the concept of single-tablet regimen (STR) was developed for this exact reason by creating pills containing two or more antivirals (1,2).

Current ART recommendations include treatment based on two or more antiretrovirals. For individuals who do not have a history of using long-acting cabotegravir (CAB) as pre-exposure prophylaxis, ART can be initiated with bicitegravir (BIC)/emtricitabine/tenofovir alafenamide (B/F/TAF), dolutegravir (DTG) plus emtricitabine or lamivudine (FTC or 3TC) plus tenofovir alafenamide (TAF) or tenofovir disoproxil or a two-drug-based regimen (2DR) with DTG/3TC (3,4).

The most commonly used regimens, particularly in Western countries, are three-drug regimens (3DRs) based on integrase strand transfer inhibitor (INSTI) plus two nucleoside reverse transcriptase inhibitors (NRTIs). Since 2007, five INSTIs have been introduced: Raltegravir (RAL), elvitegravir (EVG), DTG, BIC and CAB. Since their introduction, INSTIs have exhibited good pharmacodynamics and pharmacokinetics, granting optimal efficacy with a limited number of DDIs (5-8).

However, the efficacy of INSTIs was the critical aspect that allowed their use in naïve and experienced patients worldwide. INSTIs have been proven to have a high genetic barrier, often surpassing that of other classes of ART and, therefore, only a

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Abbreviations: HIV, human immunodeficiency virus; ART, antiretroviral therapy; PLWH, people living with HIV; DDI, drug-drug interaction; B/F/TAF, bicitegravir/emtricitabine/tenofovir alafenamide; INSTI, integrase strand transfer inhibitor; BIC, bicitegravir; RAMs, resistance-associated mutations; 3DR, three-drug regimen; STR, single-tablet regimen

Key words: HIV, bicitegravir, low-level viraemia, INSTI, lipid profile

limited number of cases of mutations have been associated with resistance to INSTIs (9-11). Second-generation INSTIs were developed with the aim of overcoming resistance-associated mutations (RAMs), which occurred in clinical practice with first-generation INSTIs (RAL and EVG), since both of these agents have a high level of cross-resistance. The second-generation INSTIs, DTG, BIC and CAB, have less cross-resistance with first generation INSTIs, with DTG and BIC retaining the highest potency overall (12).

Thus far, DTG and BIC have been found to have the highest genetic barrier, not only among INSTIs, but also among other classes of antiretrovirals, along with other molecules (13). Nevertheless, all INSTIs have been proven to have, *in vivo* and *in vitro*, a rapid and sustained action against HIV replication (14).

B/F/TAF is a three-drug co-formulation consisting of BIC, FTC and TAF. BIC is a potent unboosted INSTI that is formulated for once-daily administration with a high barrier to resistance and is available only in combined formulation with FTC and TAF with the commercial name of Biktarvy®. It was first approved in the USA, Australia and the European Union in 2018, and in the United Kingdom and New Zealand in 2019. Since its approval, it has exhibited notable efficacy, a limited number of adverse reactions and overall, has been well-received by PLWH, particularly due to the smaller size of the pill compared to that of other regimens (15-18). BIC has also been proven to be non-inferior in terms of efficacy, genetic barrier and safety, compared to other INSTIs. Previous studies were specifically conducted in comparison to compare this drug to dolutegravir (19-21). Previous studies have also proven the safe use of BIC in pregnant women, as it persists at levels indicative of efficacious exposure without affecting the foetus (22,23).

Thus far, BIC has exhibited a sustained reconstitution of the immune system: In previous studies, an improvement in the CD4⁺ count has been observed in both naïve and experienced patients (17,24,25). However, despite their efficacy and tolerability, INSTIs have also been reportedly associated with an increased risk of developing cardiovascular events and weight gain; the mechanisms behind the increased cardiovascular risk are hyperglycaemia, hypertension and metabolic syndrome. Among the INSTIs, DTG appears to be the one associated with a higher risk. Women and people of colour appear to be the most at risk, and the accompanying nucleoside reverse transcriptase inhibitor may play a role (26-28).

Of note, the RESPOND cohorts brought to light the role of not only INSTIs, but also that of TAF in weight gain in PLWH. In a cohort of 35,941 RESPOND participants, hypertension and dyslipidaemia were more common in individuals receiving an INSTI with and without TAF, rather than other ART regimens (29). Still, the role of INSTIs in the development of cardiovascular events remains controversial. Despite the evidence reporting a significant role in increasing the risk, there are a number of other cases with a more neutral position. In fact, numerous factors may contribute to increasing the cardiovascular risk, primarily the aforementioned ageing of PLWH, which leads to several comorbidities, such as diabetes, hypertension, cancer, arthropathies and, in many cases, obesity. Moreover, HIV infection itself, by increasing inflammation, contributes to the increased risk of developing cardiovascular events (30-32).

Moreover, not every INSTI is associated with the same risk of developing cardiovascular events. While in many studies BIC has shown an unfavourable profile for cardiovascular risk, in others, DTG and other INSTIs appear to have the worst lipid profile. In addition, there appears to be a difference between whether INSTIs have been commenced or switched from other INSTI-free regimens in naïve patients (31). Therefore, while BIC is considered one of the potential causes in increased cardiovascular risk and weight gain along with other INSTIs, other concomitant factors have to be included, like age, sex, previous cardiovascular events, comorbidities, other medications and previous regimens with related risks in PLWH who switched to B/F/TAF (34,35).

Over the past few years, there have been a number of debates on the efficacy of a 3DR vs. a two-drug regimen (2DRs). The efficacy of 2DRs has been confirmed in previous studies; however, uncertainties persist, particularly concerning the viral reservoir and the effectiveness of 2DRs in reducing it (36-40). However, it should be noted that reliance on two drugs, in certain conditions, is made possible by the unprecedented potency of INSTIs, whose rapid action reduces the duration of the time of exposure of both the INSTI itself and the companion drug (NRTI or NNRTI) to high numbers of virions, therefore proportionally limiting the risk of RAMs.

3DRs also usually guarantee a major forgiveness, when compared to 2DRs. Forgiveness indicates the time elapsing between the time of termination of ART and the emergence of a measurable viral load. It is closely connected to the time of persistence of inhibitory concentrations of the medications following the interruption of treatment intake.

Among the three drugs composing B/F/TAF, BIC appears to have the shortest half-life (T/2) and, therefore, the first to be cleared from blood, while TAF appears to have the longest. Thus, the formulation with three drugs has a protective effect against the onset of RAMs to BIC (39). However, previous studies have reported the onset of INSTI-related RAMs. The emergence of drug-resistance in HIV has been a matter of concern, particularly in a world dominated by the use of INSTIs (42,43). Moreover, there is a disproportion depending on the country with a major risk for RAMs in countries where drug availability is not as vast as it is in high-income countries, which regrettably occurs for HIV and other life-threatening illnesses (44).

The introduction of injectable antiretrovirals has revolutionized HIV treatment, particularly in terms of forgiveness and tolerability. To date, only the two-drug therapy with injectable long-acting CAB and rilpivirine is available, which has to be administered bi-monthly. However, this type of therapy is possible only in selected cases. Co-infection with hepatitis B virus (HBV), a higher body mass index (BMI), intolerance towards injections and naïve patients are some of the conditions in which injectable long-acting ART is not applicable. Therefore, oral 3DR remains a valuable and vastly used option for the treatment of HIV, particularly in naïve patients.

The present study analysed the safety and efficacy of treatment with B/F/TAF, the lipid profile and the immunological response in 2 years of observation. It is considered that, although the role and efficacy of INSTIs have been vastly discussed, there are a limited number of real-life studies focusing on B/F/TAF and its effects on cardiovascular risk.

Materials and methods

Study design. The present study was a retrospective observational study conducted at the Infectious Diseases Unit of the 'Gaetano Martino' Hospital (affiliated with the University of Messina) in Messina, Italy. Data were collected over a 2-year period, beginning on January 1, 2021. The study included PLWH who were either initiating B/F/TAF as first-line ART (ART-naïve individuals) or switching to B/F/TAF from a different ART regimen (treatment-experienced individuals).

Inclusion and exclusion criteria. The inclusion criteria were as follows: An age ≥ 18 years, the ability to provide written informed consent, patients of any sex, and those who were currently on or had initiated on B/F/TAF therapy during the study period. The following exclusion criteria were used: An age < 18 years, the inability or refusal to provide written informed consent and patients on an ART regimen other than B/F/TAF.

Ethics approval. The SHiNe-SHiC project adheres to ethical standards consistent with the Declaration of Helsinki. The relevant ethics committee approved the study. All participants provided written informed consent to partake in the study. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Provincial Ethics Committee of Messina (SHiCohort-protocol code 34/17 of March 22, 2017; date of approval, May 22, 2017). Data collection and management were conducted strictly with privacy laws and regulations, including the European Union General Data Protection Regulation (GDPR). Patient data were anonymized and securely stored to ensure confidentiality and data integrity.

Data collection. The following demographic and clinical data were collected: sex assigned at birth, age (calculated at the end of follow-up), and comorbidities including cardiovascular disease, hypertension, diabetes mellitus, obesity, neuropsychiatric disorders and HBV co-infection. The smoking status was also recorded. HIV-related data at diagnosis included the following: The age of the patients at the time of HIV diagnosis, baseline HIV-RNA (viral load), nadir CD4⁺ T-cell count, the availability of genotypic resistance testing (GRT), previous ART regimen (if applicable) and the reasons for switching therapy. Clinical and laboratory data were collected at three time points, spaced by at least 6 months, as follows: Time 0, baseline (first blood draw after initiating or switching to B/F/TAF); time 1, ≥ 6 months after time 0; and time 2, ≥ 6 months after time 1.

The laboratory parameters collected at each time point included the following: HIV-RNA (copies/ml, determined using RT-PCR); CD4⁺ and CD8⁺ T-cell counts and percentages (cells/mm³); CD4⁺/CD8⁺ ratio; total lymphocyte and white blood cell count (cells/mm³); alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT); serum creatinine (mg/dl); lipid profile: Total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (mg/dl); body weight (kg). All blood samples were collected following an overnight fast.

Study endpoints. The primary endpoint of the study was to evaluate virological effectiveness, defined as maintaining a viral load < 200 cps/ml, immunological effects and the safety of therapy with B/F/TAF in naïve and experienced patients. The secondary endpoint was to evaluate the effects of treatment on renal function, liver function, lipid profiles and weight in patients treated with B/F/TAF.

Statistical analyses. Statistical analyses were performed using STATA 18 software (<https://www.stata.com/stata18/>). Descriptive comparisons between treatment-naïve and treatment-experienced individuals were performed using Fisher's exact test. One-way ANOVA followed by post hoc Tukey's test were used to evaluate within-group changes across time points. Between-group comparisons over time were conducted using linear mixed-effects models with fixed effects. To adjust for baseline differences, the mixed models included age, sex, baseline CD4⁺ count, and baseline HIV-RNA as covariates. These variables were chosen based on their known relevance in influencing ART response. Concomitant medications were not systematically recorded and thus were not included in the models. Missing data were minimal and limited to baseline HIV-RNA or GRT in a small subset of patients. These cases were excluded only from the specific analyses requiring those variables. No missing data were observed in longitudinal assessments across the three timepoints. The study was conducted under the hypothesis that B/F/TAF provides sustained virological suppression and immunological benefit in both ART-naïve and ART-experienced individuals, with a favourable safety profile and low incidence of adverse events. A P-value < 0.05 was considered to indicate a statistically significant difference.

Results

Demographic data and comorbidities. The demographic data and comorbidities of the patients are reported in Table I. The study population comprised of a total of 38 participants. The vast majority of the patients were male (29 males vs. 9 females), accounting for a percentage of 76.3% of the entire population. Among the naïve patients, 9 out of 10 were males (90%); among the experienced participants, 20 out of 28 were males (71.4%).

The majority of the patients (36 out of 38) were Caucasian; all of the treatment-naïve and 26 out of the 28 treatment-experienced participants were Caucasian; only 2 of the treatment-experienced patients were of African origin.

The mean age of the participants was 46 (SD14) years, with a median of 44.5 years; the highest value was 76 years of age and the lowest 24 years of age. For the naïve participants, the mean age was 47.2 (SS 17) years and the oldest patient was 76 years of age; for the experienced patients, the mean age was 45.7 (SD 12.9) years.

By examining comorbidities, the following data were obtained: Only 1 patient out of the 38 patients had diabetes (2.6% of the population) and was naïve to previous ART. Hypertension was reported by 10 patients (26.3% of the population), mostly belonging to the experienced-participant group, as 6 of these patients (21.4%) had received previous treatment and 4 patients (40% of the naïve group) had not.

Table I. Patient demographic data and comorbidities.

Parameter	PLWH			P-value
	Total (n=38)	Naïve (n=10)	Experienced (n=28)	
Age (years)	46±14	47.2±17	45.7±12.9	0.773
Sex, n (%)				0.396
Female	9 (23.7%)	1 (10%)	8 (58.6%)	
Male	29 (76.3%)	9 (90%)	20 (71.4%)	
Race, n (%)				0.538
Caucasian	36 (94.7%)	10 (100%)	26 (92.8%)	
African	2 (5.2%)	0	2 (7.1%)	
Diabetes, n (%)				0.263
Without diabetes	37 (97.4%)	9 (90%)	28 (100.0%)	
With diabetes	1 (2.6%)	1 (10%)	0	
Hypertension, n (%)				0.404
Without hypertension	28 (73.7%)	6 (60%)	22 (78.6%)	
With hypertension	10 (26.3%)	4 (40%)	6 (21.4%)	
Cardiovascular diseases, n (%)				0.279
Without cardiovascular diseases	34 (89.5%)	8 (80%)	26 (92.9%)	
With cardiovascular diseases	4 (10.5%)	2 (20%)	2 (7.1%)	
Neuropsychiatric disorders, n (%)				0.592
Without neuropsychiatric disorders	33 (86.8%)	8 (80%)	26 (92.9%)	
With neuropsychiatric disorders	5 (13.2%)	2 (20%)	3 (10.7%)	
Dyslipidaemia, n (%)				0.441
Without dyslipidaemia	30 (79%)	7 (70%)	23 (82.1%)	
With dyslipidaemia	8 (21%)	3 (30%)	5 (17.9%)	
Obesity, n (%)				0.453
Without obesity	26 (68.4%)	8 (80%)	18 (64.3%)	
With obesity	12 (31.6%)	2 (20%)	10 (35.7%)	
Smoking status, n (%)				0.263
Not smokers	13 (34.2%)	5 (50%)	8 (28.6%)	
Smokers	25 (65.8%)	5 (50%)	20 (71.4%)	
HBV coinfection, n (%)				0.298
Without HBV coinfection	33 (86.8%)	10 (100%)	23 (82.1%)	
With HBV coinfection	5 (13.2%)	0	5 (17.9%)	
AIDS-defining disease at diagnosis				0.082
Without AIDS-defining disease	30 (78.9%)	10 (100%)	20 (71.4%)	
With AIDS-defining disease	8 (21%)	0	8 (28.5%)	
Kaposi sarcoma			4 (50%)	
Leishmaniasis			2 (25%)	
Neurotoxoplasmosis			1 (12.5%)	
Pneumocystis jirovecii pneumonia			1 (12.5%)	
Years from diagnosis, media	8.1 (n=28; 10 missing data)	1.8	11.3 (n=18; 10 missing data)	<0.00001

PLWH, people living with HIV; HBV, hepatitis B virus.

Cardiovascular diseases, such as heart failure, previous cardiovascular events or arrhythmias accounted for 10.5% (4 patients) of the population, with an equal distribution between the two groups, namely 2 patients in the naïve-patient group (20%) and 2 patients in the experienced-participant

group (7.1%). Neuropsychiatric disorders (mainly depression, anxiety, psychotic disorders) were present in 5 patients in the whole population, which accounted for 13.1%, namely 3 patients in the experienced-patient group (10.7%) and 2 (20%) patients in the naïve-patient group. Dyslipidaemia

Table II. Viro-immunological status at the time of diagnosis.

Parameter	Mean	Lowest	Highest	Missing data
Viral load (cps/ml)	(n=16) 155,000 (SD 658,232)	5,600	2,300.000	16
CD4 ⁺ count (mmc)	(n=19) 256	10.6	631	9

SD, standard deviation.

Table III. Genotypic resistance test (GRT) data.

Resistance	Positive (n=6)	Negative (n=16)	Missing data (n=16)
Resistance to INSTIs	1 (potential low-level)		
Resistance to PIs	2		
Resistance to NNRTIs	3		

GRT, genotypic resistance test; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

was found in 8 (21%) patients out of the 38 patients, with 5 (17.9%) patients belonging to the experienced-participant group and 3 (30%) patients belonging to the naïve-participant group; only 3 of the patients reported the occasional use of statins, but mostly discontinued it. Obesity, defined as a BMI >30, as per the WHO definition, was found in 31.6% of the population (12 patients), with 10 patients belonging to the experienced PLWH group (35.7%) and 2 (20%) patients belonging to the naïve-patient group. Of note, 65.8% (25 out of 38 patients) were active smokers, with 20 of them belonging to the experienced-patient group (71.4% of 28) and 5 patients belonging to the naïve-patient group (50%). HBV co-infection was found in 13.2% of the population (5 patients), belonging to the experienced-patient group only. When evaluating the years passed from the moment when HIV was diagnosed in the patients, in 10 cases, it was not possible to date back to the moment of the diagnosis, since patients came from other centres and/or did not remember nor did have documentation of that period. Of the 28 patients for which the date of diagnosis was available, the mean number of years since the time of diagnosis was calculated, with a total of 8.1 years for the general population, 1.8 years for the naïve participants and 11.3 years for the experienced participants.

Data at the time of diagnosis of HIV infection and GRT. The viro-immunological status of the patients at the time of diagnosis is reported in Table II. Data were collected data at the time of HIV diagnosis for the majority of the study population. Missing data mostly belonged to refugees and patients coming from low-income countries who had had an earlier diagnosis and carried no documents, or patients who were diagnosed in other centres and were not able to recover such data nor did they remember them. The HIV viral load was analysed at the time of diagnosis for 16 participants and the mean value of

the viral load was calculated at baseline (155,000 cps/ml; SD 658,232), with the lowest value being 5,600 cps/ml and the highest 2,300.000 cps/ml.

Data regarding CD4⁺ count (/mmc) at nadir were also collected. The authors were able to obtain data from 19 patients. The mean value was calculated (256/mmc), with a minimum of 10.6/mmc and a maximum 631/mmc.

Of note, 8 patients out of the 38 presented at diagnosis with an AIDS-defining disease: There were 4 cases of Kaposi sarcoma, 2 cases of leishmaniasis, 1 case of neurotoxoplasmosis and 1 case of pneumocystis jirovecii pneumonia. However, 5 patients were not able to remember nor report whether there was an AIDS-defining disease at the time of diagnosis (Table I).

Data on GRT performed at the time of diagnosis was recovered for 22 cases. The authors were not able to recover data on GRT in the remaining 16 cases. The present study analysed GRT performed at the time of diagnosis and the following results were obtained: In 1 case, there was a potential low-level resistance to raltegravir and elvitegravir (accessory mutation found E157Q); there were 3 cases of major resistance to NNRTIs and 2 cases of major resistance to protease inhibitors (Table III).

Previous ART regimens in experienced patients and the reasons behind the switch in treatment. In the present study population, 10 patients were commenced on B/F/TAF at the time of diagnosis, while 28 patients had received previous treatments. The authors evaluated the final treatment before the switch with the following results: A total of 23 participants were on ART with three antiretrovirals (60.5%); 3 patients were on a four-drug therapy (7.9%) and 2 patients were on 2DR (5.3%). Of note, 20 participants (71.4%) had an INSTI-based therapy, 4 (14.3%) patients were on a PI-based ART and 4 (14.3%) patients were on NNRTI-based treatments.

Table IV. Distribution of previous ART regimen for experienced participants, divided by the number of drugs (columns) and main class of ART (lines).

Regimen	2DR (n=2)	3DR (n=23) (%)	4DR (n=3)
INSTI-based	1 (50%)	16 (69.5)	3 (100%)
PI-based	0	4 (17.3)	0
NNRTI-based	1 (50%)	3 (13)	0

ART, antiretroviral therapy; 2DR, two-drug regimen; 3DR, three-drug regimen; 4DR, four-drug regimen; INSTI, integrase strand transfer inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

Among the 3DRs, 16 were INSTI-based (69.5%), four were PI-based (17.3%) and three (13%) were NNRTI-based. Among the 2DRs, one was INSTI-based and one NNRTI-based. The three 4DRs were all INSTI-based. The distribution of the therapies divided by the class of ART and the number of drugs present in the treatment is reported in Table IV.

The majority of the treatments, both switches and first-line therapy, were commenced in 2021 (47.4%, n=18), while the others were divided between 2022 (23.7%, n=9) and 2023 (23.7%, n=9). Only two switches dated back to 2020 (5.3%). The number of switches per year are reported in Table V.

The present study also analysed the reasons behind the switch: The main reasons patients switched to B/F/TAF were to pass to a STR (n=11, 39.3% of 28) and simplification (n=9, 32.1% of 28); four switches (14.3% of 28) were performed due to the toxicity of the previous regimen and three due to the virological failure of the previous treatment (10.7% of 28). No switches were made due to DDIs (Table V).

Analyses at times 0, 1 and 2 in naïve patients. The results of the analysis of the naïve PLWH are reported in Table VI. There were no missing data at the three blood checks for the naïve participants. Data were analysed from T0 and T1 and T2 vs. T0 for both the naïve and experienced patients. There were no statistically significant differences at the three times for the naïve patients for the HIV viral load (P-value 0.134).

Of note, an improvement was observed in terms of immunological reconstitution, with an increase in the lymphocyte CD4⁺ count from T0 to T1 (mean CD4⁺ elevation, +136/mmc, P-value 0.011) and T2 vs. T0 (mean CD4⁺ elevation, +207/mmc, P-value ≤0.001) and an increase in the CD4 percentage as well (T1 vs. T0: mean CD4⁺% elevation, +8%, P-value ≤0.001; T2 vs. T0: mean CD4⁺% elevation, +9%, P-value ≤0.001); there was also a statistically significant improvement in the lymphocyte CD8⁺ percentage (T1 vs. T0: mean CD8⁺%, -12%, P-value ≤0.001; T2 vs. T0: mean CD8⁺% decrease, -16%, P-value ≤0.001). These results demonstrated a statistically significant improvement in the CD4⁺/CD8⁺ ratio from T0 to T1 (mean CD4⁺/CD8⁺ elevation, +0.34, P-value 0.022) and T2 vs. T0 (mean CD4⁺/CD8⁺ elevation, +0.41, P-value 0.006).

There were no marked differences in the three time points for the hepatic profile (AST, ALT and GGT). In the first part

of the study, from T0 to T1, there were no modifications in creatinine, while a statistically significant increase was found in T2 vs. T0 (mean creatinine elevation, +0.15 mg/dl, P-value 0.031).

As regards the lipid profile, no significant differences were found for total cholesterol and HDL cholesterol at T1 vs. T0 and T2 vs. T0. However, an increase was observed for LDL cholesterol at T2 vs. T0 (mean LDL elevation, +17 mg/dl, P-value 0.043). A significant improvement was observed for triglycerides (mean triglyceride decrease, -92 mg/dl, P-value 0.024) from T0 to T1, whereas no significant differences were found at T2 vs. T0. At the third timepoint, an increase in weight was observed (T2 vs. T0: mean weight increase, +6 kg, P-value 0.003).

Analyses at times 0, 1 and 2 in experienced patients. The results for experienced participants are reported in Table VII. There were no missing data at the three blood checks for the experienced participants. In the analyses on the experienced participants (n=28) performed at the three blood checks for the observational period, no significant differences were found for the viral load (cps/ml), liver markers, creatinine, lipid asset or in CD4⁺ and CD8⁺ both count and percentage in both T1 vs. T0 and T2 vs. T0.

Viro-immunological efficacy and lipid profiles in naïve vs. experienced patients. The data obtained for both naïve and experienced participants are presented in Table VIII. Starting therapy with B/F/TAF in naïve patients resulted in a more pronounced immunological response compared to the experienced patients. Specifically, the CD4⁺ lymphocyte count (mmc), CD4⁺ percentage, CD8⁺ percentage and the CD4⁺/CD8⁺ ratio exhibited significantly greater changes over time in the naïve participants, indicating a stronger immunological improvement in this group.

Similarly, for certain metabolic parameters, the temporal evolution differed significantly between groups. For example, HDL cholesterol exhibited a statistically significant difference in the change from T0 to T1 between the naïve and experienced participants (mean HDL elevation, +4 mg/dl at T1 vs. T0; P-value 0.05), suggesting that naïve participants experienced a more favourable response. The triglyceride levels also decreased more markedly in the naïve group compared to the experienced group (mean decrease, -92 mg/dl at T1 vs. T0 and -59 mg/dl at T2 vs. T0), as indicated by statistically significant differences in the magnitude of change over time between groups. It should be noted that these P-values reflect whether the change over time in each parameter differs significantly between the two groups. They do not represent within-group comparisons, but rather test the interaction between time and group. No significant differences in change over time were observed between groups for creatinine and weight.

Key findings in both populations. In the naïve participants, an improvement was observed in the CD8⁺ count and percentage, CD4⁺ count and percentage and CD4⁺/CD8⁺ ratio, demonstrating that B/F/TAF was more effective in naïve patients as regards immunological response. An increase in weight was observed only in the naïve group, which could also be seen as an improvement in general health in some cases.

Table V. Start of B/F/TAF per year and reason behind the switch for experienced participants.

Start of B/F/TAF (n=38)	Year			
	2020	2021	2022	2023
No. of participants (%)	2 (5.3%)	18 (47.4%)	9 (23.7%)	9 (23.7%)

Experienced participants (n=28)	Reason behind the switch			
	STR	Simplification	Toxicity	Virological failure
No. of participants (%)	11 (39.3%)	9 (32.1%)	4 (14.3%)	3 (10.7%)

STR, single-tablet regimen.

Table VI. Analysis in naïve patients at T0, T1 and T2.

Parameter	Naïve patients (n=10), mean (SD)			P-value (T1 vs. T0)	P-value (T2 vs. T0)
	T0	T1	T2		
VL	152,148 (290,484)	44 (86)	26 (65)	0.134	0.134
CD4 ⁺ /mmc	284 (202)	420 (281)	491 (330)	0.011	≤0.001
CD4 ⁺ %	17 (12)	25 (15)	26 (15)	≤0.001	≤0.001
CD4/CD8	0.36 (0.33)	0.70 (0.70)	0.77 (0.76)	0.022	0.006
CD8 ⁺ /mmc	1120 (554)	868 (475)	849 (483)	0.100	0.073
CD8 ⁺ %	61 (14)	49 (16)	45 (16)	≤0.001	≤0.001
WC/mmc	4,675 (1406)	5,093 (14,91)	5,768 (1,434)	0.458	0.013
Lf/mmc	1,783 (699)	1,711 (684)	1,894 (675)	0.874	0.729
AST	26 (12)	29 (14)	27 (7)	0.595	0.979
ALT	25 (7)	28 (17)	27 (20)	0.859	0.916
Gamma-GT	20 (9)	28 (29)	24 (18)	0.440	0.799
creatinine	0.92 (0.29)	0.98 (0.23)	1.07 (0.18)	0.516	0.031
Total cholesterol	169 (39)	168 (39)	182 (40)	0.989	0.211
HDL	41 (15)	40 (12)	45 (9)	0.997	0.625
LDL	96 (26)	106 (28)	113 (22)	0.308	0.043
Triglycerides	214 (161)	122 (89)	159 (139)	0.024	0.222
Weight	76 (13)	80 (13)	82 (17)	0.085	0.003

Values in bold font indicate statistically significant differences. T0, baseline; T1, ≥6 months after T0; T2, ≥6 months after T1; VL, viral load; WC, white cells; Lf, lymphocytes; AST, aspartate aminotransferase; ALT, alanine-aminotransferase; gamma-GT, gamma-glutamyltransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

Discussion

Since being approved and introduced into clinical practice, therapy with B/F/TAF has proven to be a valuable option for HIV treatment. Males comprised the highest percentage of the population in the present study, which reflects not only the demographic of the authors' clinic in general, but also the prevalence in Italy and worldwide. The majority of the patients who switched to B/F/TAF originally had a regimen with multiple tablets per day, which explains why the majority of the

switches were made to achieve a STR, in accordance with the majority of the switches observed in previous studies (17,45).

Virological effectiveness. The largest proportion of the population who underwent a switch to B/F/TAF had a HIV viral load <50 copies/ml at the time of the switch. The therapy proved to be effective as there were no viral failures. However, in the study by Mendoza *et al* (20), a few virological failures were reported, the majority of which were in the treatment-experienced group instead of the treatment-naïve

Table VII. Analysis at T0, T1 and T2 in experienced patients.

Parameter	Experienced patients (n=28), mean (SD)			P-value (T1 vs. T0)	P-value (T2 vs. T0)
	T0	T1	T2		
VL	1,028 (3,823)	875 (3203)	43 (144)	0.969	0.574
CD4 ⁺ /mmc	713 (437)	689 (287)	648 (242)	0.966	0.585
CD4 %	32 (12)	32 (10)	32 (10)	0.995	0.394
CD4/CD8	0.90 (0.52)	0.84 (0.39)	0.88 (0.39)	0.866	0.825
CD8 ⁺ /mmc	1,075 (959)	879 (328)	762 (316)	0.218	0.138
CD8 ⁺ %	40 (11)	41 (10)	40 (9)	0.998	0.605
WC/mmc	8,431 (7,116)	6,460 (1,673)	6,098 (2,009)	0.204	0.119
Lf/mmc	2,162 (756)	2,139 (545)	2,021 (583)	0.990	0.384
AST	22 (10)	23 (8)	25 (10)	0.956	0.337
ALT	20 (9)	20 (10)	23 (13)	0.979	0.275
gammaGT	26 (18)	22 (9)	21 (8)	0.306	0.176
creatinine	0.92 (0.25)	0.93 (0.24)	0.95 (0.22)	0.928	0.960
Total cholesterol	188 (39)	184 (31)	187 (36)	0.711	0.983
HDL	48 (10)	47 (10)	47 (10)	0.457	0.639
LDL	116 (36)	116 (30)	122 (29)	0.991	0.721
Triglycerides	113 (50)	110 (54)	108 (54)	0.977	0.989
Weight	75 (14)	78 (16)	78 (16)	0.574	0.189

T0, baseline; T1, ≥6 months after T0; T2, ≥6 months after T1; VL, viral load; WC, white cells; Lf, lymphocytes; AST, aspartate aminotransferase; ALT, alanine-aminotransferase; gamma-GT, gamma-glutamyltransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

group. Similar results were obtained in naïve patients, with a prominent decrease in viral load following the commencement of B/F/TAF. As support of the evidence from other studies, a strong response to the start of B/F/TAF was observed in naïve patients in the present study, with a rapid reduction in viral load in the majority of the patients (17,19,20,25).

Nevertheless, in a number of cases, particularly regarding experienced patients, detectable viraemia was found at the three blood checks, mostly inferior to 500 copies/ml, but >50 copies/ml. Even though the efficacy of B/F/TAF was proven, the detectability of the HIV viral load, even if not statistically significant, has to be taken into account.

Low-level viraemia (LLV), as in viral load <1,000 copies/ml and >50 copies/ml, has been found to be associated with greater virological failure, viral genotype resistance, adherence difficulties and AIDS events. Moreover, there are data demonstrating that persistent LLV can lead to residual immune activation and inflammation, with an increased risk of virological failure and a pro-inflammatory cytokine level. LLV observed in a few cases may be attributable to various mechanisms, including archived drug-resistant mutations, intermittent adherence, or subtherapeutic drug levels due to pharmacokinetic variability. Additionally, persistent viral reservoirs in lymphoid tissues may contribute to transient viral blips. All these factors may contribute to an increased senescence. The threshold at which LLV becomes predictive of disease progression varies between studies (46-50).

In the study by Elvstam *et al* (50), LLV was shown to be associated with an increased mortality rate compared to

viro-suppression and it is also divided into two sub-groups: LLV of 50-199 and 200-999 copies/ml. In the same study, the clinical outcomes were different for the sub-groups: The 200-999 group was more at risk of developing severe non-AIDS events (48). To date, LLV remains an unsolved issue for clinicians and its role in the onset of RAMs, in senescence, inflammation and long-term effects is uncertain and controversial (51-55).

Immunological effectiveness. Supporting evidence in the literature (17,25), the present study also found a statistically significant improvement in the immunological status, in particular in the CD4⁺ count, CD4⁺ percentage and CD4⁺/CD8⁺ ratio, mostly in naïve patients rather than in experienced patients. These data are in agreement with data from the cohorts reported by in the studies by Tseng *et al* (25) and Esser *et al* (17), particularly as regards the improvement in the CD4⁺ count and CD4⁺/CD8⁺ ratio in treatment-naïve patients rather than in experienced patients.

Immune reconstitution, particularly in newly diagnosed patients, is a fundamental factor that contributes to the efficacy of ART, along with the effectiveness in reducing the viral load. A number of antiretrovirals have been associated with a strong immune reconstitution, such as NNRTI and PI. Among INSTI based regimens, the three-drug combination with B/F/TAF was shown to be associated with a more rapid CD4⁺ cell count recovery compared to other regimen in the OPERA cohort (56).

Renal impact. In the present study, renal function remained mostly unaltered during the observational period, even though

Table VIII. Comparison between naïve PLWH and experienced PLWH at times 0, 1 and 2.

	Experienced PLWH (n=28), median (SD)			Naïve PLWH (n=10), median (SD)			P-value (naïve vs. experienced PLWH for T1 vs. T0)	P-value (naïve vs. experienced PLWH for T2 vs. T0)
	T0	T1	T2	T0	T1	T2		
VL	152,148 (290,484)	44 (86)	26 (65)	1028 (3,823)	875 (3,203)	43 (144)	0.008	0.010
CD4 ⁺ /mmc	284 (202)	420 (281)	491 (330)	713 (437)	689 (287)	648 (242)	0.001	0.003
CD4 ⁺ %	17 (12)	25 (15)	26 (15)	32 (12)	32 (10)	32 (10)	0.008	0.008
CD4/CD8	0.36 (0.33)	0.70 (0.70)	0.77 (0.76)	0.90 (0.52)	0.84 (0.39)	0.88 (0.39)	0.016	0.002
CD8 ⁺ /mmc	1,120 (554)	868 (475)	849 (483)	1075 (959)	879 (328)	762 (316)	0.918	0.987
CD8 ⁺ %	61 (14)	49 (16)	45 (16)	40 (11)	41 (10)	40 (9)	≤0.001	0.001
WC/mmc	4675 (1,406)	5093 (1,491)	5768 (1,434)	8431 (7,116)	6460 (1,673)	6098 (2,009)	0.029	0.082
Lf/mmc	1,783 (699)	1,711 (684)	1,894 (675)	2,162 (756)	2,139 (545)	2,021 (583)	0.054	0.229
AST	26 (12)	29 (14)	27 (7)	22 (10)	23 (8)	25 (10)	0.109	0.345
ALT	25 (7)	28 (17)	27 (20)	20 (9)	20 (10)	23 (13)	0.031	0.082
gammaGT	20 (9)	28 (29)	24 (18)	26 (18)	22 (9)	21 (8)	0.957	0.799
Creatinine	0.92 (0.29)	0.98 (0.23)	1.07 (0.18)	0.92 (0.25)	0.93 (0.24)	0.95 (0.22)	0.698	0.391
Total cholesterol	169 (39)	168 (39)	182 (40)	188 (39)	184 (31)	187 (36)	0.137	0.325
HDL	41 (15)	40 (12)	45 (9)	48 (10)	47 (10)	47 (10)	0.050	0.185
LDL	96 (26)	106 (28)	113 (22)	116 (36)	116 (30)	122 (29)	0.141	0.152
Triglycerides	214 (161)	122 (89)	159 (139)	113 (50)	110 (54)	108 (54)	0.024	0.011
Weight	76 (13)	80 (13)	82 (17)	75 (14)	78 (16)	78 (16)	0.959	0.918

Values in bold font indicate statistically significant differences. PLWH, people living with HIV; T0, baseline; T1, ≥6 months after T0; T2, ≥6 months after T1; VL, viral load; WC, white cells; Lf, lymphocytes; AST, aspartate aminotransferase; ALT, alanine-aminotransferase; gamma-GT, gamma-glutamyltransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation.

there was a statistically significant increase in creatinine levels in naïve participants at T2 vs. T0 (P-value 0.031).

Impact on lipid profiles and cardiovascular risk. In the present study, a worsening in lipid profiles in naïve participants was observed compared to the treatment-experienced participants. In particular, an increase in LDL cholesterol levels was observed. These data support the evidence from the study by Pérez-Barragán *et al* (34) and also the comparison between the lipid profile in patients in treatment with B/F/TAF vs. dolutegravir/abacavir/lamivudine in the study by Orkin *et al* (21). The worsening of the lipid profile that was observed may lead to an increased risk of developing cardiovascular events at 10 years, which would be consistent with the RESPOND cohort (29). The study by Rebeiro *et al* (57) also demonstrated an association with the onset of cardiovascular events in the first 2 years following exposure to INSTIs in treatment-naïve patients.

These results may bring once again the highlight the cardiovascular risk associated with INSTI-based regimens. As confirmed by the SCOLTA study, the risk of developing cardiovascular events first peaked 6 months following the initiation of INSTIs and gradually increased in the first 2 years from the start of therapy, then gradually dissipated, as compared to

non-INSTI-treated PLWH (31). The brief observational period of the present study did not allow for further investigation; a longer period of observation is necessary to confirm whereas there is a concrete risk. However, no significant increase in the cholesterol profile was found in the experienced PLWH who mostly switched from INSTI-based regimens. Therefore, it can be hypothesised that the increased risk of developing cardiovascular events can be observed only in the first 2 years since the commencement of an INSTI-based regime, consistently with the results of the SCOLTA study (31).

Moreover, pre-existent factors that could increase the risk of developing cardiovascular events should be taken into account. Diabetes, cardiovascular diseases, hypertension, obesity and dyslipidaemia also play a role in the occurrence of cardiovascular events. The present study was for the observation of the co-formulated ART with three antiretrovirals in a one-pill fixed dose; it should be considered that TAF and FTC may also play a role in the development of cardiovascular events; thus, bictegravir should be compared to other INSTIs to evaluate the real risk for this category of drugs. Of note, the literature reports a role of TAF in weight gaining and, therefore, it may increase the risk of developing cardiovascular events (26).

Table IX. Adverse effects.

Adverse effects	No. of participants (%)
Nausea	5 (13,1)
Insomnia	10 (26,3)

Studies have also linked INSTIs to an increased risk of developing diabetes mellitus and insulin resistance, although no significant connection has been proven in the general population, although such a connection has been observed in the African population (58).

Moreover, the present study observed an increase in weight gain in the naïve participants who reported a significant increase in weight immediately after the third blood check following the start of B/F/TAF (T2 vs. T0 P-value 0.003). These results are consistent with data from literature, as weight gain has been reported in treatment with INSTIs and the aforementioned TAF (26,34).

Although inflammatory markers, such as IL-6 or metabolic parameters, such as insulin-resistance indices were not included in the present study, they represent valuable tools for assessing systemic immune activation and metabolic complications in PLWH. Notably, INSTIs have also been connected to modifications in adipokines and inflammation markers and their production by affecting genes expression; BIC, in particular, has been shown to suppress gene expression and the release of pro-inflammatory cytokines in differentiating adipocytes (59). Future studies incorporating these biomarkers could provide further insight into the long-term effects of B/F/TAF on inflammation and cardiometabolic risk.

Based on the authors' experience, it is recommended that lipid and inflammatory markers are monitored every 6 months for at least 2 years from the start of B/F/TAF or other INSTI-based regimens, particularly in patients who have an increased risk of developing cardiovascular events, such as patients with pre-existing risk factors (diabetes, comorbidities, smoke, diet rich on fats, etc.).

Tolerability and adherence. During the 2-year observation period, no notable adverse effects were observed. In the first 3 months of observation, 5 patients reported nausea, although defined as mild; 10 patients reported difficulty sleeping, which normalized after a few months following the start of B/F/TAF. Adverse effects are reported in Table IX. No discontinuation of the therapy was needed or observed. Consistent with previous data from the literature, B/F/TAF exhibited a favourable safety profile (17,20).

The majority of the experienced patients, mostly coming from regimens with more than one tablet, reported an improvement in QoL and referred to the new regimen as 'easier' to adhere to, when interrogated about the differences with the previous therapy. Since the introduction of STR, a number of studies have in fact reported an improvement in adherence and tolerability in continuation of ART (60). Patient' comfort should be considered, as this guarantees an optimal compliance, thus reducing the opportunities for onset of RAMs when adherence is sub-optimal (61-64).

Therapy with B/F/TAF not only allowed a STR, but was in the form of tablets of smaller dimensions compared with other STRs. This critical aspect may have played a key role in improving PLWH adherence to therapy. A frequently overlooked issue is, in fact, eventual issues in swallowing drugs that patients may experience, particularly in cases with comorbidities that can lead to dysphagia. Consequently, dysphagia can lead to a sub-optimal adherence to therapy (65). The smaller dimension of B/F/TAF tablets may represent a notable improvement for those patients who report difficulties in swallowing, since, while smaller in dimension, B/F/TAF tablets do not need to be crushed in order to guarantee optimal efficacy (66).

Therefore, B/F/TAF has proven to be effective in maintaining an optimal viro-immunological effectiveness, contributing to PLWH adherence to therapy. The present study provides a perspective on the effects of B/F/TAF distinguishing between naïve and experienced patients. B/F/TAFI remains a rather new regimen in therapies for HIV. The present study aimed to address the lack of available data on the effects on the kidneys, cardiometabolic risk and weight gain in PLWH on B/F/TAF. Some cases of LLV were also observed, which is deemed of utmost importance and is rarely discussed in the literature on this regimen.

Limitations of the study. The present study had several limitations which should be acknowledged. The time of observation was brief and, although the study is still ongoing, the results may be partial due to the short time period and the limited blood checks. The population examined herein consisted of a very limited number of PLWH. The majority of the participants included in the present study were Caucasian and only two were of African origin; therefore, the population cannot be considered representative of all ethnic groups. Another limitation of the present study was the absence of detailed data on concomitant medications, which may influence treatment tolerability and/or immune response. While key baseline characteristics were adjusted for in the statistical models, unmeasured confounders cannot be entirely excluded.

In conclusion, the present study confirms the efficacy of the B/F/TAF treatment for a sustained immunological response. In particular, an improvement in the group of naïve participants was observed, namely in the CD4⁺ count (P-value 0.011 and P-value ≤0.001, respectively) and percentage (P-value ≤0.001) and CD8⁺ percentage (P-value ≤0.001) at both times of observation, which is in accordance with data from the literature (17,25,67).

However, some concerning cases of detectable viraemia (>50 cps/ml) were observed, even if its significance in the progression of disease has yet to be demonstrated. Moreover, therapy with B/F/TAF has exhibited an unfavourable effect on lipid profile and weight gain, particularly in naïve patients; that may be related to an increased risk of developing cardiovascular events, which may be linked to the use of INSTIs (30,33).

Notably, in consideration of the fact that the experienced participants mostly switched from a INSTI-based regimen and exhibited no significant worsening of the lipid profile, the present study contributes to previous literature that report an increased risk of developing cardiovascular events only in the first 2 years from the start of an INSTI-based regimen (31).

The present study proves that, despite being a three-drug INSTI-based regimen, B/F/TAF may not be as effective in maintaining undetectable viraemia and may also lead to an increased cardiovascular risk. Despite remaining a valuable option in both naïve and experienced participants, B/F/TAF should be considered carefully when starting or switching to highly active ART and further studies on this regimen are mandatory to prove its effectiveness.

On the whole, the findings of the present study may be of interest to both clinicians managing HIV care and researchers focused on antiretroviral treatment strategies, given the observed efficacy of B/F/TAF in both naïve and experienced individuals.

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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

YR, AGS, LS and GFP conceptualized the study. YR and LS was involved in the writing and preparation of the original draft of the proofs. EVR, LS and AGS were involved in the writing, reviewing and editing of the manuscript. EVR performed the statistical analyses. AGS and LS was involved in the creation of the tables. GFP supervised the study. All authors have read and agreed to the published version of the manuscript. YR, GFP and EVZ confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The SHiNe-SHiC project adheres to ethical standards consistent with the Declaration of Helsinki. The relevant ethics committee approved the study. 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 (SHiCohort-protocol code 34/17 of March 22, 2017; date of approval May 22, 2017). Data collection and management were conducted strictly with privacy laws and regulations, including the European Union General Data Protection Regulation (GDPR). Patient data were anonymized and securely stored to ensure confidentiality and data integrity.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have not competing interests.

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