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MAJOR ARTICLE

Effectiveness and Safety of Bictegravir/Emtricitabine/Tenofovir Alafenamide in Late-Presenting People With HIV-1 Infection

Xiaoyan Yang,[1] Xiaoxin Xie,[1] Yanhua Fu,[1] Lin Gan,[1] Shujing Ma,[1] and Hai Long[1]

[1]Infectious Department of Guiyang Public Health Clinical Center, Guiyang, China

Background. The efficacy and safety of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) have been demonstrated in treatment-naive clinical trials. However, real-world evidence for this regimen in late-presenting patients with HIV-1 (PWH) is lacking. We investigated the virologic and safety outcomes of BIC/FTC/TAF in late-presenting PWH.

Methods. This retrospective cohort analysis consisted of late-presenting PWH who initiated an antiretroviral regimen of BIC/FTC/TAF between June 2021 and June 2023. Treatment effectiveness, defined as HIV-1 RNA <50 copies/mL, was analyzed. Changes in immunologic, metabolic, liver, and renal parameters were evaluated. Late-presenting PWH were defined as surviving PWH with CD4 <200 cells/μL or surviving patients who met the criteria for AIDS-defining conditions with a CD4 ranging from 200 to 499 cells/μL.

Results. A total of 130 participants were included in the study. At week 48, 93.8% (122/130) of the patients achieved HIV-1 RNA levels <50 copies/mL. CD4 increased by 150.0 cells/μL, and CD4/CD8 increased by 0.16 ($P < .001$). Sixteen (12.3%) participants experienced adverse events, and 6 (4.6%) experienced drug-related adverse events. None of the participants discontinued treatment due to either a lack of effectiveness or adverse events.

Conclusions. BIC/FTC/TAF demonstrated robust virologic suppression and tolerability in patients presenting late in the course of HIV infection.

Keywords. antiretroviral therapy; BIC/FTC/TAF; HIV-1 infection; late presenting; effectiveness.

Current international guidelines recommend initiating antiretroviral therapy (ART) in patients with HIV-1 (PWH), regardless of their CD4, as early ART initiation has been found to be associated with reduced morbidity and mortality [1, 2]. Particularly, early ART has been beneficial in reducing the incidence of serious AIDS-related events, serious non–AIDS-related events, and death from any cause. However, a substantial proportion of patients, up to 50% in high-income countries, are still diagnosed with HIV at low CD4 or at the time of occurrence of AIDS-defining illness [3], suggesting that efforts to ensure a timely diagnosis of HIV are still needed. Late-presenting PWH can encounter a delay in optimal timing of antiviral treatment, affecting treatment effectiveness and increasing the risk of opportunistic infections and, in turn, the risk of death [4, 5]. Late presentation without treatment is a common problem in the global HIV infection prevention and control strategy [6]. The late detection of PWH in China is one of the reasons that affect the prevention and control of HIV infection [7]. Although late presentation is common, this is an area where there is a paucity of data and providers are often left without guidance. Theoretically, starting treatment as soon as possible after diagnosis should be a priority in late presenters, except for those diagnosed with certain opportunistic infections for which deferred ART is recommended to avoid immune reconstitution inflammatory syndrome [8]. Yet, studies on the efficacy of ART in patients with advanced disease are limited. Ideally, the optimal antiretroviral regimen for late presenters should have high efficacy and a high genetic barrier; thus, treatment may be started early before obtaining genotypic resistance test results, which is time-consuming in most clinical settings. Second-generation integrase inhibitors such as bictegravir exhibit these aforementioned characteristics, as well as high tolerability and a low potential for drug-drug interactions [9]; therefore, current guidelines recommend it as the preferred anchor drug in first-line regimens [1, 2]. Nevertheless, the performance of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF) as an initial ART for late presenters has not been sufficiently evaluated. Furthermore, in

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Correspondence: Hai Long, MD, Infectious Department of Guiyang Public Health Clinical Center, 6 Daying Rd, Yunyan District, Guiyang 550004, China (longlong1225@126.com).

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initial phase 3 trials for new HIV drugs, patients with serious infections or AIDS-related diseases were excluded [10, 11]. Additionally, data from real-world observational studies analyzing this scenario are limited [12]. Therefore, it is of clinical value to provide more evidence in literature regarding the effectiveness and safety of BIC/FTC/TAF as an initial therapy for late presenters. This study aimed to evaluate the effectiveness and durability of BIC/FTC/TAF regimens in ART-naive late-presenting PWH in clinical practice.

METHODS

Study Design and Participants

This single-center retrospective cohort study was conducted at the Guiyang Public Health Clinical Center, one of the largest southwest infectious disease hospitals in China, which is responsible for treating 20% of the patients with HIV in Guizhou province and 80% in Guiyang city. We analyzed patients who presented late with HIV and initiated an antiretroviral regimen of BIC/FTC/TAF between June 2021 and June 2023. Treatment effectiveness, defined as HIV-1 RNA <50 copies/mL, was analyzed. Changes in immunologic, metabolic, liver, and renal parameters were evaluated after 48 weeks of treatment. The inclusion criteria were as follows: age >18 years, positive for HIV-1 antibodies on immunoblotting, ART-naive status, ART regimen including BIC/FTC/TAF therapy, and CD4 <200 and/or diagnosis of AIDS-defining illness. The exclusion criteria were pregnancy and loss to follow-up or death, as well as missing HIV viral load (VL), CD4 count, CD4/CD8 ratio, and blood biochemistry data at baseline or 48 ± 4 weeks.

The primary end point was the virologic suppression rate, as determined by the proportion of patients with <50 copies/mL of HIV-1 RNA after 48 weeks of BIC/FTC/TAF use. The secondary end points were the proportion of patients with <200 copies/mL of HIV-1 RNA and changes in CD4, CD4/CD8 ratio, safety (ie, adverse events [AEs]), and parameters (metabolic, liver, and renal) after 48 weeks of treatment.

Definitions

Late-presenting PWH were defined as surviving PWH with CD4 <200 cells/μL or surviving patients who met the criteria for AIDS-defining conditions with CD4 ranging from 200 to 499 cells/μL at the first visit. AIDS-defining conditions were as follows [13]: persistent irregular fever of unknown cause, diarrhea for >1 month (>3 bowel movements/d), a decrease in body mass >10% within 1 month, recurrent oral fungal infections, recurrent herpes simplex virus infection or herpes zoster virus infection, *Pneumocystis jirovecii* pneumonia, recurrent bacterial pneumonia, active tuberculosis or nontuberculosis mycobacteria disease, deep fungal infection, central nervous system space-occupying lesions, development of dementia as a middle-aged or young person, active cytomegalovirus infection, *Toxoplasma gondii* encephalopathy, *Penicillium marneffei* infection, recurrent sepsis, Kaposi sarcoma, and lymphoma.

Virologic suppression was defined as HIV-1 RNA <50 copies/mL at week 48. Virologic nonsuppression was defined as HIV-1 RNA ≥50 copies/mL at week 48. Virologic failure was defined as HIV-1 RNA ≥200 copies/mL at week 48. Body mass index was calculated as weight/height (kg/m^2).

Data Collection and Laboratory Inspection

Demographic baseline characteristics and HIV-related information were obtained from the China HIV Infection Prevention and Control Database and hospital case system. The following data were obtained from the hospital's laboratory information system/hospital information system: age, sex, height, weight, CD4, HIV-1 RNA level, HIV-1 diagnosis time, ART start date, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, blood lipid, and creatinine concentrations. The reasons for BIC/FTC/TAF selection and termination and AEs were also extracted from the medical record system.

Ethics Approval and Informed Consent

This study conformed to the Declaration of Helsinki. The Ethics Committee Board waived the requirement for written informed consent because this was a retrospective study and all patient data were analyzed anonymously.

Statistical Analysis

Excel was used to input data, and SPSS version 23.0 (IBM) was used for the statistical analysis. Based on the data distribution type, qualitative variables were reported as frequency distributions, whereas quantitative variables were described as median (IQR) or mean (SD). The Kolmogorov-Smirnov test was used to determine whether numerical variables fit the assumptions for normality of distribution. A Student *t* test was used to compare normally distributed independent variables between baseline and week 48, while a Mann-Whitney *U* test was used for continuous numeric variables that followed a nonnormal distribution. All statistical tests were bilateral, and $P < .05$ was considered statistically significant.

RESULTS

Patient Characteristics

The patient selection process is illustrated in Figure 1. A total of 159 late-presenting ART-naive patients received BIC/FTC/TAF between June 2021 and June 2023. The study sample comprised 130 late-presenting ART-naive patients.

The baseline patient characteristics are shown in Table 1. The patients were predominantly men (76.1%) with a median age of 45.5 years (IQR, 34.0–58.0). At baseline, the median log_{10} HIV-1 RNA was 5.0 copies/mL (4.6–5.8), which contained 26.2% (34/130) of cases with HIV-1 RNA ≥500 000 copies/mL. The median CD4 was 75.5 cells/μL (28.0–141.0).

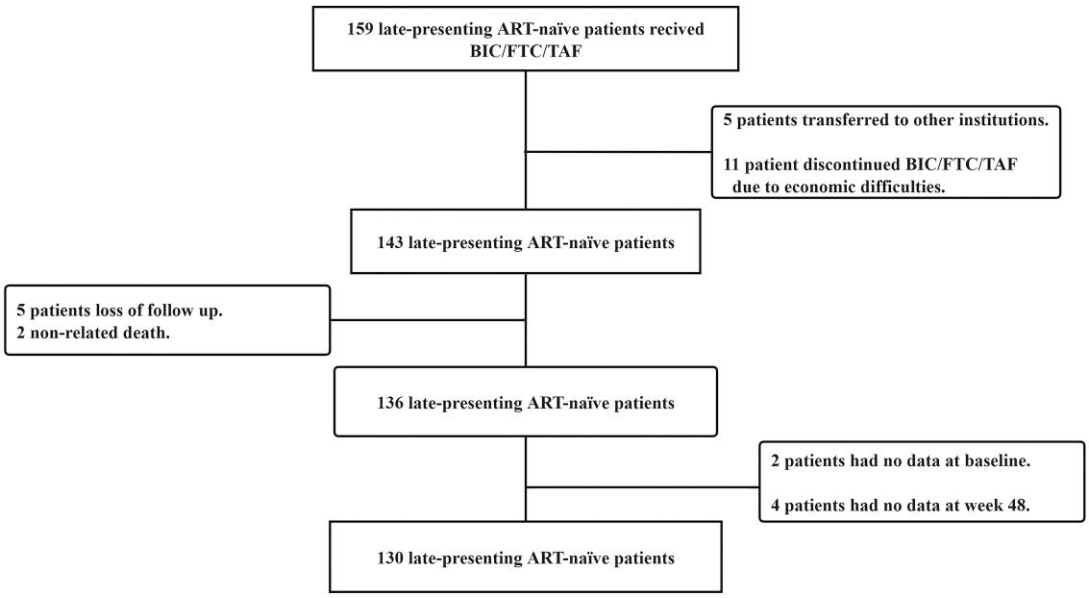

Figure 1. Flowchart of patients with BIC/FTC/TAF. ART, antiretroviral therapy; BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide.

The proportion of individuals who initiated ART in ≤7 days was 27.7%. The prevalence rates of cardiovascular disease and hepatitis B infection were 16.1% and 15.3%, respectively. Among all AIDS-related opportunistic infections (n = 84), the most common was *P marneffei* infection (n = 23, 27.4%) followed by *P jirovecii* pneumonia (n = 20, 23.8%), candidiasis (n = 20, 23.8%), invasive fungal disease (n = 11, 13.1%), cryptococcosis (n = 9, 10.7%), and tuberculosis (n = 9, 10.7%). The main reasons for choosing BIC/FTC/TAF included low potential for drug-drug interactions (60.8%), efficacy (55.4%), liver impairment (35.4%), and ease of use (23.1%).

Virologic Response

At week 48, the proportion of participants with HIV-1 RNA levels <50 copies/mL and <200 copies/mL was 93.8% (122/130) and 99.2% (129/130) in the BIC/FTC/TAF group, respectively. The virologic suppression rates at week 48 for baseline CD4 <200 cells/μL and ≥200 cells/μL were 93.5% and 100%. The virologic suppression rates at week 48 for patients with VL ≥500 000 copies/mL and <500 000 copies/mL at baseline were 91.2% and 94.8%. The virologic suppression rates at week 48 for those with initiation of ART ≤7 and ≥7 days at baseline were 94.4% and 93.6% (Figure 2).

Among the 8 late-presenting ART-naive patients with an HIV-1 RNA ≥50 copies/mL at week 48, 4 experienced persistent low-level viremia during ART, but no information was available regarding drug resistance. Three patients had VL >50 copies/mL at 48 weeks due to discontinuation of BIC/FTC/TAF for 30, 10, and 15 days during follow-up. Virologic suppression was observed in 5 patients during subsequent follow-up (Table 2).

Immunologic Response and Clinical Outcomes

In terms of immunologic changes in the BIC/FTC/TAF group, CD4+ increased by 133 cells/μL, and CD4/CD8 increased by 0.17 ($P < .001$; Table 3). In terms of liver function, after 48 weeks of treatment, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and lactate dehydrogenase levels decreased as compared with baseline levels ($P < .05$), and these have no clinical significance. In terms of renal function, the creatinine clearance rate of patients decreased as compared with that at baseline ($P < .001$). Weight and low-density lipoprotein, high-density lipoprotein, and total cholesterol levels significantly increased ($P < .001$). There were no significant changes in triglyceride from baseline to week 48 ($P > .05$; Figure 3).

Adverse Events

Sixteen (12.3%) AEs and 6 (4.6%) drug-related side effects were reported. Two patients experienced serious AEs (hospitalization) due to diarrhea and lymphoma, and the serious AEs were non–drug-related hospitalizations. During the study, none of the participants discontinued the medication because of a lack of effectiveness or adverse reactions (Table 4).

DISCUSSION

A meta-analysis showed that the incidence of late-presenting PWH in China was 35% [7]. Although the frequency of HIV testing in the Guizhou province has risen annually over the

Table 1. Baseline Demographic and Clinical Characteristics: ART-Naive Patients With HIV-1 (N = 130)

Characteristic	No. (%) or Median (IQR)
Sex	
Male	99 (76.1)
Female	31 (23.9)
Age, y	45.5 (34.0–58.0)
≥50 y	52 (40.0)
Infection characteristics	
Heterosexual transmission	108 (83.0)
Homosexual transmission	22 (17.0)
CD4, cells/μL	75.5 (28.0–141.0)
<200	124 (95.4)
≥200	6 (4.6)
HIV-1 RNA $\log_{10}$, copies/mL	5.0 (4.6–5.8)
HIV-1 RNA, copies/mL	
<100 000	64 (49.2)
100 000–499 999	32 (24.6)
≥500 000	34 (26.2)
Initiation of ART, d	
≤7	36 (27.7)
>7	94 (72.3)
Comorbidities	
Cardiovascular disease	21 (16.1)
Hepatitis B infection	20 (15.3)
AIDS-related opportunistic infections	84 (64.6)
Penicillium marneffei infection	23 (27.4)
Pneumocystis jirovecii pneumonia	20 (23.8)
Candidiasis	20 (23.8)
Invasive fungal disease	11 (13.1)
Cryptococcosis	9 (10.7)
Tuberculosis infection	9 (10.7)
Cytomegalovirus	8 (9.5)
Toxoplasma infection	5 (6.0)
Primary reasons for use of BIC/FTC/TAF	
Low potential for drug-drug interaction	79 (60.8)
Efficacy	72 (55.4)
Liver impairment	46 (35.4)
Easy to take	30 (23.1)
Dyslipidemia	28 (21.5)
Renal impairment	9 (6.9)

Abbreviations: ART, antiretroviral therapy; BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide.

years, the late-presenting rate of PWH continues to be high (from 35.46% in 2014 to 38.80% in 2018), resulting in a higher risk of HIV infection among healthy people and an increase in the number of reported cases, seriously hindering the prevention and control of HIV in the area [14].

In this retrospective study on BIC/FTC/TAF treatment in late-presenting PWH with 64.6% AIDS-related opportunistic infections, a high viral suppression rate (93.8%) was observed at week 48, even with a baseline HIV-1 RNA ≥500 000 copies/mL and rapid initiation of antiviral therapy. The CD4 increased by 133 cells/μL at week 48, and none of the participants stopped taking the drugs because of a lack of efficacy or AEs.

BIC/FTC/TAF has been demonstrated to be noninferior to dolutegravir-based regimens in individuals who are ART naive and virologically suppressed by another regimen [10, 11, 15]. Additional data are required to guide the selection of antiretroviral regimens among late presenters. In this study, we analyzed a population of patients with advanced HIV infection and evaluated the effectiveness and durability of the BIC/FTC/TAF regimen, which has a high genetic barrier and is often recommended in this setting. The BIC/FTC/TAF regimen showed a high virologic suppression rate, with HIV-1 RNA <50 copies/mL at an estimated rate of 93.8% at 48 weeks, similar to results of a study in Spain (93.2%) [16] and the BICSTaR study (96.0%) [17]. This is in accordance with data showing that late presenters, a difficult-to-treat population, can achieve high rates of virologic success with current antiretroviral regimens [18]. Our findings support the robust efficacy and safety profile observed among late presenters who participated in BIC/FTC/TAF phase 3 clinical trials [10, 11]. Late-presenting PWH have characteristics such as a high baseline VL and multiple adverse drug reactions that require high clinical attention [18]. In our study, the virologic inhibition rates at week 48 for patients with initiation of ART ≤7 days and baseline VL ≥500 000 copies/mL were 94.4% and 91.2%, respectively, consistent with other studies [19, 20], indicating that late-presenting PWH should receive early initiation of ART to avoid delays in controlling complications, even in those with baseline VL ≥500 000 copies/mL. Patients with different baseline characteristics can achieve similar curative effects, indicating that BIC/FTC/TAF therapy can be initiated rapidly, positively affecting the long-term prognosis of patients infected with HIV-1 and accelerating virologic suppression, thus controlling the risk of HIV transmission [21]. Medication compliance is an important factor that affects the effectiveness of ART. Poor compliance is a major risk factor for the limited effectiveness of ART in patients with HIV. If medication is not taken regularly, the virus cannot be suppressed easily [22]. Eight patients had HIV-1 RNA <50 copies/mL at 48 weeks; among them, 3 patients experienced virologic rebound due to missing doses of medication, demonstrating that individuals with HIV infection require education on the impact of medication adherence on therapeutic efficacy.

To evaluate immunologic recovery, we focused on CD4 and the CD4+/CD8+ ratio. The CD4+/CD8+ ratio, which naturally decreases with age, is associated with greater mortality and is considered a marker of acute and chronic inflammation. A low CD4+/CD8+ ratio has been associated with non–AIDS-defining events and mortality. After ART initiation, CD4 increases and the CD8 count decreases [23]. In our study, the CD4 of the patients rose at week 48 of BIC/FTC/TAF treatment, suggesting that the immune function of the patients improved after ART with BIC/FTC/TAF, which is consistent with the results of most previous studies [24, 25].

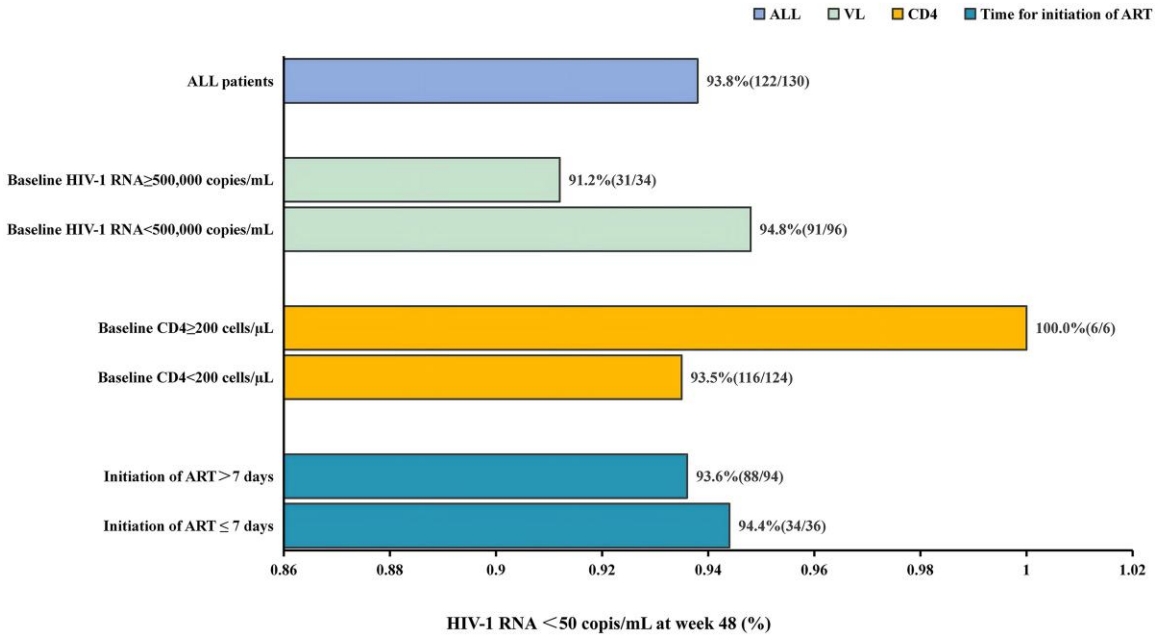

Figure 2. Analysis of patients with an HIV-1 RNA <50 copies/mL at week 48. At week 48, 93.8% of ART-naive patients had an HIV-1 RNA <50 copies/mL. HIV-1 RNA <50-copies/mL rates at week 48 for baseline HIV-1 RNA ≥500 000 and <500 000 copies/mL were 91.4% and 94.8%, respectively. Among patients with baseline CD4 cell count <200 cells/μL, 93.5% had an HIV-1 RNA <50 copies/mL. Among patients with initiation of ART >7 and ≤7 days, 93.6% and 94.4% of patients had an HIV-1 RNA <50 copies/mL. ART, antiretroviral therapy; VL, viral load.

Table 2. Characteristics of Individuals With ≥50 Copies/mL of HIV-1 RNA After 48 Weeks

			HIV-1 RNA, Copies/mL				CD4, Cells/μL			
No.	Age, y	Sex	Baseline	Week 24	Week 48	Other Comments	Baseline	Week 24	Week 48	Skipping Pills, d
1	34	Female	4836	67.5	55.9	TND for tests at week 72	167	288	140	30
2	63	Female	1 550 000	56.0	63.7	<20 copies/mL for tests at week 96	164	344	389	10
3	35	Male	271 000	<30	147	<20 copies/mL for tests at week 72	182	350	350	0
4	57	Male	295 000	TND	52	TND for 2 consecutive tests from week 72 to week 96	173	412	283	0
5	65	Male	1 080 000	172.0	169	NA	28	381	223	15
6	35	Male	21 800	133.0	81.4	NA	195	431	303	0
7	50	Male	494 000	<40	323	NA	48	218	307	0
8	49	Female	2 150 000	TND	76.7	TND for tests at week 60	22	189	218	0

Abbreviations: NA, not applicable; TND, target not detected.

Table 3. Changes in CD4 and CD4/CD8 at Week 48

	Median (IQR)			
Marker	Baseline	Week 48	*Z*	*P* Value
CD4, cells/μL	75.5 (28.0–140.3)	225.5 (159.8–306.3)	−10.010	<.001
CD4/CD8	0.15 (0.07–0.23)	0.31 (0.18–0.43)	−7.337	<.001

After 48 weeks of BIC/FTC/TAF treatment, the body weight of patients significantly increased as compared with baseline, comparable to the results of an observational study [26]. During the same period, the rise in median body weight in this study exceeded that of GS-US-380-1489 and GS-US-380-1490 [10, 11]. In the present study, 64.6% of patients had opportunistic infections at baseline and were in the late stages of AIDS, which may explain this result. In patients with HIV-1 infection, health recovery may cause weight gain owing to the alleviation of HIV-related inflammation and accelerated catabolism [27].

Moreover, as compared with baseline values after 48 weeks of treatment, creatinine levels increased, and the CKD-EPI$_{Scr}$

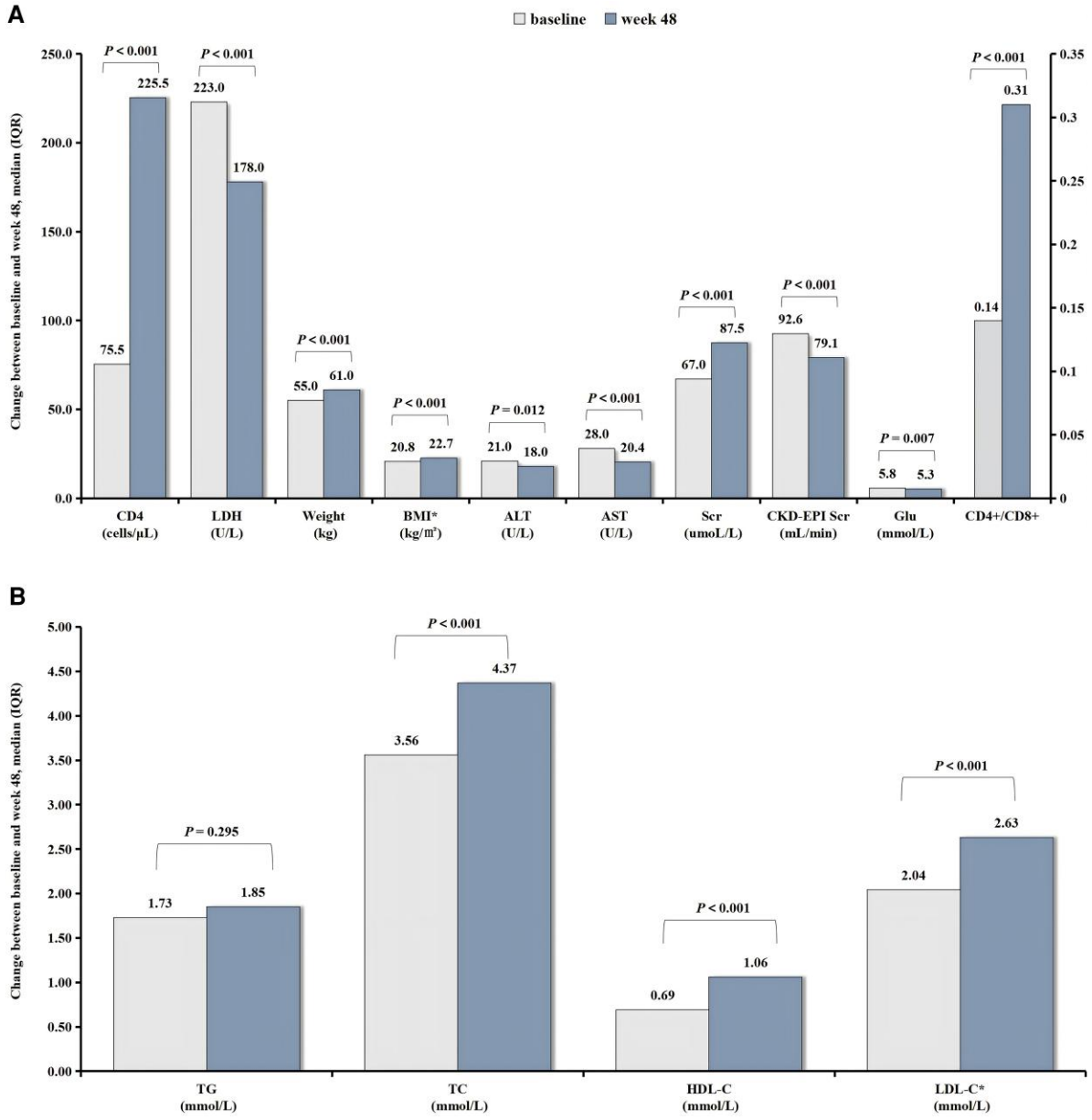

Figure 3. Changes in biochemical indexes between baseline and week 48. *A*, Body weight and biochemical indexes of patients at week 48 after using the BIC/FTC/TAF regimen. *B*, Serum lipid indexes of patients at week 48 after using the BIC/FTC/TAF regimen. *Data expressed as mean ± SD. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BIC/FTC/TAF, bictegravir/emtricitabine/tenofovir alafenamide; BMI, body mass index; CKD-EPI Scr, Chronic Kidney Disease Epidemiology Collaboration serum creatinine; Glu, glucose; HDL-C, high-density lipoprotein cholesterol; LDH, lactate dehydrogenase; LDL-C, low-density lipoprotein cholesterol; Scr, serum creatinine; TC, total cholesterol; TG, triglyceride.

value decreased but remained within the reference range. BIC can raise serum creatinine levels by inhibiting renal organic cation transporter 2 [28], which may explain this result. However, creatinine levels at 48 weeks did not accurately reflect the decline in glomerular filtration rate or renal function. We found no evidence of adverse renal events, and no patients stopped taking the medication because of renal function side effects, supporting this conclusion. Our research showed that after 48 weeks of treatment, total cholesterol and high- and low-density lipoprotein levels increased significantly but were still within the normal range. The 5-year data on BIC/FTC/TAF use also showed that the blood lipid levels of patients fluctuated slightly after 5 years of treatment [29]; therefore, we surmised that BIC/FTC/TAF had little influence on blood lipids.

In this study, the BIC/FTC/TAF regimen was not discontinued because of adverse drug-related events at week 48. This shows that BIC/FTC/TAF is tolerable and safe and plays an important role in ensuring adherence to long-term treatment.

Table 4. Adverse Events

Adverse Event	No. (%)
Any	
Limb numbness	3 (2.3)
Arthralgia	2 (1.5)
Dizziness	1 (0.8)
Anxiety	1 (0.8)
Herpes zoster infection	1 (0.8)
Serious	2 (1.5)
Drug related	
Erythra	4 (3.1)
Pruritus	2 (1.5)
Discontinuation	0 (0)

The limitations of our study include its retrospective, single-center, open-label, and noncomparator group design, as well as the limited information on the effectiveness and safety of BIC/FTC/TAF in the excluded population.

CONCLUSIONS

BIC/FTC/TAF demonstrated robust virologic suppression and tolerability in patients presenting late in the course of HIV infection. In summary, BIC/FTC/TAF is an excellent choice for initiating therapy in late HIV presenters, particularly those with AIDS-defining conditions. This was attributed to its remarkable effectiveness in swift HIV replication and good tolerability.

Notes

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Author contributions. X. Y., H. L., and X. X. contributed to the conception and design of the research. Y. F. constructed the methodology and analysis plan. H. L. and X. Y. were responsible for the study design and analysis plan and carried out the data monitoring. S. M. and L. G. collected all required data. L. G. performed the statistical analysis. X. X. and Y. F. contributed to the interpretation of data. X. Y. wrote the original draft.

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Potential conflicts of interest. All authors: No reported conflicts.

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