Efficacia e sicurezza di B/F/TAF nelle persone con HIV naïve: dati real-life dal gruppo di ricerca SHiNeSHiC.

Efficacy and safety of B/F/TAF in naïve people with HIV: real life data from the SHiNeSHiC research group.

Giulia Moi[1], Andrea De Vito[1,2], Giuseppe Conti[3], Benedetto Maurizio Celesia[3], Serena Spampinato[3], Andrea Marino[3], Claudia Calì[4], Maria Antonietta Di Rosolini[4], Laura Corda[1], Giovanna Sanna[5], Goffredo Angioni[5], Giuseppe Nunnari[3], Giordano Madeddu[1].

[1] Unit of Infectious Disease, Department of Medicine, Surgery and Pharmacy, University of Sassari, 07100 Sassari, Italy
[2] PhD School in Biomedical Science, Biomedical Science Department, University of Sassari, 07100 Sassari, Italy
[3] Department of Clinical and Experimental Medicine, University of Catania, 95123 Catania, Italy
[4] Infectious and Tropical Diseases Unit, Modica Hospital, I-97015 Ragusa, Italy
[5] Infectious Diseases Unit, SS Trinità Hospital, Cagliari, Italy

Corresponding Author:

Andrea De Vito
Unit of Infectious Disease, Department of Medicine, Surgery and Pharmacy, Sassari, Italy

andreadevitoaho@gmail.com

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Riassunto

La combinazione di bictegravir/emtricitabina/tenofovir alafenamide (B/F/TAF) è un regime antiretrovirale in un'unica compressa con una elevata barriera genetica, un'ottima tollerabilità e poche interazioni farmacologiche. Trial clinici hanno dimostrato la sua efficacia e sicurezza sia come regime di prima linea sia come regime di switch nelle persone che vivo con HIV (PWH). Questo studio indaga l'efficacia e la sicurezza di B/F/TAF come primo regime terapeutico nelle PWH. È stata condotta un'analisi osservazionale retrospettiva multicentrica utilizzando i dati del gruppo di ricerca SHiNe-SHiC, che raccoglie dati da quattro centri in Sardegna e Sicilia, Italia. Lo studio ha incluso tutte le PWH che hanno iniziato B/F/TAF come loro primo trattamento antiretrovirale. Sono stati raccolti dati demografici, clinici, viro-immunologici e biochimici al basale, a 6 e a 12 mesi. Cambiamenti significativi in questi momenti sono stati identificati usando il test di Wilcoxon.

In totale sono state incluse 159 PWH naive, con un'età mediana di 42,3 anni (IQR 33,5-52,5). La maggior parte erano maschi (79,9%), con il 18,9% di femmine cisgender e l'1,2% di femmine transgender. Il principale fattore di rischio era essere MSM (58,5%), seguito da eterosessuali (37,7%) e IDU (3,7%). Alla diagnosi, il 57,2% aveva una conta di CD4 <350 celle/mL, mentre il 30,8% aveva <200 celle/mL e l'11,9% aveva una patologia AIDS-relata.

A 6 mesi, il 79,8% aveva l'HIV-RNA inferiore a 50 copie/mL e il 99,2% inferiore 200 copie/mL. A 12 mesi, la percentuale con HIV-RNA inferiore a 50 copie saliva all'87,6%. Dopo l'inizio della terapia si è assistito ad un aumento significativo della

Abstract

The combination of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) is a single-tablet antiretroviral regimen with a high genetic barrier, favorable tolerability, and few drug interactions. It has shown to be effective and safe treatment for both naïve and experienced people with HIV (PWH) in clinical trials. This study investigates the real-life effectiveness and safety of B/F/TAF in naive PWH. We conducted a multicenter retrospective observational analysis using data from the SHiNe-SHiC research group, which collects data from four centers in Sardinia and Sicily, Italy. The study included all PWH who started B/F/TAF as their first antiretroviral treatment. Demographical, clinical, viro-immunological, and biochemical data were collected at baseline, 6 months, and 12 months. Significant changes across these time points were identified using the Wilcoxon rank-sum test, with a p-value of <0.05.

A total of 159 naive PWH were included, with a median age of 42.3 years (IQR 33.5-52.5). The majority were male (79.9%), with 18.9% cis females and 1.2% transgender females. The main risk factor was being MSM (58.5%), followed by heterosexuals (37.7%) and IDU (3.7%). At diagnosis, 57.2% had CD4 counts <350 cells/mL, 30.8% had <200 cells/mL, and 11.9% had AIDS-defining conditions. At 6 months, 79.8% had HIV RNA <50 copies/mL, and 99.2% had <200 copies/mL. At 12 months, 87.6% had HIV RNA <50 copies/mL, and 98.9% had <200 copies/mL. Median CD4 cells/mL and

conta di CD4 e del rapporto CD4/CD8. Si è inoltre osservata una riduzione dell'indici di necrosi epatica ed un aumento della creatinina a 6 mesi, per poi stabilizzarsi al controllo a 12 mesi. Per quanto riguarda il profilo lipidico, i livelli di colesterolo totale e LDL sono aumentati, ma con un rapporto colesterolo totale/HDL invariato. Diciotto (11,3%) PWH hanno interrotto B/F/TAF, di cui solo 3 per tossicità.
Il nostro studio dimostra la grande efficacia del B/F/TAF nelle PWH naive, indipendentemente dal carico virale all'inizio del trattamento; la tollerabilità del regime è ulteriormente evidenziata dai minimi effetti avversi che hanno necessitato di interruzione, sottolineando la sua idoneità come terapia di prima linea.

CD4/CD8 ratio increased significantly. Transaminase levels decreased, while creatinine levels stabilized after an initial increase. Cholesterol and LDL levels increased modestly with an unchanged total cholesterol/HDL ratio. Eighteen (11.3%) PWH discontinued B/F/TAF. Our study demonstrates the great efficacy of B/F/TAF in naive PWH, regardless of the viral load at the treatment onset; the regimen's tolerability is further highlighted by the minimal adverse effects that necessitated discontinuation, underscoring its suitability as a first-line therapy.

Introduction

The advent of antiretroviral therapy (ART) has significantly transformed HIV infection in a manageable chronic condition (1). Over the past few decades, the development of various ART regimens has provided people with HIV (PWH) the opportunity to achieve and maintain viral suppression, improve immune function, and enhance their quality of life. Among these regimens, the single-tablet combination of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) has emerged as a potent and favorable option for both treatment-naive and experienced PWH (2–4).
Bictegravir (BIC) is an integrase strand transfer inhibitor (INSTI) that offers a high genetic barrier to resistance, making it an effective option in HIV treatment. Emtricitabine (FTC) and tenofovir alafenamide (TAF) are nucleoside reverse transcriptase inhibitors (NRTIs) that work synergistically with BIC to inhibit viral replication(5). This combination not only provides robust antiviral activity but also boasts a favorable safety profile and minimal drug-drug interactions, which are critical factors in long-term HIV management(5).
The clinical efficacy of B/F/TAF has been well-documented in randomized controlled trials (RCTs)(2–4). Studies have demonstrated that this regimen achieves high rates of viral suppression and is well-tolerated among diverse populations, including those with varying degrees of baseline viral load and CD4 cell count. These trials have shown that B/F/TAF can rapidly reduce HIV RNA levels to undetectable thresholds and maintain these levels over extended periods, with a low incidence of adverse events leading to discontinuation.
Despite the promising results from clinical trials, real-world evidence is crucial to understanding the effectiveness and safety of B/F/TAF in broader, more heterogeneous populations. Clinical trial participants often represent a more controlled subset of the overall HIV population, excluding individuals with certain comorbidities or those who may not adhere strictly to treatment protocols(6). Real-world studies, on the other hand, encompass a wider range of patient demographics, health conditions, and behavioral patterns, providing a more comprehensive picture of how the regimen performs in everyday clinical practice.
This need for real-world evidence is particularly pertinent in regions like Sardinia and Sicily, Italy, where the demographics and healthcare access for PWH can differ significantly from those in other parts of the world. Understanding how B/F/TAF performs in these settings can help inform local treatment guidelines and optimize care strategies tailored to the specific needs of the population.
Furthermore, the evolving landscape of HIV treatment highlights the importance of continually assessing the long-term efficacy and safety of ART regimens. In addition to virological efficacy, the tolerability of ART regimens is a key factor influencing patient adherence and long-term treatment success. Adverse effects, even if mild, can significantly impact a patient's willingness to continue therapy, leading to suboptimal adherence and potential virological failure(7). Therefore, assessing the safety profile of B/F/TAF, including its effects on renal function, liver enzymes, and lipid levels, is essential for guiding clinical decision-making and improving patient outcomes.
Our study aims to address these critical gaps in knowledge by investigating the real-world effectiveness and safety of B/F/TAF among treatment naive PWH in Sardinia and Sicily.

Methods

We conducted a retrospective cohort study utilizing data from the Sardinian HIV Network and Sicilian HIV Cohort (SHiNe-SHiC) research group. The SHiNe-SHiC project, initiated in 2019, collects comprehensive data from people with HIV (PWH) at multiple infectious disease centers in Sardinia and Sicily, Italy. The study included all PWH enrolled in the SHiNe-SHiC database who started B/F/TAF as the first antiretroviral treatment.

The primary objective was to assess the efficacy of the B/F/TAF regimen in naive PWH, defined by achieving and maintaining an HIV RNA level of <50 copies/mL. The secondary objectives included evaluating the safety of the treatment, the durability of the regimen, and the reasons for any treatment discontinuation.

Data Collection

Data were extracted from the SHiNe-SHiC database, including demographic details, risk factors for HIV acquisition, viro-immunological data (such as CD4 cells count and HIV RNA copies/mL), lipid profiles, creatinine, transaminases, blood glucose, and information regarding treatment interruptions. This data collection allowed for a detailed analysis of the characteristics and outcomes of individuals on B/F/TAF regimen.

Statistical Analysis

Descriptive statistics summarized demographic and clinical characteristics. Quantitative variables were presented as medians with interquartile ranges (25th–75th percentiles) or means with standard deviations (SD), depending on the distribution normality. Qualitative variables were described using absolute and relative frequencies (percentages). The Shapiro-Wilk test assessed the normality of quantitative data.

We analyzed data at three time points: baseline, 6 months (± 1 month), and 12 months (± 1 month). Student T test and the Wilcoxon rank-sum test, after assessing distribution normality, were used to identify significant changes across these time points. A p-value of <0.05 was considered statistically significant.

Ethical Considerations

The SHiNe-SHiC project adheres to ethical standards consistent with the Declaration of Helsinki. The study was approved by the relevant ethics committee (Protocol no.). All participants provided written informed consent to partake in the study.

Data collection and management were conducted in strict compliance 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.

Results

A total of 159 treatment naive PWH were included in this study. The median age of the cohort was 42.3 (IQR 33.5-52.5) years. The majority of participants were cisgender male, accounting for 127 individuals (79.9%), while 30 participants were cisgender females (18.9%), and 2 participants were transgender females (1.2%).

The primary risk factor for HIV acquisition in this cohort was men who have sex with men (MSM), comprising 58.5% of the population. Heterosexual transmission was the second most common risk factor, accounting for 37.7% of the cases, followed by injection drug use (IDU), which represented 3.7% of the participants.

Regarding immunological status at diagnosis, 91 (57.2%) participants had CD4 cell counts less than 350 cells/mL. Of these, 49 participants (30.8%) had CD4 counts below 200 cells/mL, and 19 participants (11.9%) presented with AIDS-defining conditions at the time of diagnosis. These baseline characteristics are summarized in **Table 1**.

Efficacy

At the 6-month, 107 out of 134 participants (79.8%) achieved an HIV RNA level of <50 copies/mL, indicating successful viral suppression. Additionally, 133 participants (99.2%) had HIV RNA levels below 200 copies/mL.

At the 12-month follow-up, 78 out of 89 participants (87.6%) maintained HIV RNA levels of <50 copies/mL, while 88 participants (98.9%) had HIV RNA levels below 200 copies/mL (**Figure 1**). This data illustrates the sustained efficacy of the B/F/TAF regimen over a year of treatment.

Of the 107 participants who achieved undetectable viral loads at 24 weeks, only 6 experienced a viral rebound at 48 weeks, indicating a robust and durable response to the therapy. Conversely, of the 26 participants who had HIV RNA levels >50 copies/mL at 24 weeks, 14 out of 18 (77.8%)

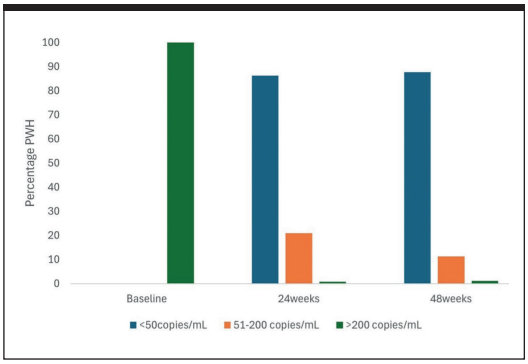

Figure 1. HIV-RNA copies/ml changes after 6 and 12 months of ARV therapy with BIC/TAF/FTC in 159 naïve people with HIV.

	Characteristics
Age (years), median (IQR)	42.3 (33.5-52.5)
Sex, n (%) Cisgender Male Cisgender Female Transgender Female	 127 (79.9) 30 (18.9) 2 (1.2)
Italian, n (%)	189 (87.4)
Risk factor for acquiring HIV, n (%) Heterosexual MSM IDU	 60 (37.7) 93 (58.5) 6 (3.8)
Smoke, n (%)	45 (28.3)
Alcohol, n (%)	41 (25.8)
Comorbidities, n (%) Hypertension Hypercholesterolemia Psychiatric disorders Diabetes	 25 (15.7) 20 (12.6) 14 (8.8) 11 (6.7)
HCV coinfection, n (%)	8 (5)
HBsAg positive, n (%)	3 (1.9)
Not ART drugs, n (%) 0 1 2 3 4 >4	 86 (54) 47 (29.5) 10 (6.3) 6 (3.8) 8 (5) 2 (1.2)
Zenith HIV-RNA (log_{10} copies/mL), median (IQR)	5.12 (4.35-5.60)
HIV-RNA > 100'000 copies/mL	91 (57.2)
Nadir CD4+ (cells), median (IQR)	310 (160-472)
AIDS defining conditions at baseline	19 (11.9)

IQR: interquartile range; **MSM:** men who have sex with men; **IDU:** intravenous drug users

Table 1. Characteristics of 159 people with HIV treatment-naïve who started bictegravir/ emtricitabine/tenofovir alafenamide regimen.

	Baseline	6 months	12 months
CD4 cells/ml, median (IQR)	331 (154-508)	484.5 (310-780)*	552 (394-843) *#
CD8 cells/mL, median (IQR)	839 (516-1214)	824 (647-1159)	851 (645-1242.3)
CD4/CD8 cells/ml, median (IQR)	0.35 (0.16-0.53)	0.57 (0.35-0.83)*	0.65 (0.39-0.95)*#
Creatinine mg/mL, median (IQR)	0.8 (0.67-0.92)	0.88 (0.78-1)*	0.87 (0.8-1.01)*
ALT UI/L, median (IQR)	26 (18-38)	22 (16-29.5)*	21 (16-29)*
AST UI/L, median (IQR)	27 (22-36)	23.5 (19.5-29)*	23 (19-29)*
Blood glucose mg/dl, median (IQR)	87 (78-93)	86 (78-94)	91 (82-104)
Total cholesterol mg/ dl, median (IQR)	160 (136-186)	176 (149-199)*	174 (150-204)*
HDL mg/dl, median (IQR)	40 (33-49)	44 (37-53)	45 (39-52)
LDL mg/dl, median (IQR)	95.4 (78.2-115)	104 (87.4-127.3)*	102.6 (87.2-136.4)*
Triglycerides mg/dl, median (IQR)	91 (71-130)	96 (68-139)	91 68-123)
Total cholesterol/HDL	3.8 (3.3-4.8)	3.7 (3.3-4.8)	3.9 (3.3-4.7)

* p-value <0.05 when compared with Baseline;
# p-value <0.05 when compared with 6 months.

Table 2. Characteristics at baseline and after 6 and 12 months of follow-up of 159 naïve people with HIV initiating a regimen with bictegravir/emtricitabina/tenofovir alafenamide.

achieved undetectable levels by 48 weeks, highlighting the regimen's effectiveness even in those who initially had a slower response.
Immunological improvement was also evident, with significant increases in median CD4 cell counts and the CD4/CD8 ratio at both 24 and 48 weeks. These findings underscore the regimen's ability to enhance immune function in addition to achieving virological suppression (**Table 2**).

Safety

The safety profile of the B/F/TAF regimen was assessed through monitoring changes in biochemical parameters over the study period.
A notable observation was the reduction in transaminase levels, which suggests an improvement in liver function among participants. On the contrary we observed a significant increase of creatinine levels at 24 weeks but stabilized by 48 weeks.

Lipid profiles revealed a modest increase in total cholesterol and low-density lipoprotein (LDL) levels over the observation period. Despite these changes, the total cholesterol/high-density lipoprotein (HDL) ratio remained unchanged (**Table 2**).

Treatment Discontinuation

During the study period, 18 participants (11.3%) discontinued the B/F/TAF regimen. The reasons for discontinuation varied and are detailed in **Table 3**. The overall low discontinuation rate due to toxicity (1.8%) highlights the regimen's tolerability and suitability for long-term use in treatment naive PWH.

	Reasons for dropout
Toxicity n (%)	3 (16.6)
DDI n (%)	1 (5.6)
LTFU n (%)	4 (22.2)
Switch to LA cabotegravir + rilpivirine n (%)	1 (5.6)
Switch to dual therapy n (%)	4 (22.2)
Patient's choice n (%)	1 (5.6)
Moved to other hospital n (%)	2 (11.1)
Others n (%)	2 (11.1)

DDI: drug-drug interactions;
LTFU: lost to follow up;
LA: long acting.

Table 3. Reasons for discontinuation of bictegravir/emtricitabina/tenofovir alafenamide in 18 naïve people with HIV.

Discussion

This study provides real-world evidence supporting the efficacy and safety of the B/F/TAF regimen in treatment naive PWH in Sardinia and Sicily. Our findings align with previous randomized controlled trials, demonstrating that B/F/TAF is a potent and well-tolerated option for initiating antiretroviral therapy(3).

In our study, the B/F/TAF regimen achieved substantial viral suppression, with 79.8% of participants reaching HIV RNA levels of <50 copies/mL at 6 months and 87.6% maintaining this suppression at 12 months. In the Phase 3 trial, the percentage of people with HIV RNA <50 copies/mL after 48 weeks was higher (92.4%)(3); however, participants in our study were older (median age 42.3 vs. 31 years) and had higher baseline HIV RNA levels (log 5.12 vs. 4.42), with a higher percentage of individuals having more than 100,000 copies/mL (57.2% vs. 17%). Additionally, a larger proportion of our population had advanced disease, with 57.2% having fewer than 350 CD4 cells/mL and 11.9% having AIDS-defining conditions (vs. 33% and 4%, respectively, in the Phase 3 trial). These factors likely explain why the percentage of participants with HIV RNA <50 copies/mL was lower in our cohort.

Similar results have been reported in other real-world studies. Ciccullo et al. reported 86.7% of participants with HIV RNA <50 copies/mL after 48 weeks, and Hidalgo-Tenorio et al. reported 84.1%. Notably, in our study, 99.2% of participants had HIV RNA levels below 200 copies/mL at 6 months, and this high rate persisted at 98.9% at 12 months(8,9). These high rates of viral suppression underscore the regimen's effectiveness in achieving and maintaining virological control, reaching the "untransmittable" status(10).

Additionally, we observed that only 6 out of 107 (5.6%) participants experienced a viral rebound at 48 weeks after achieving undetectable levels at 24 weeks, which is lower than the 10.1% reported in the study by Hidalgo-Tenorio et al(8).

We observed significant increases in median CD4 cell counts and the CD4/CD8 ratio further demonstrate the regimen's ability to enhance immune function alongside achieving viral suppression, confirming what already been observed in both randomized clinical trials and real-life studies(2,8,9).

The safety profile of B/F/TAF observed in this study is consistent with prior clinical data. The reduction in transaminase levels suggests an improvement in liver function, which is particularly relevant for PWH who may have underlying liver conditions or co-infections, such as hepatitis B or C.

We observed a significant increase in creatinine levels at 24 weeks, which then stabilized by 48 weeks. This increase is compatible with the inhibition of the organic cation transporter 2 (OCT2) and MATE-1, a known effect of both bictegravir and dolutegravir(11,12). OCT2 inhibition can lead to increased serum creatinine levels without necessarily indicating a true decline in renal function.

Regarding lipid profiles, we noted a modest increase in total cholesterol and low-density lipoprotein (LDL) levels over the observation period. However, the total cholesterol/high-density lipoprotein (HDL) ratio remained unchanged, suggesting that the overall lipid balance did not shift towards a more atherogenic profile. The increases in cholesterol and LDL levels are consistent with the "return to health" phenomenon, where metabolic parameters normalize as patients' health im-

proves with effective ART. This phenomenon has been documented in other studies and reflects the restoration of normal metabolic processes as HIV replication is controlled(13).

The low discontinuation rate of 11.3% (1.8% due to toxicity) highlights the regimen's tolerability and suitability for long-term use. The reasons for discontinuation varied, with adverse effects, patient preference, and virological failure being among the factors. Detailed examination of these reasons can inform clinical practice by identifying potential areas for intervention to enhance adherence and persistence with therapy.

This study has several limitations. As a retrospective observational analysis, it is subject to potential biases related to data collection and patient selection.

Additionally, the relatively small sample size and the specific geographical focus on Sardinia and Sicily may limit the generalizability of the findings to broader populations.

Conclusion

Our study affirms the high efficacy and favorable safety profile of B/F/TAF in treatment-naive PWH, supporting its use as a first-line therapy. The regimen's ability to achieve and sustain viral suppression, improve immune function, and maintain a manageable safety profile makes it a valuable option for initiating ART. These findings contribute to the growing body of real-world evidence supporting B/F/TAF and underscore its pivotal role in contemporary HIV management.

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