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Review article

Bictegravir/emtricitabine/tenofovir alafenamide: A review of the real-world experience in Spain within the last five years

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ABSTRACT

Integrase strand inhibitor (INSTI)-based antiretroviral regimens are the preferred choices for treating people with human immunodeficiency virus (PWH). The once-daily single-tablet combination of INSTI bictegravir, co-formulated with emtricitabine and tenofovir alafenamide (BIC/FTC/TAF), has shown effectiveness and good tolerability in randomized clinical trials, both in treatment-naïve (TN) and virologically suppressed patients switched to this regimen. Real-world evidence represents clinical practice and may fill data gaps left by pivotal studies. Based on literature search for real-world studies in Spain within five years, and using clinical trial data as a contextual framework, this narrative review synthesizes observational experience with BIC/FTC/TAF, focusing on the interplay between comorbidities, advanced age, and treatment outcomes from underrepresented subgroups in clinical trials. This fixed-dose combination proved effective and well-tolerated for TN and treatment-experienced PWH, with low virological failure even in difficult-to-treat patients. Low rates of treatment discontinuations due to adverse events or drug-drug interactions aligned with clinical trial findings.

Palabras clave:
Terapia antirretroviral
Combinación de dosis fijas
Bictegravir
Evidencia del mundo real
Efectividad
Seguridad

RESUMEN

Los regímenes antirretrovirales basados en inhibidores de la integrasa (INSTI) son la primera opción para tratar a las personas con virus de la inmunodeficiencia humana (VIH). La combinación en un solo comprimido diario del INSTI bictegravir, coformulado con emtricitabina y tenofovir alafenamida (BIC/FTC/TAF), ha demostrado su eficacia y buena tolerabilidad en ensayos clínicos aleatorizados, tanto en pacientes sin tratamiento previo como en pacientes con supresión virológica que cambiaron a este régimen. La evidencia del mundo real representa la práctica clínica y puede rellenar las lagunas de datos que dejan los ensayos clínicos. Basándose en una búsqueda bibliográfica de estudios del mundo real realizados en España en los últimos cinco años, y utilizando como referencia contextual los datos de los ensayos clínicos, esta revisión narrativa sintetiza la experiencia observacional

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con BIC/FTC/TAF, centrándose en la interacción entre las comorbilidades, la edad avanzada y los resultados del tratamiento en subgrupos infrarrepresentados en los ensayos clínicos. Esta combinación de dosis fijas demostró ser eficaz y bien tolerada en personas con VIH sin tratamiento previo y con experiencia en el tratamiento, con una tasa baja de fracaso virológico incluso en pacientes difíciles de tratar. Las proporciones de interrupción del tratamiento debido a acontecimientos adversos o interacciones entre medicamentos fueron bajas y acordes con los resultados de los ensayos clínicos.

Introduction

With the availability of antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection has become a manageable chronic condition. Almost all people with HIV (PWH) achieve durable and effective viral suppression and immune restoration with appropriate therapy, allowing them to live for nearly as long as people without HIV.[1,2] However, patient adherence to ART is a key determinant of treatment efficacy. As a result, there has been a growing trend toward the use of fixed-dose single-tablet regimens to reduce the pill burden on patients, improve compliance, and enhance ART effectiveness.[3] Globally, integrase strand inhibitor (INSTI)-based ART regimens are the recommended combinations for most PWH.[4,5] The INSTI bictegravir, co-formulated with emtricitabine and tenofovir alafenamide (BIC/FTC/TAF), is a once daily single-tablet that has been shown to be effective and well tolerated in high-quality randomized clinical trials, both in treatment-naïve (TN)[6,7] and virologically suppressed PWH on antiretroviral therapy who were switched to this regimen.[8,9] This regimen has demonstrated a high genetic barrier to resistance, a low risk of potential drug-drug interactions, and is active against hepatitis B virus (HBV) co-infection.[10,11]

BIC/FTC/TAF (Biktarvy®) is indicated as a complete regimen for the treatment of HIV-1 infection in individuals with no history of viral resistance to the INSTI class or individual components of the regimen.[12] Recently, the U.S. Food and Drug Administration approved to expand the indication of Biktarvy® to treat PWH with known or suspected M184V/I resistance.[13] Since its approval in 2019, several studies have explored the effectiveness, safety, and tolerability of BIC/FTC/TAF in real-world cohorts of PWH in Spain and many other countries.[14,15] Such studies are relevant as the participants are typically more diverse and have a more complex treatment and clinical status than those enrolled in clinical trials. Once a treatment is available on the market, clinicians should identify which patients are most likely to benefit or be harmed, and under what circumstances. To this end, the use of real-world data can help make evidence-based clinical decisions and adapt therapies to the individual needs of patients, complementing the results of clinical trials.[16]

Despite the implementation of public health strategies, including widespread access to antiretroviral therapy (ART) and comprehensive HIV prevention programs, Spain continues to report a significant number of new HIV diagnoses each year, with rates above the European Union average.[17] Within this context, the purpose of this narrative review is to synthesize real-world experience with BIC/FTC/TAF since its marketed authorization in Spain, focusing on the effectiveness and tolerability of the regimen and trying to fill the data gaps left by the clinical trials. We also examined the interplay between comorbidities, advanced age, and treatment outcomes, and sought information from subgroups underrepresented in clinical trials.

Methods

A literature search was performed on MEDLINE (PubMed) and EMBASE to identify real-world studies and clinical trials conducted in Spain within the last five years (since marketing authorization) that included individuals receiving Biktarvy®. The following search terms were used, alone or in various combinations using Boolean operators: “bictegravir”, “emtricitabin*”, “tenofovir alafenamid*”, “Spain”, “Spanish”, “real-world” or “real world” or “RWE”. Websites and online repositories were also searched to capture outstanding communications from conferences held from January 2023 to April 2024 which had not enough time to be published in peer-reviewed journals. Experts met online and discussed the final studies to be included based on their clinical expertise and relevance of the data.

Effectiveness of BIC/FTC/TAF in treatment-naïve persons

Two phase 3 randomized, double-blind, active-controlled trials compared the combination of BIC/FTC/TAF with two dolutegravir (DTG)-based 3-drug regimens for the initial treatment of HIV-1 infection: DTG/abacavir/lamivudine (DTG/ABC/3TC) in the study 1489[7] and DTG plus FTC/TAF in the study 1490.[6] Both trials showed that BIC/FTC/TAF was non-inferior to the DTG-based regimens, with high rates of viral suppression at week 48 (92.4% and 89%, respectively) and no treatment-emergent resistance in the BIC/FTC/TAF arm through five years, according to last report.[18]

Cohort studies and trials conducted in Spain included PWH with characteristics not usually observed in pivotal clinical trials, such as TN individuals with baseline viral loads > 100 000 copies/mL, very low CD4 cell levels, and patients with AIDS-defining events (Table 1). Despite these severity markers, on treatment viral suppression rates at week 48 were generally high, ranging from 86% to 98.7%, and virologic failures were rare (Table 1).[19–25] When compared with alternative regimens such as DTG/ABC/3TC and DTG + TDF/3TC, initiating BIC/FTC/TAF was associated with a shorter time to viral suppression in late presenter patients.[22] Moreover, the BIC-NOW and BIFAST studies showed that this combination was effective as a test-and-treat strategy (rapid initiation of ART after HIV diagnosis), achieving high viral suppression rates after 48 weeks of treatment, even in patients with elevated viral loads (>100 000 copies/mL) at baseline.[19,24]

In this regard, using a dynamic transmission model customized to the Spanish setting, early ART initiation with BIC/FTC/TAF within 9 days of HIV infection diagnosis (*vs.* a clinical practice scenario of 35 days) would be associated with a reduction in the number of new cases (−992 in 20 years) and potential savings for the Spanish National Health System and society of almost €*G*323 million.[26] Moreover, a pilot study evaluated viral decay in genital and rectal fluids in TN individuals treated with BIC/FTC/TAF ($N = 23$). This regimen achieved undetectable HIV-1 RNA levels within the first 4 weeks in most individuals, even when the plasma viral load was still detectable, confirming its inhibitory activity at the sites where HIV is sexually transmitted.[27]

It has been shown that the prevalence of transmitted drug resistance to dolutegravir/bictegravir and nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) in newly diagnosed PWH naïve to ART in Europe is about 6%.[28] In Spain, three studies examined the presence of baseline resistance mutations in TN people. In the BICNOW study, resistance mutations to NNRTIs were detected in 3.8% and resistance to NRTIs in 0.5%, but none experienced a virologic failure.[19] The BIFAST study found that 6 patients out of 99 (6.1%) had resistant strains,[24] whereas only 2 out 213 harbored resistant substitutions for NRTIs in the study conducted by Ambrosioni et al.[21] These two patients achieved a viral load of <50 copies/mL at week 24. None of the Spanish cohort studies reported the emergence of resistance mutations during treatment in TN individuals.

Table 1
Summary of the studies evaluating the effectiveness of BIC/FTC/TAF in TN patients.

	Hidalgo-Tenorio et al.[19] (*N* = 208)	Torralba et al.[20] (*N* = 79)	Ambrosioni et al.[21] (*N* = 213)	Corona et al.[22] (*N* = 158)	Suárez-García et al.[23] (*N* = 949)	Al-Hayani et al.[24] (*N* = 99	Savorido Alconchel et al.[25] (*N* = 238)
Cohort baseline characteristics							
Male, n (%)	182 (87.5)	66 (84)	194 (91)	133 (84.2)	NA (~85)	97 (98.0)	214 (90.0)
Age, median (IQR)	35.9 (10.9)[a]	43 (34–53)	35 (29–42)	40 (33–51)	NA	33.4 (NA)[a]	33 (27–43)
Time since HIV diagnosis (years), median (IQR)	NA	0.02 (0.01–0.01)	0 (0–3)	NA	NA	NA	NA
History of AIDS, n (%)	47 (22.6)	12 (15)	NA	51 (32.3)	NA	NA	18 (7.6)
Viral load (copies/mL), median (IQR)	398 107 (NA)[a]	~79 000 (10 000– 501 187)	68 500 (19 600–261 000)	249 621 (86 500–851 138)	NA	NA	205 500 (43 975–658 500)
HIV > 100 000 copies/mL, *n* (%)	90 (43.3)	31 (39)	92 (44)	9 (5.7)	NA (~44)	22 (22.2)	NA
HIV > 500 000 copies/mL, *n* (%)	NA	17 (22)	NA	NA	NA	4 (4.0)	NA
CD4 (cells/μL) median (IQR)	393.5 (252.3)[a]	243 (63–472)	357 (194–496)	103 (51–154)	NA	431 (NA)	331 (201–473)
CD4 < 200 cells/μL, *n* (%)	46 (22.1)	28 (42)	55 (27)	152 (96.2)	NA (~23)	6 (6.1)	NA
Active HBV co-infection, n (%)	9 (4.3)	6 (8)	2 (1)	NA	NA	2 (2.0)	NA
Virological outcomes							
Viral suppression at week 24, (%)							
ITT	NA	65%	62%	72.1%	83.1%	NA	NA
OT	NA	85%	77%	NA	83.1%	NA	NA
Viral suppression at week 48, (%)							
ITT	84.1%	62%	83%	86.1%	88.6%	84.4%	90.5%
OT	98.3%	94%	92%	~86%	89.8%	96.6%	98.7%
Virological failure, n (%)	3 (1.7)	3 (3.8)	NA	2 (1.3)	8 (1.7)	NA	3 (1.2)

[a] Mean (standard deviation); IQR, interquartile range; ITT, intention-to-treat; NA, not available; OT, on treatment.

Effectiveness of BIC/FTC/TAF in treatment-experienced (TE) people

Previously treated PWH require tailored treatment according to their acute and chronic comorbidities, possible drug-drug interactions, and proven/suspected resistance. In the clinical trials, BIC/FTC/TAF proved to be very effective and well tolerated in TE patients who switched to this combination from boosted protease inhibitor-based regimens (study 1878),[8] DTG/ABC/3TC (study 1844),[9] and DTG plus FTC/TAF or FTC/TDF (study 4030),[29] achieving viral suppression rates of 98%, 99%, and 99.6% at week 48, respectively. Subsequent detailed resistance analyses showed that participants with baseline antiretroviral resistance mutations, including M184V/I, had similar high rates of suppression.[30,31] After a 96-week open-label extension period, the participants of the trials 1489 and 1490 who switched to BIC/FTC/TAF (*N* = 519) maintained high levels of virologic suppression (99.5% and 99.1% in those switching from DTG/abacavir/lamivudine and DTG + FTC/TAF, respectively).[32]

Several real-world studies have been conducted in Spain to examine the effectiveness of BIC/FTC/TAF in TE people, including the studies of Torralba et al.[20] and Ambrosioni et al.,[21] described in the previous section. Three studies (the ones conducted by Ambrosioni et al., Micán et al., and Troya et al. [RETROBIC study]) included patients harboring drug-resistant HIV-1 strains,[21,33,34] and the one conducted by Knobel et al. included PWH at high-risk of non-adherence.[35] Perez et al. included people on effective ART who switched to a BIC/FTC/TAF from regimens without INSTI,[36] whereas Martínez Vera et al. examined BIC/FTC/TAF *vs.* doravirine-containing regimens as a switch strategy.[37] The participants of all these studies were mainly male (Table 2). An additional real-word study, conducted by Pousada et al., included pretreated and suppressed women switching to BIC/FTC/TAF and evaluated the efficacy and immune status at 48 and 96 weeks after the switch.[38]

As shown in Table 2, on treatment viral suppression was generally maintained at high rates, with no differences between patients with and without baseline NRTI resistance. In the study conducted by Micán et al., all patients (*N* = 9) with high-level tenofovir resistance plus M184V mutation had a viral load < 50 copies/mL at week 48,[33] whereas 34 out 38 patients with an M184V/I substitution and five out of 32 cases with integrase substitutions identified in historical genotypes also had HIV-RNA < 50 copies/mL at week 24 in the study by Ambrosioni et al.[21] Only one participant of the Micán et al. study acquired a resistance-associated mutation (M184V).[33] A recent systematic review and meta-analysis that included Spanish studies supported the high rates of virological suppression in TE PWH treated with BIC/TAF/FTC (pooled estimate = 95%), and the high genetic barrier to HIV drug resistance of the regimen, as suppression rates in individuals carrying M184V substitution from three different studies was 95% at 48 weeks, very similar to the overall suppression rate.[39]

Two other studies evaluated BIC/FTC/TAF treatment in special situations. One study (Santos et al., 2023) included people with persistent low-level viremia and observed a 72% viral response at 48 weeks.[40] Podzamczer et al., in the BIDA study, examined the combination of BIC/FTC/TAF with darunavir/cobicistat in PWH with "heavy antiretroviral experience"; at 48 weeks of follow-up, 100% of PWH had undetectable viral load.[41]

Table 2
Summary of studies evaluating the effectiveness of BIC/FTC/TAF in TE patients.

	Torralba et al.[20] (*N* = 426)	Ambrosioni et al.[21] (*N* = 1371)	Micán et al.[33] (*N* = 506)	Troya et al.[34] (*N* = 1966)	Knobel et al.[35] (*N* = 61)	Pérez et al.[36] (*N* = 79)	Martínez Vera et al.[37] (*N* = 72)	Pousada et al.[38] (*N* = 376)	Santos et al.[a,40] (*N* = 123)	Podzamczer et al.[b,41] (*N* = 63)
Male, n (%)	326 (77)	1185 (86)	424 (83.8)	1568 (79.9)	51 (83.6)	NA	55 (76.6)	0	99 (80.5)	95.1 (58)
Age, median (IQR)	48 (39–56)	44 (36–53)	52.3 (43.5–57.8)	51.0 (42.0–57.0)	39.6 (10.9)[c]	NA	48 (NA)	53.0 (45.0–58.0)	52.0 (42.0–57.0)	57.5 (49.9–60.6)
Time since HIV diagnosis (years), median (IQR)	11 (5–20)	10 (5–17)	18.9 (9.4–26.4)	18.0 (10.0–27.0)	NA	NA	15.3 (NA)	22.0 (13.3–29.0)	30.0 (24.0–39.0)	18.9 (9.4–26.4)
History of AIDS, n (%)	51 (12)	NA	NA	436 (22.2)	NA	NA	21 (29.2)	105 (27.8)	31 (25.6)	NA
HIV RNA < 50 copies/mL, n (%)	379 (89)	1068 (82)	440 (86.6)	1966 (100)	0	64 (81)	59 (81.9)	368 (97)	0	63 (100)
Previous ARV combinations, median (IQR)	2 (2–4)	2 (1–4)	5 (3–8)	NA	NA	NA	NA	NA	NA	NA
CD4 (cells/μL) median (IQR)	670 (466–891)	628 (441–846)	645 (411–854)	694 (486–910)	286 (139–435)	747 (497–1028)	347.7 (NA)	725 (517–950)	675 (386–1000)	NA
Active HBV co-infection, n (%)	28 (7)	46 (3)	24 (5)	70 (3.6)	NA	NA	NA	NA	NA	NA
ARV-resistance mutations, n (%)	NA	371 (27)	98 (19.3)	52 (2.6)	0	NA	NA	NA	NA	33 (52.4)
Viral suppression at week 48, (%)										
ITT	75%	78%	83%	NA	NA	92.4%[d]	NA	NA	NA	95%
OT	91%	93%	94.4%	95.6%	88.6%	96.1%[d]	92.9%	95.8%	72.9%	100%
Virological failure, n (%)	NA	NA	8 (1.6)	14 (0.7)	3 (0.9)	NA	NA	3 (0.07)	NA	0

[a] Patient with persistent low-level viremia.
[b] In this study, BIC/TFC/TAF was combined with duranavir/cobicistat.
[c] Mean (standard deviation).
[d] At week 24.
ARV, antiretroviral; IQR, interquartile range; ITT, intention-to-treat; NA, not available; OT, on treatment.

Table 3
Summary of rates and reasons for BIC/FTC/TAF discontinuation (week 48).

	Torralba et al.[20] (*N* = 505)	Ambrosioni et al.[21] (*N* = 1371)	Corona et al.[22] (*N* = 158)	Micán et al.[33] (*N* = 506)	Troya et al.[34] (*N* = 1966)	Knobel et al.[43] (*N* = 332)	Rocabert et al.[44] (*N* = 1231)
Discontinuations, n (%)	57 (11.3)	151 (13)	12 (7.6)	61 (11.8)	201 (10.2)	51 (15.4)	89 (7%)
Reason for discontinuation							
Loss to follow-up	26 (5.1)	90 (6.6)	0	23 (4.5)	24 (1.2)	35 (10.5)	15 (1.2)
Toxicity/AE	9 (1.8)	42 (3.1)	4 (2.5)	19 (3.7)	24 (1.2)	7 (2.1)	47 (4.0)
Virological failure	0	7 (0.5)	2 (1.3)	0	14 (0.7)	0	2 (0.2)
Simplification	0	4 (0.3)	1 (0.6)	5 (1.0)	66 (3.4)	0	2 (0.2)
Avoidance of DDI	2 (0.4)	3 (0.2)	0	0	17 (0.9)	2 (0.6)	1 (0.1)
Death	3 (0.6)[a]	0	0	6 (1.2)[a]	0	7 (2.1)[a]	4 (0.3)[a]
Other causes	17 (3.4)	5 (0.4)	5 (3.1)	8 (1.6)	56 (2)	0	18 (1.5)

[a] None related with BIC/FTC/TAF treatment.
AE, adverse event; DDI, drug–drug interaction.

Tolerability of BIC/FTC/TAF

Although ART is increasingly better tolerated and simpler than it was a few years ago, adherence and persistence to therapy is essential to reduce the transmission, morbidity, and mortality of HIV; however, adverse effects and intolerance can negatively affect compliance. Moreover, ART and its toxicity have a substantial impact on the health-related quality of life of PWH, which may be an important contributor to treatment discontinuation and therapeutic failure. The BIC/FTC/TAF combination generally has a good tolerability profile, being the most common adverse events associated with the regimen in clinical trials gastrointestinal disorders (diarrhea, nausea) and headache in TN patients.[6,7] In the trials comparing BIC/FTC/TAF and triple DTG-containing regimens, drug-related adverse events were less common with BIC/FTC/TAF during the 48-week follow-up.[6,7,9] After 144 weeks of treatment, adverse events that led to study drug discontinuation were reported for no participants receiving BIC/FTC/TAF in the 1489 study and only six (2%) of 320 in the 1490 study.[30] Similarly, rates of treatment discontinuation due to adverse events were very low and comparable between BIC/FTC/TAF and 2-drug DTG-based regimens.[42]

In the Spanish cohort studies, the rates of treatment discontinuation in TN and TE people ranged between 7.6% and 15.4%, but only around 3% were due to adverse events (Table 3).[20–22,33,34,43,44] The most common adverse events were gastrointestinal disorders, neuropsychiatric symptoms, weight gain, and dyslipidemia. In a systematic review of real-life studies performed by Perez-Valero et al.,[45] the median rate of total discontinuation (any cause) with BIC/FTC/TAF was 5.7%, whereas the median rates of discontinuation due to drug-related adverse events and neuropsychiatric symptoms were 2.95% and 0.7%, respectively. These rates were numerically lower than those observed with DTG-based regimens, that encompassed both triple (6.78% and 2.8%, respectively) and dual therapies (6.1% and 2.35%, respectively).[45] Velasco et al. compared the safety and tolerability profile of BIC/FTC/TAF between TN and TE PWH and showed that it was similar in both groups, except for an increase in BMI and metabolic parameters in TN patients,[46] which, according to the authors, may reflect the return-to-health phenomenon. In the BIC-NOW study (*N* = 208), 48-week treatment was associated with a small increase in body weight, BMI, and abdominal circumference, but there were no adverse events leading to BIC/FTC/TAF withdrawal, with optimal adherence to therapy and high patient-reported satisfaction with the treatment.[19] In another cohort of TE patients (METABIC study), switching from ART regimens without TDF/TAF to BIC/FTC/TAF improved total and LDL cholesterol and was neutral for the rest of the metabolic parameters after one year of follow-up,[47] whereas Buzón et al. showed a significant weight and BMI increase in patients switched from different regimens after 96 weeks of treatment.[48] Podzamczer et al. did not found differences in quality of life of heavily TE PWH after optimizing their treatment to BIC/FTC/TAF plus darunavir/cobicistat, but satisfaction with the treatment and perception of adherence significantly increased from 55% and 44% to 70% and 71%, respectively.[41] In the Spanish cohort of the prospective and multinational BICSTaR study (*N* = 186) significant decreases were observed in the overall bothersome symptom count from baseline to 24 months of BIC/FTC/TAF treatment in both TN and TE patients; the physical/mental component summary scores of the 36-item short-form survey improved in TN and remained stable in TE participants.[49] In summary, evidence coming from clinical trials and real word studies suggests no additional benefit regarding the tolerability profile for DTG-containing regimens when compared to BIC/FTC/TAF combination.

Comorbidities and aging

PWH, due to long-term antiretroviral toxicity, increasing age, and the proinflammatory and immune-activated state caused by HIV, even in patients on effective ART, may suffer from a high number of comorbidities such as dyslipidemia, hypertension, cardiovascular disease, diabetes, osteoporosis, or renal disease.[50] Some patients may also require concomitant medications because of co-infection with other pathogens, psychiatric diseases, neoplasms, or solid organ transplantation.[51–53] Thus, multimorbidity and polypharmacy, especially in older PWH, pose challenges for clinicians who have to address multiple conditions in a single patient while avoiding possible drug–drug interactions. In this regard, switching to BIC/FTC/TAF from different ART regimens has been shown to be associated with a decline in the incidence and severity of drug-drug interactions among TE PWH.[54] Moreover, a phase 3b, open-label, multicenter, single-arm trial including virologically suppressed persons aged > 65 years who received elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide or a tenofovir disoproxil fumarate-based plus a third agent has demonstrated that switching to BIC/FTC/TAF was effective and safe for 96 weeks in this population who had a high burden of comorbidities and concomitant medications.[55]

Cohort studies in Spain showed that the most prevalent comorbidities were dyslipidemia, hypertension, and psychiatric disorders.[34,38,43,46] As shown in the RETROBIC study, individuals older than 60 years[34] and TE patients from the COMESEN cohort[46] suffered more baseline comorbid conditions, but this did not affect the effectiveness of BIC/FTC/TAF. Dyslipidemia is a key indicator of metabolic health that can be associated with the use of ART, mainly ritonavir- or cobicistat-boosted regimens or efavirenz. Although increases in body weight and BMI were seen in both TN and TE patients initiating treatment with BIC/FTC/TAF in some Spanish real-world studies,[19,48,56] the 3-drug combination was neutral with respect to the lipid profile.[19,42,47] It has been shown that bictegravir has a weaker action than DTG in dis-

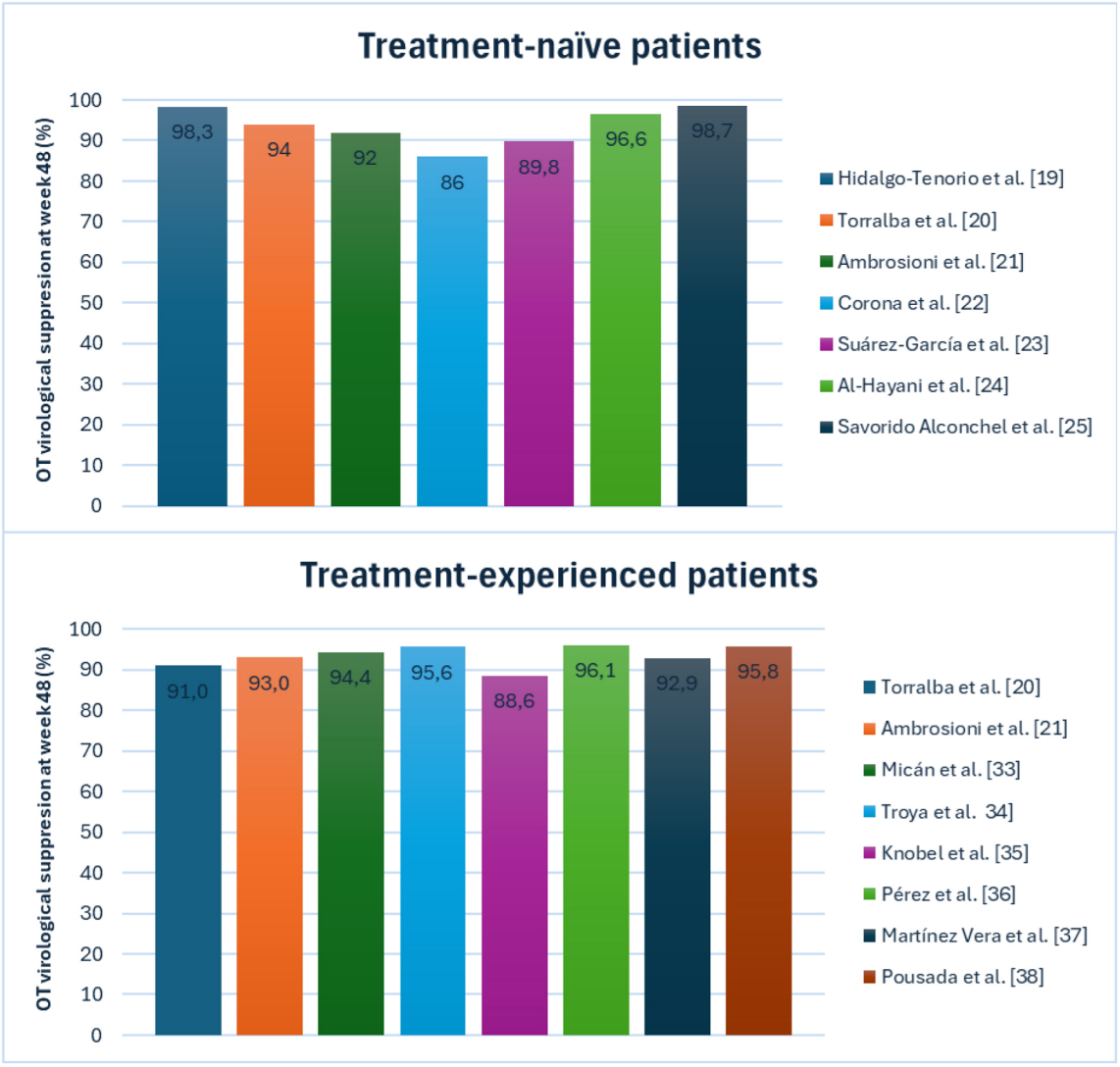

Fig. 1. Rates of virological suppression observed in the Spanish real-world cohorts treated with BIC/FTC/TAF. OT, on treatment.

turbing the adiponectin system in human adipocytes *in vitro* and to inhibit the expression and release of the pro-inflammatory cytokine IL-6, which could be favorable for those with already excessive weight and metabolic alterations.[57] Moreover, although no differences are found in the first 48 weeks of treatment,[58] maintaining a 3-drug regimen is associated with a more favorable long-term inflammatory profile than switching to a 2-drug regimen, regardless of virological suppression in plasma.[59]

As stated above, neuropsychiatric disorders are prevalent in PWH. The exposure to integrase inhibitors such as DTG in the central nervous system has been associated with its antiviral effect in this compartment, as well as with the occurrence of neuropsychiatric adverse events, particularly in real life cohorts.[45] This is also a possibility in the case of bictegravir, as total and unbound drug concentrations in cerebrospinal fluid were above the EC50 value in subjects with HIV viral suppression in plasma.[60] Few cohort studies have examined the effects of BIC/FTC/TAF on neuropsychiatric symptoms. For example, Tiraboschi et al.[56] prospectively evaluated virologically suppressed individuals ($N = 96$) switching from elvitegravir/cobicistat/FTC/TAF to BIC/FTC/TAF over 24 weeks and found that sleep quality, anxiety, and depressive symptoms remained stable, were mild, and tended to occur in those with previous neuropsychiatric symptoms.[56] In the BICSTaR study, patients with baseline symptoms of depression/anxiety and/or insomnia, some of whom were recruited from Spain, showed stable self-reported HIV symptom scores over the course of BIC/FTC/TAF treatment with small improvements in mental well-being and treatment satisfaction.[61]

Conclusions

Real-world studies are generally representative of clinical practice and complement the findings of clinical trials. Overall, according to real-world experience from Spain, a single daily tablet of BIC/FTC/TAF is an effective regimen for TN and TE PWH (Fig. 1), with a low rate of virological failure even in patients with pre-existing resistance mutations, advanced age, and/or high burden of comorbidities. This fixed-dose combination provides a versatile regimen that is also suitable for people who have received multiple prior antiretroviral therapies, representing a good option for therapy optimization.[62] In naïve patients, the rapid initiation of BIC/FTC/TAF showed high effectiveness, indicating potential public health benefits by reducing the risk of transmission. The good tolerability profile was consistent with the finding from the clinical trials, showing low rates of treatment discontinuations due to AEs or drug-drug interactions, and neutral lipidic and metabolic effects, which could contribute to long term health of PWH. When assessed, PROs indicated good adherence and satisfaction with the regimen, as well as reduced

symptom burden. The overall experience from the use of BIC/FTC/TAF in Spain may be of interest for geographical regions and countries with similar epidemiology and ART prescription policies.

Authorship

All authors have made substantial contributions to the conception and design of the work, the acquisition, analysis, and interpretation of data, and drafting and revising the manuscript. All authors have read and approved the final version of the manuscript for submission.

Ethical considerations

This study did not involve human participants, animals, or sensitive data. As it synthesizes published literature, ethical approval was not required.

Informed consent

Not applicable.

Use of artificial intelligence

No generative or analytical artificial intelligence (AI) tools were used in the preparation, analysis, or writing of this manuscript. All content is original and created by the authors.

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Conflicts of interest

CA has consulted for Gilead Sciences, and has received financial compensation for presentations from Gilead Sciences, Janssen ViiV Healthcare and Merck Sharp & Dohme. She has received grants for congresses attendance from Angellini, Pfizer, Janssen and Gilead Sciences

JA has received personal fees from and participated in advisory boards for ViiV, Gilead, Janssen, and MSD; has received funding for research from ViiV, Gilead, and MSD; and has been a member of data safety monitoring boards for HIPRA and Grifols.

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