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Bictegravir/emtricitabine/tenofovir alafenamide as first-line treatment in naïve HIV patients in a rapid-initiation model of care: BIC-NOW clinical trial

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ABSTRACT

Objective: Multiple strategies have been utilised to reduce the incidence of HIV, including PrEP and rapid antiretroviral therapy initiation. The study objectives were to evaluate the efficacy, safety, satisfaction, treatment adherence, and system retention obtained with rapid initiation of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) in naïve patients.

Methods: This phase IV, multicenter, open-label, single-arm, 48-week clinical trial enrolled patients between January 2020 and June 2022. Adherence to treatment was evaluated with the SMAQ questionnaire and patient satisfaction with the EQ-5D.

Results: Two hundred eight participants were enrolled with mean age of 35.6 years; 87.6% were males; mean CD4 count was 393.5 cells/uL (<200 cells/uL in 22.1%); viral load log was 5.6 (VL>100 000 cop/mL in 43.3%); 22.6% had AIDS, and 4.3% were coinfected with HBV. BIC/FTC/TAF was initiated on the day of their first visit to the HIV specialist in 98.6% of participants, and 9.6% were lost to follow-up. The efficacy at week 48 was 84.1 % by intention-to- treat (ITT), 94.6% by modified ITT, and 98.3% by per protocol analysis. The regimen was discontinued in two subjects (0.9%) during week 1 for grade 3 adverse events. Treatment adherence (weeks 4 [90%, IQR: 80–99%] vs. 48 [90%, IQR: 80–95%; $P = 0.49$]) and patient satisfaction (weeks 4 [90%, IQR: 80–99%] vs. 48 [90%, IQR: 80–95 $P = 0.49$]) rates were very high over the 48- week study period.

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Conclusions: BIC/FTC/TAF is an appropriate option for rapid ART initiation in naïve HIV patients, offering high efficacy, safety, durability, treatment adherence, retention in the healthcare system, and patient satisfaction. Number Clinical Trial registration: NCT06177574.

1. Introduction

Over the past two decades, antiretroviral treatment (ART) has delivered an exponential increase in the survival and life expectancy of people living with HIV (PLHIV), with a reduction in their morbidity and mortality rates, leading HIV to become a chronic infection [1]. Given the association between HIV transmissibility and plasmatic viral load (VL); the World Health Organization launched the *Undetectable = Untransmittable* (U = U) initiative in 2016, based on solid data that ART-treated individuals who reach and maintain an undetectable plasmatic VL cannot sexually transmit the virus to others [2]. Since the publication of START trial results in 2015, ART has been universally recommended for PLHIV, regardless of their CD4 count or VL [3]. However, the continued rise in HIV incidence has prompted the implementation of novel strategies, including post-exposure prophylaxis (PEP), pre-exposure prophylaxis (PreP), and rapid ART initiation [4].

Clinical practice guidelines currently recommend the single-table regimen (STR) of bictegravir/emtricitabine/tenofovir alafenamide (BIC/TAF/FTC) and dolutegravir/lamivudine (DTG/3TC) for naïve patients [5,6]. This regimen is ideal for rapid initiation because it achieves faster virologic suppression in comparison to protease inhibitors (PIs) [7] and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [8]. STRs are associated with higher adherence rates in comparison to multiple-tablet regimens (MTRs) because their simplicity favours reliable daily intake of the medication [9].

The main objective of the present trial was to evaluate the efficacy at 48 weeks of BIC/FTC/TAF as a rapid ART initiation strategy in naïve HIV subjects with no available data on immunity or VL status, starting this STR on the same day as the first visit to the HIV specialist. Secondary objectives were to assess the reduction in VL, the safety and durability of the treatment, and the retention in the healthcare system, adherence to the regimen, and satisfaction of the participants.

2. Material and methods

2.1. Study design

a phase IV, non-randomized, single-arm, open-label, 48-week multicenter clinical trial was conducted in naïve patients with confirmed HIV prescribed BIC/TAF/FTC on the day of their first visit to an HIV specialist, with no data on plasma HIV VL or lymphocyte counts (CD4, CD8, CD4/CD8). Patients were enrolled between October 2020 and June 2022. from Departments/Units of Infectious Disease or Internal Medicine from 15 hospitals in the Spanish national health system.

Inclusion criteria were ELISA-positive and WB-positive HIV serology, age ≥18 years, normal renal function, and signing of informed consent to study participation. Exclusion criteria were pregnancy, shorter life expectancy than the study period, prediction of treatment changes (to avoid incompatibility with future drug therapies); an active opportunistic infection; drug-drug interactions; and treatment protocol violations.

2.2. Intervention

Epidemiological, clinical, analytical, and imaging data were gathered according to national data protection legislation (Organic Law 3/2018, December 5). The study followed the principles of the Helsinki Declaration and was approved by the biomedical ethics committee of Central Andalusia (decree 8/2020, January 30) and the other participating centres.

At the first visit (baseline), patients were informed about the study objectives and inclusion criteria and asked for their signed consent to participation. Measurements were then taken of their height, weight, body mass index (BMI), and waist circumference, and blood was drawn for analysis before receiving BIC/TAF/FTC on the same day. Analyses included complete blood, biochemical values (creatinine, blood urea nitrogen, CKD-EPI, AST, ALT, GGT, alkaline phosphatase (AP), calcium, phosphorus, total cholesterol (TC), HDL, LDL, TC/HDL), CD4 and CD8 lymphocyte counts (calculating the CD4/CD8 ratio), HIV VL genotypic resistance testing (GRT), and serology for HBV, HAV, HCV, syphilis, cytomegalovirus IgG, and toxoplasma IgG. The same anthropometric measurements and blood analyses were repeated during follow-up visits at weeks 4, 24, and 48. Patients also completed a questionnaire on any adverse events and questionnaires on their satisfaction (EQ-5D [10]) and treatment adherence (SMA-Q [11]). Retention in the healthcare system was evaluated as a function of treatment withdrawals and losses to the follow-up. A genotypic resistance test (GRT) was ordered when confirmed virologic failure (VF) was observed at any follow-up visit.

In the first 2 weeks and at week 48 of treatment, a subgroup of participants (n = 15) from the coordinating hospital (HUVN) agreed to undergo dual-energy X-ray absorptiometry (DEXA) to evaluate the percentage of fat and lean mass (muscle) and body water variations, taking age and sex into consideration. It is a fast, safe, non-invasive method to precisely determine the body composition of individuals with very low radiation levels. It requires no special preparation and takes only 10 min [12].

2.3. Definition of variables

Efficacy: defined by a plasmatic VL <50 cop/mL at week 48 and calculated according to the FDA Snapshot algorithm: by intention-to-treat (ITT) [13], including loss to the follow-up, drug withdrawal for adverse events, and treatment changes and failures; by modified ITT (mITT), excluding losses to the follow-up [14]; and by per-protocol (PP), including all patients completing the follow-up [15].

Virological failure (VF): defined by two consecutive HIV VLs >50 cop/mL following previous undetectability under BIC/TAF/FTC treatment.

Viral blip was defined as transient plasma HIV RNA levels >50 cop/mL preceded and followed by HIV RNA <50 copies/mL.

Rapid initiation strategy: defined by "*immediate treatment,*" started on the same day as the first visit to the HIV specialist (with only hemogram and biochemistry results and HIV serology), or "*rapid treatment,*" started during the first two weeks after the first visit to the HIV specialist (with no data on VL or lymphocyte counts).

ART discontinuations, defined by patient- or doctor-requested change to a different antiretroviral regimen due to adverse events, pregnancy, or drug-drug interactions, among other reasons (losses to the follow-up were not included in this concept).

System retention, is defined by the percentage of patients completing the 48-week follow-up. *Weight classification,* defined by BMI (kg/m^2) values as *underweight*, <18.5; *normal weight*, 18.5–24.9; *overweight*, 25–29.9; *obese: class 1,* 30–34.9; *class 2,* 35–39.9; or *class 3,* ≥40 [16].

Adverse events, defined as: *mild (Grade 1),* requiring no antidote/treatment or only a short hospital stay (<72 h); *moderate (Grade 2),* requiring treatment modification (e.g., dose adjustment or additional drug) and possibly a longer hospital stay or additional therapy but not mandatory discontinuation of the treatment; *severe* (Grade 3): not life-threatening, requiring treatment withdrawal and new therapeutic approach; *life-threatening (Grade 4),* requiring treatment withdrawal and a new therapeutic approach; and *lethal* [5], directly or indirectly contributing to the patient's death. The dichotomized HIV symptoms Index (HIV-SI) were used for the adverse events questionnaire. It is a validated PRO tool to assess the burden of 20 symptoms associated with HIV treatment or disease [17] and is considered the gold standard in HIV symptom research [18]. Respondents described their experience of the following symptoms (as bothersome or not bothersome): fatigue/energy loss, insomnia, tension/anxiety, diarrhoea, body composition changes, feelings of sad/depressed feelings, abdominal distension/stomach ache/flatulence, muscle soreness/joint pain, decreased sexual capacity, poor memory, headache, hand/foot pain/numbness/tingling, skin problems/rash/itching, coughing/breathing difficulty, fever/chills/sweating, dizziness, weight loss/weight gain, nausea/vomiting, alopecia, and loss of appetite/loss of food taste. *Grade 3* and *Grade 4* adverse effects were reported to the Pharmacovigilance System by the attending clinician under the yellow card scheme.

Self-perceived quality of life / Satisfaction, defined by patient VAS score (range from 0 to 100) for items in the EQ-5D questionnaire on mental and physical health status, expressing results as percentages [10].

Adherence to ART, evaluated by the self-completed SMAQ questionnaire, with a dichotomous response (adherent/non-adherent) to each item [11].

Sample size. Based on previous clinical trial reports of 92% efficacy for BIC/TAF/FTC in naïve patients by FDA Snapshot, it was estimated that 139 patients were needed to achieve the study objectives with a confidence interval (CI) of 95% and margin of error of 5%, assuming losses to the study of 10%. The sample finally comprised 208 individuals to increase the statistical power and reduce the margin of error.

2.4. Statistical analysis

In a descriptive analysis, means with standard deviation were calculated for quantitative variables with a normal distribution (Kolmogorov–Smirnov test) and medians with interquartile range (IQR) for those with a non-normal distribution. Qualitative variables were expressed as absolute and relative frequencies (%). In bivariate analyses, the chi-square test was used to compare qualitative variables with a normal distribution, the Mann–Whitney U test for those with a non-normal distribution, and the Student's t-test to compare quantitative variables.

3. Results

3.1. Study population

The study included 208 participants with a mean age of 35.9 years; 87.5% were male, and 70.2% were men who have sex with men (MSM). At baseline, the mean CD4 count was 393.5 cells/uL (<200 cells/uL in 22.1%) and mean VL was 5.6 log10 (± 6.2) (VL> 100 000 cop/mL in 43.3%); 22.6% had AIDS, and 4.3% had a positive hepatitis B surface antigen. BIC/TAF/FTC was started within 7 days of the first visit to the HIV specialist in 100% of patients (median of 0 days; range, 0–7 days) and on the same day in 98.6%, always with no available data on VL or lymphocyte counts. At baseline, resistance mutations were detected in 4.3% of PLHIV, resistance to NNRTIs in 3.8%, and resistance to nucleoside reverse transcriptase inhibitors (NRTIs) in 0.5%; no patient had resistance mutations against BIC, TAF, or FTC. Table 1 lists results for the remaining study variables.

Table 1
General description of the population.

Variable	N = 208
Age (year), mean (± SD)	35.9 (±10.9)
Male, n (%)	182(87.5)
Rapid initiation, n (%)	208 (100)
- ART initiated on day 1, n (%)	205 (98.6)
- ART initiated during week 1 (after day 1), n (%)	3 (1.4)
Baseline HIV Viral load, log10, mean (± SD)	5.6 (6.2)
Viral load >100 000 cop/mL, n (%)	90 (43.3)
Resistance mutations at baseline, n (%)	
Y188L	1 (0.5)
V106I	1 (0.5)
M46L	1 (0.5)
K103, H221Y	1(0.5)
K103, P22, K238T	1 (0.5)
E138G	1 (0.5)
E138A	1 (0.5)
D67N, T215L, K219Q	1 (0.5)
138A, 199A	1 (0.5)
Baseline CD4, cell/uL, mean (± SD)	393.5 (252.3)
CD4<200 cell/uL, n (%)	46 (22.1)
Baseline CD4/CD8 ratio, mean (± SD)	0.43 (0.29)
CDC AIDS stage (A3, B3, C), n (%)	47 (22.6)
A1, n (%)	59 (28.4)
A2, n (%)	96 (46.2)
A3, n (%)	34 (16.3)
B1, n (%)	1 (0.5)
B2, n (%)	4 (1.9)
B3, n (%)	7 (3.4)
C1, n (%)	1 (0.5)
C2, n (%)	1 (0.5)
C 3, n (%)	4 (1.9)
HCV antibody positive, n (%)	5 (2.4)
HBV co-infection, n (%)	9 (4.3)
Risk factor for HIV infection, n (%)	
Heterosexual	55 (26.4)
MSM	146 (70.2)
IDU	2 (0.9)
Smoker, n (%)	88 (42.3)
Social drinker, n (%)	37 (18.8)
Weight, kg, median (IQR)	76 (69–81)
BMI, kg/m^2, median (IQR),	25 (23.1–26.5)
Waist circumference, cm, median (IQR)	78 (74–89)
Underweight, n (%)	8 (3.8)
Normal weight, n (%)	114 (55.3)
Overweight, n (%)	67 (33.2)
Obese	19 (8.7)

3.2. BIC/TAF/FTC efficacy

During follow-up, treatment was discontinued by 12.9% (n = 27) of participants, due to loss to the follow-up in 9.6% (n = 20), adverse events during week 1 in 0.9% (n = 2); pregnancy at weeks 4 and 24 in 0.9% (n = 2), and drug-drug interactions in 1.4% (n = 3) (Fig. 1). At week 48, VL< 50 cop/uL was achieved in 84.1% of patients by ITT [no differences by CD4 count (CD4<200 cell/uL (84.8%) vs. CD4 >200 cell/uL (80.1%), P = 0.48), plasma VL (<100 000 cop/mL (82.1%) vs. >100 000 cop/mL (80%), P = 0.71),

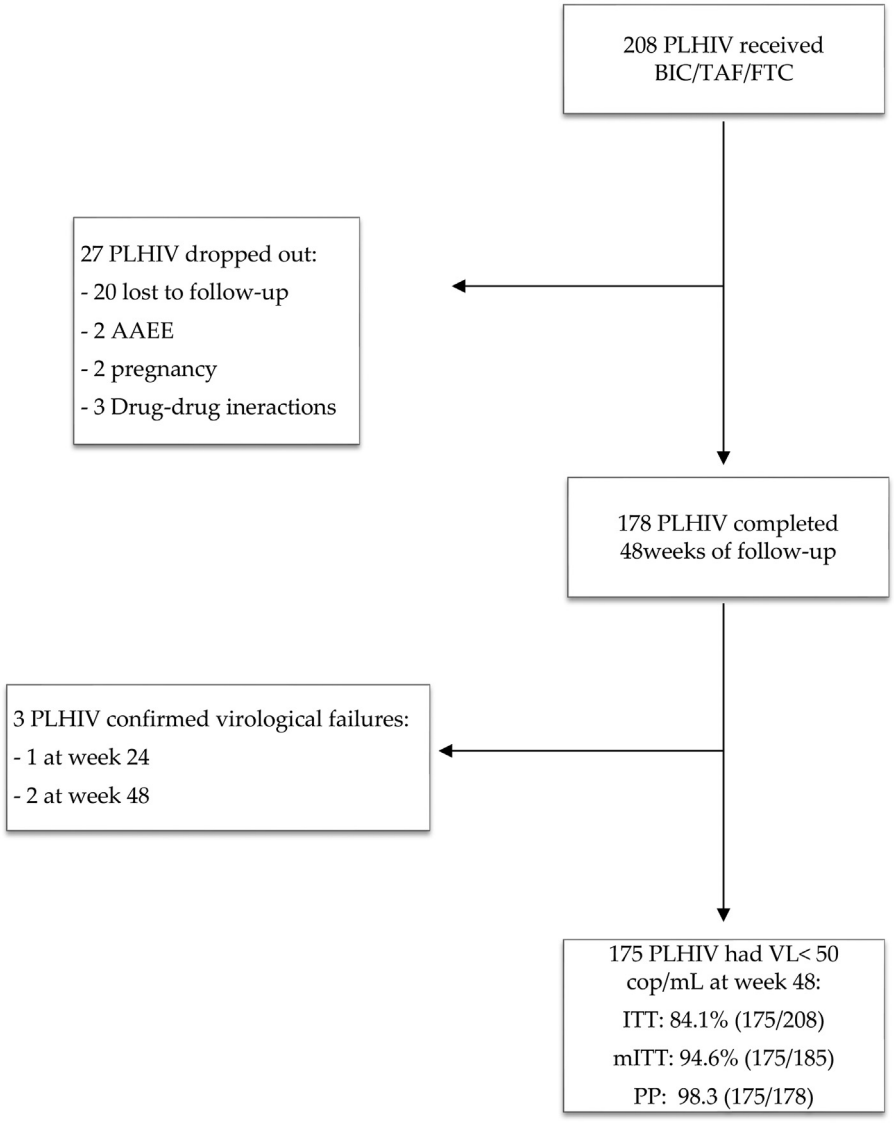

Fig. 1. Flowchart of the clinical trial.

or sex (82.4% male vs. 73.1% female, $P = 0.28$)], 94.6% by mITT, and 98.3% by PP [no differences by CD4 count (CD4<200 cell/uL (95.1%) vs. CD4 >200 cell/uL (94.9%), $P = 0.95$), plasma VL (<100 000 cop/mL (96%) vs. >100 000 cop/mL (93.5%), $P = 0.45$), or sex (95.5% male vs. 90.5% female, $P = 0.29$)] (Table 2). At week 48, a median value of 90 (IQR: 80–95) was obtained for adherence and a median value of 100 (IQR: 90–100 for satisfaction, which is the maximum score on the self-reported questionnaire used.

VF was observed in three patients (1.7%), who had no resistance mutations; it was attributed to poor adherence at week 24 in one and at week 48 in the other two. BIC/TAF/FTC was continued in 2 of these patients, who resuppressed to VL<50 cop/mL after correctly adhering to the regimen. In the third patient, who was lost to the follow-up, darunavir/cobicistat in STR was associated with BIC/TAF/FTC (Table 3).

Blips were observed in 19 (10.1%) of the participants during the follow-up, but none of these developed VF. Adherence to treatment declined by 10% in the IQR between weeks 4 and 24 (100% [100–100] vs. 100 [90–100], $P = 0.0001$) but remained stable between weeks 24 and 48 (100 [90–100] vs. 100 [90–100]; $P = 0.379$). The median satisfaction of patients with the treatment was consistently 90% throughout the trial (week 4 [90%, IQR: 80–99%] vs. 48 [90%, IQR: 80–95%] $P = 0.49$).

Table 2
Outcomes at 48 weeks.

	N = 208	
Losses to the follow-up, n (%)	20 (9.6)	*P**
Intention-to-treat (ITT)	84.1%	
- CD4 < 200 cell/uL	84.8%	0.48
- CD4 >200 cell/uL	80.1%	
- VL>100 000 cop/uL	82.1%	0.71
- VL<100 000 cop/uL	80%	
- Sex:		
Male	82.4%	0.28
Female	73.1%	
Modified intention-to-treat (mITT)	94.6%	
Per-Protocol (PP)	98.3%	*P**
- CD4 <200 cell/uL	95.1%	0.95
- CD4 >200 cell/uL	94.9%	
- VL>100 000 cop/uL	93.5%	0.45
- VL<100 000 cop/uL	96%	
- Sex:		
Male	95.5%	0.29
Female	90.5%	
Blips during follow-up, n (%)	19 (10.1)	
Virological failure, n (%)	3 (1.7)	
Adherence, median (IQR)	100 (90–100)	
Satisfaction median (IQR)	90(80–95)	

*P** significance.

Table 3
Virologic failures.

Patient	Age (y)	Sex	Baseline VL Cop/uL	Baseline CD4	VL in VF	Baseline GRT	GRT in VF	Week of VF	Comments
1	41	Male	72 300	651	178 Cop/mL	No resistance mutations	No resistance mutations	W48	Adherence problems DRV/COB was added (he was lost to the follow-up)
2	42	Male	78 891	334	10 491 Cop/mL	No resistance mutations	No resistance mutations	W48	Adherence problems. He continued with BIC/TAF/FTC, returning to VL <20 cop/mL
3	53	Male	10 000 000	1350	307 Cop/mL	No resistance mutations	Not amplified	W24	Adherence problems He continued with BIC/TAF/FTC, returning to VL < 20 cop/mL

M, male; F, female; ART, antiretroviral therapy; 3TC, Lamivudine; BIC, bictegravir; FTC, emtricitabine; TAF, tenofovir alafenamide; DRV/cob, darunavir/cobicistat; VL, HIV viral load; VF: virologic failure; GRT: genotypic resistance test.

Table 4
Analytical changes between baseline visit and weeks 4, 24, and 48.

	Baseline (B)	Week 4	*P*-value: B vs. week 4	Week 24	*P*-value: B vs. week 24	Week 48	*P*-value: weeks 24 vs. 48	*P*-value: B vs. week 48
CD4 (cell/uL), mean (± SD)	393.5 (253.4)	551.4 (331.1)	0.0001	608.3 (343.1)	0.0001	707 ± 424.8	0.0001	0.0001
CD4/CD8 ratio, mean (± SD)	0.4 (0.3)	0.6 (0.4)	0.0001	0.72 (0.4)	0.0001	0.8 ± 0.6	0.00001	0.0001
Creatinine clearance (mL/h), mean (± SD)	111 (15.3)	101.1 (17.7)	0.0001	96.5 (18.7)	0.0001	97.7 ± 16.4	0.992	0.0001
Total cholesterol (mg/dL), mean (±SD)	157.6(35.7)	168.4 (37.3)	0.0001	167.9 (36.9)	0.0001	172.8 ± 35.1	0.07	0.0001
HDL cholesterol (mg/dL), mean (± SD)	41.6 (0.9)	45.8 (11.9)	0.0001	46.4 (10.8)	0.0001	47.9 ± 13.8	0.6	0.0001
LDL cholesterol (mg/dL), mean (± SD)	102.1(47.9)	101.7 (34.5)	0.3	106.4 (32.3)	0.0001	106 ± 32.5	0.7	0.09
TC/HDL ratio, mean (± SD)	4.4 (4.9)	3.9 (0.9)	0.01	3.9 (1.1)	0.005	3.9 ± 1.1	0.2	0.061
Triglycerides (mg/dL), mean (± SD)	105.2(49.2)	114.1 (55.8)	0.07	110.4 (66.9)	0.02	120.8 ± 79.3	0.3	0.03
Bilirubin (mg/dL), mean (± SD)	0.6 (0.3)	1.7 (12.9)	0.4	0.7 (0.3)	0.0001	1.1(6.7)	0.008	0.1
ALT (UI/dL), mean (± SD)	43.2 (76.8)	33.2 (59.6)	0.004	23.4(17)	0.0001	24(14)	0.5	0.0001
GGT (UI/dL), mean (± SD)	42.7 (63.7)	33.8 (44.6)	0.0001	30.9(31.4)	0.0001	34.5(53)	0.021	0.035
AP (UI/dL), mean (± SD)	79.9(43.5)	76.9(32.5)	0.03	78.5(25.5)	0.9	81(5.6)	0.0001	0.06
Weight Kg, mean (±SD)	74.3 (13.5)	75.3 (13.9)	0.0001	76.9(14)	0.0001	78.3(14.9)	0.001	0.0001
Body mass index, Kg/m^2, mean (± SD)	24.5 (3.9)	24.9 (3.9)	0.0001	25.4(4.1)	0.0001	25.8(4.3)	0.001	0.0001
Waist circumference cm, mean (± SD)	84.5 (12.1)	85.9 (12.4)	0.0001	87.3(12)	0.0001	88.5(12.6)	0.06	0.0001

3.3. Analytical parameters

The mean CD4 count significantly increased between baseline and week 4 (CD4 393.5 ± 252.3 cells/uL at baseline vs. 551.4 ± 331.1 cells/uL at week 4; $P = 0.0001$); statistically significant increases were also recorded at weeks 24 (CD4 608.3 ± 343.1 cells/uL, $P = 0.0001$) and 48 (707 ± 424.8; $P = 0.0001$). The mean CD4/CD8 ratio also significantly increased between baseline and week 48 (0.4 ± 0.3 vs. 0.8 ± 0.6, $P = 0.0001$) (Table 4). At week 4, HIV VL <50 cop/mL was observed in 53.4% (n=111), < 200 cop/mL in 77.9% (n = 162), and < 1000 cop/mL in 98.6% (n = 205) of patients.

Mean creatinine clearance (CKD-EPI) values were slightly decreased between weeks 4 and 24 (111 ± 15.3 vs. 96.5 ± 18.7 mL/h, $P = 0.001$) but remained in the normal range, and they did not change between weeks 24 and 48 (96.5 ± 18.7 vs. 97.7 ± 16.4 mL/h) ($P = 0.992$). Significant reductions were found in hepatic transaminases (ALT) between baseline and week 24 (43.2 ± 76.8 vs. 24 ± 14; $P = 0.0001$) and in GGT levels between baseline and week 48 (42.7 ± 63.7 vs. 34.5 ± 53; $P = 0.0001$).

Total cholesterol/HDL ratios significantly decreased between baseline and week 24 ([4.4 ± 4.9] vs. [3.9 ± 1.1 mg/dL; $P = 0.005$]) but remained stable between weeks 24 and 48 ([3.9 ± 1.1 mg/dL] vs. [3.9 ± 1.1]; $P = 0.2$), (Table 4).

3.4. Anthropometric parameters and body fat distribution

Over the study period, there were significant mean increases of 4 kg in weight (74.3 vs. 78.3, $P = 0.0001$), 0.9 kg/m^2 in BMI (24.9 vs. 25.8; $P = 0.0001$), and 4 cm in waist circumference (84.5 vs. 88.5 cm; $P = 0.0001$) (Table 4). As depicted in Figure 2, 3.8% were classified by their BMI as low weight at baseline vs. 3.5% at week 48 ($P = 0.65$), 55.3% as normal weight at baseline vs. 43.9% at week 48 ($P = 0.001$), 33.2% as overweight at baseline vs. 38% at week 48 ($P = 0.08$); and 8.7% as obese at baseline vs. 14.6% at week 48 ($P = 0.013$).

Comparison of DEXA results for body fat distribution in the subgroup of 15 participants showed no significant differences between the first 2 weeks and week 48 in the grams/percentage of lean mass, fat mass, or total fat or in the distribution of gynoid or android fat (Table 5).

3.5. Adverse effects

Two (0.96%) participants discontinued ART due to a grade 3 adverse event (anaphylactic reaction and nausea/vomiting, respectively) during the first week of treatment. The most frequent symptoms reported by patients at weeks 4, 24, and 48, respectively, were nervousness/anxiety (26.4%, 26.2%, and 19.6%), depressive mood (24.1%, 18.7%, and 20.2%), and insomnia (25.9%, 26.7%, and 25.8%). Other reported symptoms are displayed in Table 6.

4. Discussion

The PLHIV in this trial were mostly young MSM. At baseline, around one-quarter met AIDS criteria and more than two-fifths had HIV plasmatic VL >100 000 cop/mL. All started ART within 1 week of their first specialist visit, with no data on their virologic or immunological status. In relation to efficacy, 98.3% of participants were undetectable at 48 weeks by PP. Virological failure was observed in only 3 patients, attributable to poor treatment adherence, with no development of resistance mutations; two of these continued with BIC/TAF/FTC and were resuppressed, while darunavir/cobicistat was added in STR in the third, but he was lost

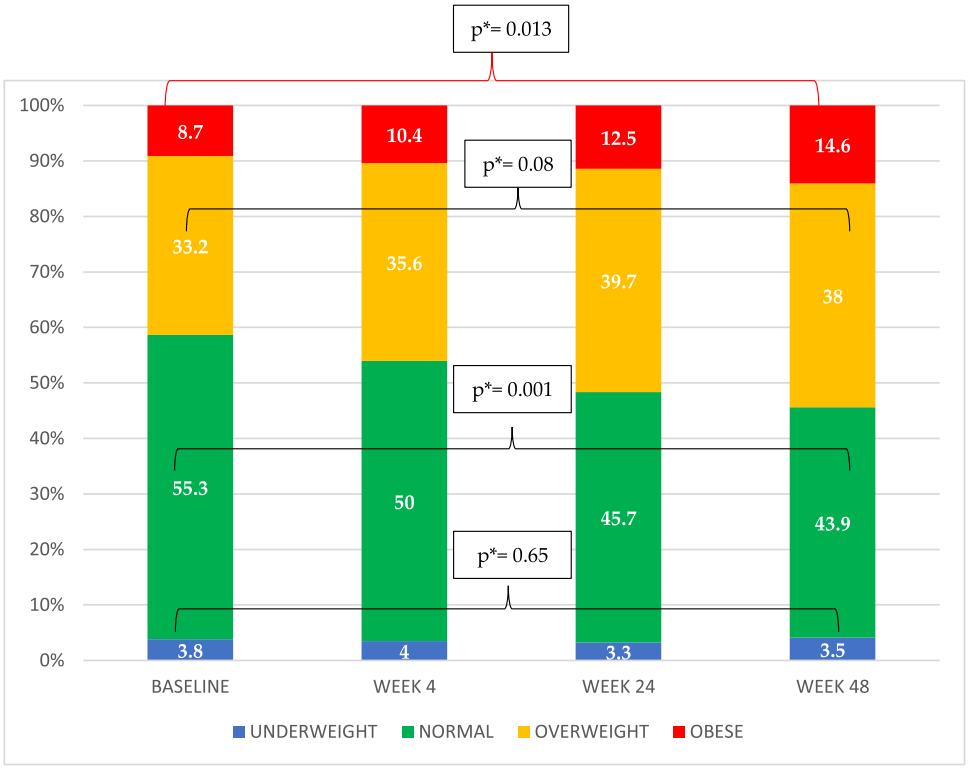

Fig. 2. Percentage distribution of BMI values over the study period. *P* significance <0.005.

Table 5
DEXA fat scan results at baseline and week 48 in sub-group (n = 15).

	Baseline		Week 48		
	(grams) mean (±SD)	(%) median (IQR)	(grams) mean (±SD)	(%) median (IQR)	*P*
Left arm					
Fat mass	1381.6 (341.7)	31.2 (26.7–39.7)	1626.6 (639.1)	34.9 (27.9–37.8)	0.1
Lean mass	2882.4 (484.5)	76 (65–95)	2983.5 (639.1)	85.5 (56.5–96.8)	0.2
Total mass	4264.3 (601.9)	77 (73–95.5)	4167.8 (1003.4)	88.5 (69.8–96.8)	0.1
Right Arm					
Fat mass	1363.3 (354.9)	28.9 (25.9–37.8)	1514.7 (588)	32.4 (25.7–36.3)	0.4
Lean mass	3025.8 (564.3)	71.5 (56.5–87)	3039.2 (523.9)	79 (47–93)	0.5
Total mass	4329 (702.1)	73.5 (68.5–90.5)	4558.2 (918)	80.5 (66–93.5)	0.2
Trunk					
Fat mass	11 503 (4081.4)	29.1 (25.2–37.6)	12 765.5 (4921.2)	29.9 (27.7–39.1)	0.1
Lean mass	2395.7 (3742.4)	59 (35.5–83)	23 103 (2309.2)	52 (42.5–92)	0.5
Total mass	34 798.9 (6198.1)	66.5 (49.5–86.5)	35 868.7 (6629.5)	70 (60–93)	0.1
Left Leg					
Fat mass	4311.6 (1106)	37.7 (26.3–41.7)	4473.3 (958)	36.9 (31.8–42.1)	0.3
Lean mass	7789.3 (1000.2)	77.5 (52–97.5)	7650.1 (958.1)	88 (66–98)	0.9
Total mass	12 131.9 (1413)	77 (54–97)	12 121.6 (1847.3)	87.5 (66.5–98)	0.6
Right Leg					
Fat mass	4313.1 (1088.8)	37.4 (29.8–41.3)	4582 (1613.9)	36.1 (30.7–40.7)	0.5
Lean mass	7852.1 (1017.3)	88 (50.5–98)	7776.8 (1065.8)	81.5 (59.5–97)	0.8
Total mass	12 156.7 (1432.9)	88 (43.2–98.8)	12 226.9 (1938.4)	83 (61.5–97)	0.4
Android					
Fat mass	1893.9 (755.9)		1971.7 (940.9)		0.1
Lean mass	3348.5 (869.8)		3250.9 (496.9)		0.4
Total mass	3348.5 (1225.4)		5222.6 (1325.6)		0.2
Gynecoid					
Fat mass	4299.1 (1242.7)		4372.9 (1308.6)		0.8
Lean mass	7316.1 (1297)		7108.1 (1229.4)		0.9
Total mass	11 633.1 (2107.3)		11 487.7 (2137.6)		0.8

Table 6
Adverse events of BIC/TAF/FTC.

Type of adverse event	Week 4 (n = 208)	Week 24 (n = 187)	Week 48 (n = 178)
Any adverse event	140 (67.3%)	121 (64.7%)	91 (51.1%)
Grade 3 or 4 adverse event	2 (0.9)	0	0
Discontinuation due to treatment-related AE	2 (0.9)	0	0
Death due to treatment-related AE	0	0	0
Most frequent adverse events			
Nervousness/anxiety	55 (26.7%)	49 (26.2%)	35 (19.6%)
Insomnia	54 (25.9%)	50 (26.7%)	46 (25.8%)
Depressed mood	50 (24.1%)	35 (18.7%)	36 (20.2%)
Aerophagia	34 (16.3%)	31 (16.7%)	26 (14.6%)
Headache	34 (16.3%)	26 (13.9%)	28 (15.7%)
Fatigue	45 (21.6%)	38 (20.3%)	25 (14.4%)

to the follow-up and there is no record of subsequent VLs. No patient in whom blips were observed during the follow-up developed VF.

Frequent blips or plasmatic VL >200 cop/mL have been associated with a higher risk of VF and the emergence of multiresistance [19,20]. However, one of our patients had a VL >1000 cop/mL, likely attributable to poor ART adherence, but he did not develop resistance mutations, which may be explained by the high barrier of BIC/TAF/FTC to resistance, as reported by clinical trial in naïve patients starting with this ART [21].

Three non-randomized, multicenter clinical trials studied the efficacy of an ART regimen as rapid initiation treatment in naïve patients: DIAMOND, using darunavir/cobicistat/emtricitabine/tenofovir alafenamide [22]; STAT, using dolutegravir plus lamivudine in STR [23]; and FAST [24], using BIC/FTC/TAF, as in the present investigation. In the DIAMOND trial, treatment was started in 109 patients within 2 weeks of diagnosis and before analytical data were available; the efficacy rate at 48 weeks was similar to the present findings, being 84% by FDA Snapshot and 96% by PP, and no patient developed VF or genotypic resistance mutations [22]. The STAT trial included 131 patients, with the treatment of 8 patients being modified during the first 24 weeks (5 for HBV, 1 for M184V mutation in baseline GRT, 1 for adverse effects, and 1 by patient request). Plasmatic VL <50 cop/mL was achieved in 78% by FDA Snapshot at week 24 and in 82% by FDA Snapshot and 92% by PP at week 48, with no development of VF or resistance mutations by any patient [23]. Finally, the FAST trial [24] in France included 112 patients and reported an efficacy of 84.8% by ITT at week 48, describing VF in 12.5% but no resistance mutations, as observed in all clinical trials of BIC/TAF/FTC in naïve patients [24–26].

In the present trial, 9.6% of patients were considered lost to the healthcare system. The study was conducted during the COVID-19 pandemic, with recruitment starting in January 2020 and the follow-up ending in July 2023. This rate of retention loss is lower than reported in the pre-pandemic DIAMOND 11% [22], STAT 14% [23], and FAST 12.5% [24] trials.

By week 4 of treatment, around 80% of the present patients achieved <200 cop/mL and 98.6% <1000 cop/mL of HIV VL. Rapid viral suppression is one of the advantages of the rapid ART initiation strategy [27] and is achieved faster with antiretrovirals of the integrase inhibitor-based regimen than with PI or NNRTI-based regimens [7,8]. In July 2023, a WHO report classified HIV VL results into three categories: unsuppressed (>1000 cop/mL), suppressed (detected, but ≤1000 cop/mL), and undetectable (no VL detection); accordingly, HIV-infected individuals with suppressed but detectable VL (<1000 cop/mL) who adhere to their ART regimen were considered to have a negligible or no risk of transmitting the virus to sexual partners [28]. Almost all (98.6%) of the present patients had <1000 cop/mL by week 4, supporting the selection of BIC/TAF/FTC as ART for a rapid initiation approach. In naïve patients, rapid ART initiation has demonstrated both individual and public health advantages over conventional care, even in vulnerable populations, reducing the transmission risk and improving treatment adherence and retention in the healthcare system [29].

Regarding the renal profile of the present patients, creatinine clearance values slightly decreased over the first 4 weeks and then remained constant until the end of the follow-up, as previously observed with the BIC/TAF/FTC regimen [28]; this effect is expected due to BIC-induced inhibition of creatine excretion and does not represent true renal toxicity [28]. Their hepatic profile was characterized by a reduction in enzyme levels throughout the follow-up. In relation to their lipid profile, CT/HDL ratios decreased from baseline to week 24 and subsequently remained stable, as previously found in naïve patients prescribed BIC/TAF/FTC [30].

The present patients gained weight (by around 4 kg), and their BMI and waist circumference increased over the follow-up. However, no increase in lean mass, fat mass, or total mass was observed in the subgroup studied by DEXA fat scan, who also showed no lipid accumulations or anomalous fat deposits at week 48. A rise in weight has been described by most trials and observational/cohort studies investigating the impact on naïve HIV patients of integrase inhibitors (including bictegravir) as first-line antiretroviral. A greater weight increase was reported for the combination of dolutegravir with TAF, but the causal mechanism remains unknown and may or may not be related to lipid hypertrophy with visceral fat deposits [31]. On the other hand, the weight gain may reflect a return to health, being more frequent in individuals with CD4 <200 cells/uL, although the authors also considered that it may result from the effects of uncontrolled and prolonged replication of the virus on the structure and healthy functioning of adipose tissue [32].

A very low rate of adverse effects was recorded, despite the administration of a specific questionnaire for their detection. Furthermore, patients completing the follow-up reported a high level of satisfaction and full adherence to the regimen. In the DIAMOND trial, only 1 patient changed treatment due to an adverse effect (rash), and the satisfaction level of participants was close to the maximum on the scale. Likewise, the STAT trial [22] described a treatment change due to an adverse effect (rash) in less than 1% of cases. The FAST trial [24] also found BIC/FTC/TAF to be well tolerated, with a low frequency of grade 3 or 4 adverse events (15/100 people/year), and highly regarded by the patients.

This study is limited by its open and non-randomized design, which is also a limitation of the three previous clinical trials of rapid initiation strategies in naïve HIV patients; in addition, the small percentage of injecting drug users and patients co-infected with HBV, and the fact that adherence was evaluated using a questionnaire completed by the patients themselves. Study strengths include the large sample size, almost double that in the other trials; the high percentage of patients in AIDS stage and with baseline VL >100 000 copies/mL; and the analysis of participant satis-

faction, retention in care, and treatment adherence. In addition, a DEXA fat scan was applied in a subgroup of patients to contribute further knowledge on the weight gain observed in these individuals.

In conclusion, BIC/TAF/FTC appears to be an ideal ART regimen for rapid initiation in naïve patients. It offers high efficacy, safety, and swift virologic suppression, and it is associated with high patient satisfaction and retention in care.

Declarations

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Competing Interests: The funders had no role in the design of the study or the collection of the information.

Ethical Approval: Ethical Committee of Investigación Biomédica de Andalucía Octubre 2020 number of protocol CHT-BIC-20-01. Informed consent was obtained from all participants before inclusion in the trial.

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Data Availability: The authors will provide the journal and reviewers with access to the study database on request

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